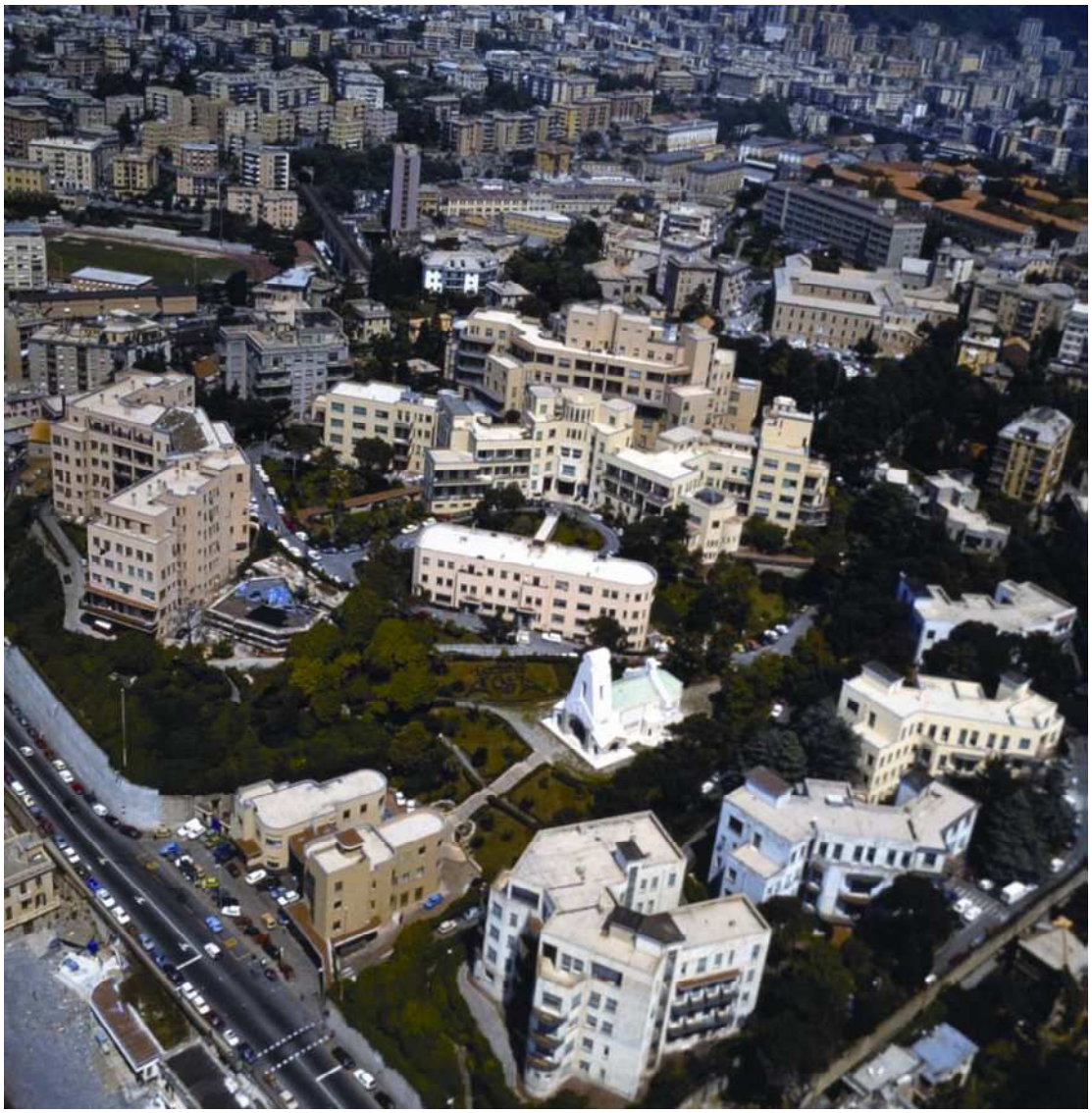


SCIENTIFIC REPORT 2013
ONGOING RESEARCH 2014

IRCCS "Istituto Giannina Gaslini"
Via Gerolamo Gaslini, 5
16147 Genova – Italy
Tel. +39 010 5636 806/807
Fax +39 010 3776590
e-mail: dirscientifica@ospedale-gaslini.ge.it
www.gaslini.org

Some pictures of the Istituto Giannina Gaslini

Nobel laureates at Gaslini: Renato Dulbecco and Rolf Zinkernagel

Pope Benedict XVI visiting Gaslini


Monsignor Angelo Bagnasco visiting Gaslini




Some moments of the visit of the International Scientific Committee
(Professors Alain Fischer, Max Cooper, Sergio Romagnani and Anthony Fauci)


Annual Meeting of the SIOP Brain Tumor Sub-Committee




The Germana International Centre for Studies and training (CISEF): a center of excellence which carries out educational activities in the fields of scientific research, prediatrics, organization and quality of health care services.


TRIPR (Translational Research in Pediatric Rheumatology) Congress 2009



The 2nd Training Course on Blood and Marrow Trasplantation: a course for paediatricians and pediatric nurses on HSCT in children and adolescents

Despite the economic crisis afflicting our country and particularly the public health care sector, Gaslini's scientific production remains at qualitative and quantitative levels of excellence (over 350 publications with IF). This is especially appreciable if we consider the size of Gaslini compared to other Government-funded research institutes, and if data are normalized according to the number of researchers. High quality is also attested to by the fact that Gaslini now counts among its staff 32 "Top Italian Scientists" (see table), i.e., researchers with a Hirsch index (h-index) over 30, a value considered to be of excellence (Via Academy).

Advanced technology and technological innovation are essential for modern research. For this reason, thanks to co-funding from the Ministry of Health and the Regione Liguria, important investments were made in 2013 for equipment of pivotal relevance for both research and advanced diagnostics. This is essential for an institution like Gaslini, where complex diseases are diagnosed and treated. For instance, equipment for next generation sequencing (NGS) enabling the rapid diagnosis of genetic diseases was purchased, as were a cell sorter and a state-of-the-art cytofluorimeter for our Core Facilities. Furthermore, very sophisticated imaging studies are now possible thanks to the acquisition of an image streaming system and of a high-performance confocal microscope. In addition, a 3-tesla MRI scanner, an essential tool for refined diagnostics and advanced clinical research, will soon be available.

Although public funding is becoming increasingly scarce, it was possible for us to award numerous two-year contracts of excellence on a competitive and strictly meritocratic basis to our most productive young researchers. Thanks to the generous and enlightened support of the Gaslini Foundation, three prizes ("Gerolamo Gaslini Awards") were awarded to young authors of publications of particular international impact. In 2014, new calls for contracts of excellence and for prizes for the best publications were published. These actions, undertaken and implemented over the last few years, provide a definite incentive and send a clear signal that merit is held in high regard (which is certainly not a given in our country!). I want to stress my firm conviction that the application of meritocratic criteria is essential, not only for

ethical reasons, but also – and mainly – to guarantee the proper functioning of any activity and to promote progress. While investing in young researchers is crucial, it is clear that actions aimed at rewarding the most deserving individuals should not be limited to prizes and contracts of excellence. Indeed, young researchers should be offered permanent positions, not only for the fair recognition of merit, but also to guarantee the continuity of research of excellence and an appropriate generational turnover. I also believe that, in a Ministry of Health-funded research institute, research should be able to rely on an appropriate number of physician-researchers who, after receiving training in a laboratory, are well acquainted with the potential of research and can speak the same language as the biologist or the biotechnologist. A well-qualified M.D. has a broader vision and a better understanding of the pathophysiological mechanisms on which he or she can base relevant experimental questions and pursue research of clinical relevance. Unfortunately, these professionals are by now very rare. Furthermore, the increasingly higher burden of clinical activities limits to a great extent the possibility to visit laboratories and to study the most recent scientific literature. In conclusion, even though today the status of research at Gaslini can be considered very positive, reduced public spending and an inadequate generational turnover are warning signs that must not be underestimated for the future of our institute. Research must be truly seen as an investment and not as a cost. Unfortunately, these words, repeated with emphasis by politicians and authorities, are rarely applied in practice. Researchers and the entire staff of Gaslini reject the idea that the institute will in the future become emblematic of a country in decline and demand that research be respected, supported, and stimulated. Research must be recognized as an important resource, a driving force of Gaslini's progress. It would, moreover, be unacceptable to disregard what our Founder Gerolamo Gaslini declared with extraordinary acumen and foresight: *"I am not a man of science, but I am perfectly aware that only by starting from scientific research, conducted under proper direction, can physicians conscientiously accomplish their difficult task".*

Lorenzo Moretta

ANNUAL REPORT 2013

INDEX

CONTRIBUTION OF UNITS TO SCIENTIFIC PRODUCTION IN 2013

Table 1 – Publications assigned to each unit (first author, last author or indermediate author)

Unit	N.	IF	Normalized IF
Pediatric Neurology and Muscular Diseases	59	234.01	198.7
Laboratory of Molecular Genetics	28	141.654	127
Oncology, Hematology, and BMT	26	137.935	84.3
Pediatric Rheumatology	27	137.791	137.55
Clinical and Experimental Immunology	24	106.758	95
Lab. Physiopathology of Uremia	12	106.201	65
Nephrology, Dialysis and Transplantation	12	99.845	49.1
Laboratory of Hematology and Hemophilia	11	89.455	46
Lab. of Oncology	16	81.219	75
Cardiology	5	58.504	11
Pediatric Pneumology and Allergology	17	42.317	59
Pediatric Clinic	12	40.295	25.9
Centre of Genetic Diagnostics and Bioch. of Diseases	9	39.481	35
Laboratory of Clinical Chemical Analysis	12	38.724	51.2
Child Neuropsychiatry	11	35.254	33.6
Lab. Postnatal Stem Cells and Cell Therapies	8	33.805	31
Pediatric Gastroenterology with Endoscopy	1	29.978	7.5
Epidemiology, Biostatistics, and Committees	8	23.881	21.6
Neuroradiology	5	25.072	25
Neurosurgery	8	18.968	24
Infectious Diseases	7	16.74	19.2
Lab. of Molecular Biology	4	15.778	22
Lab. Cytogenetics	5	14.56	15
Clinical Radiology	7	12.51	20
Neonatal Diseases	6	11.526	17.4
Pathologic Anatomy	5	11.297	10.5
Surgery	4	7.719	13
Pediatric Emergency/Urgency	2	4.958	3.2
Physical Medicine and Rehabilitation	1	3.73	3
Dermatology	1	3.73	6
Obstetrics and Gynecology	1	2.259	1
Cardiovascular Surgery	1	1.342	2
Immunohematology and Transfusion Medicine	1	1.225	0.5
Ophthalmology	1	0.671	1
Total	**357**	**1629.192**	**1336.25**

N: Number of publications in extenso (including those written in collaboration with other units) listed in the Journal of Citation Reports
IF: Impact Factor reported in the Journal of Citation Reports
Normalized IF: Normalized Impact Factor according to ministerial indications
*In case of collaborative papers of one or more units, the paper is assigned (in this order) to the first author, to the last author, or to the author appearing in the first intermediate position in order to calculate the IF of a single publication only once.

Table 2 - Total publications and related IF assigned to units in 2013

Unit	N.	IF	Normalized IF
Pediatric Neurology and Muscular Diseases	65	247.233	218.7
Oncology, Hematology, and BMT	45	228.021	187.3
Nephrology, Dialysis, and BMT	27	216.576	126.3
Laboratory of Molecular Genetics	35	212.832	167.2
Pediatric Rheumatology	36	170.808	169.55
Laboratory of Clinical Chemical Analysis	28	150.396	122.2
Clinical and Experimental Immunology	34	149.134	146
Lab. Of Uremia Physiopathology	17	129.151	86.2
Epidemiology, Biostatistics, and Committees	25	96.087	101.3
Lab. of Oncology	17	89.47	89
Cardiology	7	64.161	19
Pathologic Anatomy	16	63.288	71.5
Centre of Genetic Diagnostics and Biochem. of Diseases	13	55.983	56
Neuroradiology	16	51.823	60.2
Pediatric Clinic	16	51.532	43.9
Child Neuropsychiatry	16	42.538	45.1
Pediatric Pneumology and Allergology	17	42.317	59
Neurosurgery	10	40.736	45
Lab. Postnatal Stem Cells and Cell Therapies	8	33.805	31
Pediatric Gastroenterology with Endoscopy	1	29.978	7.5
Clinical Radiology	10	28.342	38
Lab. Cytogenetics	9	26.78	31
Lab. of Molecular Biology	6	26.003	34
Lab. of Hematology and Hemophilia	6	25.581	30
Infectious Diseases	8	20.309	25.2
Surgery	8	16.214	30
Neonatal Diseases	7	14.535	23.4
Pediatric Emergency/Urgency	3	8.688	4.4
Pharmacy	3	7.441	7.2
Dermatology	2	5.072	8
Cardiovascular Surgery	4	4.855	8
Physical Medicine and Rehabilitation	1	3.73	3
Orthopedics	1	2.304	2
Obstetrics and Gynecology	1	2.203	5
Immunohematology and Transfusion Medicine	1	1.225	0.5
Hospital Medical Coordinator	1	0.825	1
Ophthalmology	1	0.671	1

N: Number of publications in extenso (including those written in collaboration with other units) listed in the Journal of Citation Reports
IF: Impact Factor reported in the Journal of Citation Reports*
Normalized IF: Normalized Impact Factor according to ministerial indications

Table 3 – Impact Factor-related data in the period 1999-2013

Year	N. Publications	Impact Factor	Normalized Impact Factor (according to ministerial indications)	IF / Publication	Normalized IF / Publication
1999	193	**441.6**	N.D.	2.29	N.D.
2000	170	**583**	**679.3**	3.43	4.00
2001	214	**755.8**	**892.9**	3.53	4.17
2002	218	**807.9**	**930.1**	3.71	4.27
2003	231	**924.9**	**1094.5**	4.00	4.74
2004	248	**1067.5**	**1083**	4.30	4.37
2005	280	**1154**	**1197.2**	4.12	4.28
2006	297	**1187.4**	**1293.5**	4.00	4.36
2007	274	**1244.8**	**1152.7**	4.54	4.21
2008	261	**1247.8**	**1105**	4.78	4.23
2009	311	**1420.6**	**1239.8**	4.57	3.99
2010	227	**1155.6**	**929**	5.09	4.09
2011	327	**1705.449**	**1366.8**	5.22	4.18
2012	343	**1651.338**	**1341.9**	4.81	3.90
2013	357	**1629.192**	**1336.25**	4.56	3.74

Table 4 – H-index of the Top Italian Scientists (TIS*) of the Giannina Gaslini Institute

Researcher	Area	H-index**
Lorenzo Moretta	Immunology/Hematology	112
Cristina Bottino	Immunology	67
Alberto Martini	Rheumatology	62
Francesco Frassoni	Cell Therapies/Hematology	59
Roberto Biassoni	Molecular Biology/Immunology	57
Angelo Ravelli	Rheumatology	53
Vito Pistoia	Oncology	46
Nicolino Ruperto	Rheumatology	47
G. Marco Ghiggeri	Nephrology	46
Giovanni A. Rossi	Pneumology	45
Angela Pistorio	Epidemiology and Biostatistics	45
Luigi Varesio	Molecular Biology	43
Claudia Cantoni	Immunology	43
Carlo Minetti	Neuromuscular Diseases	42
J.L.V. Galietta	Medical Genetics	40
Isabella Ceccherini	Medical Genetics	39
Michela Falco	Immunology	38
Roberto Ravazzolo	Medical Genetics	37
Mirco Ponzoni	Oncology	37
Claudio Bruno	Neuromuscular Diseases	37
Mohamed Maghnie	Endocrinology	35
Bruno Azzarone	Immunology	34
Marco Gattorno	Rheumatology	34
Federico Zara	Neuromuscular Diseases	34
Elio Castagnola	Infectious Diseases	33
Edoardo Lanino	Oncology, Hematology, and BMT	33
Marina Podestà	Cell Therapies/Hematology	33
Riccardo Haupt	Oncology/Epidemiology	32
Pasquale Striano	Neuromuscular Diseases	32
Carlo Dufour	Oncology/Hematology	31
Renata Lorini	Endocrinology	31
Giorgio Gimelli	Medical Genetics	31
		1388

* H-index > 30

** ISI or Via Academy

RESEARCH LINES

Number	Title
1	**Innovative diagnostic strategies**
2	**Clinical Pediatrics, Perinatal Medicine, and Pediatric Surgery**
3	**Clinical and Experimental Immunology and Rheumatology**
4	**Oncology-Hematology and Cell Therapies**
5	**Muscular and Neurological Diseases**

SCIENTIFIC PRODUCTION YEAR 2013 FOR RESEARCH LINE

Fig. 1 - Impact Factor for main research lines year 2013

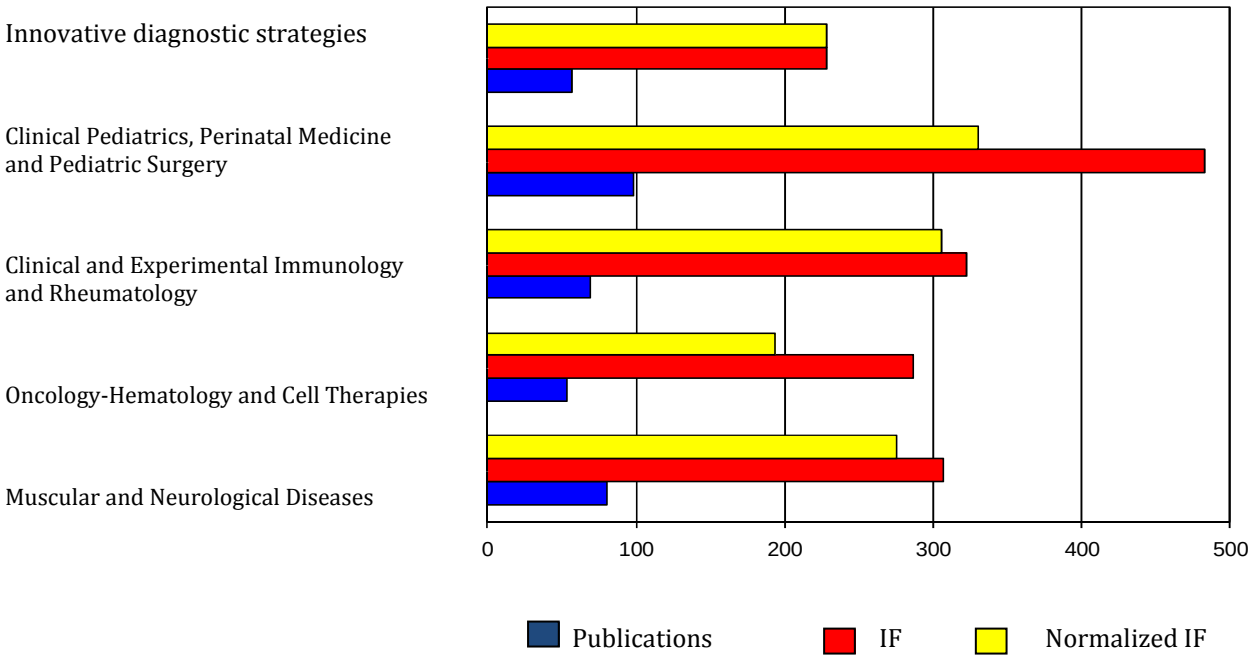


Figure 2 – Number of Publications

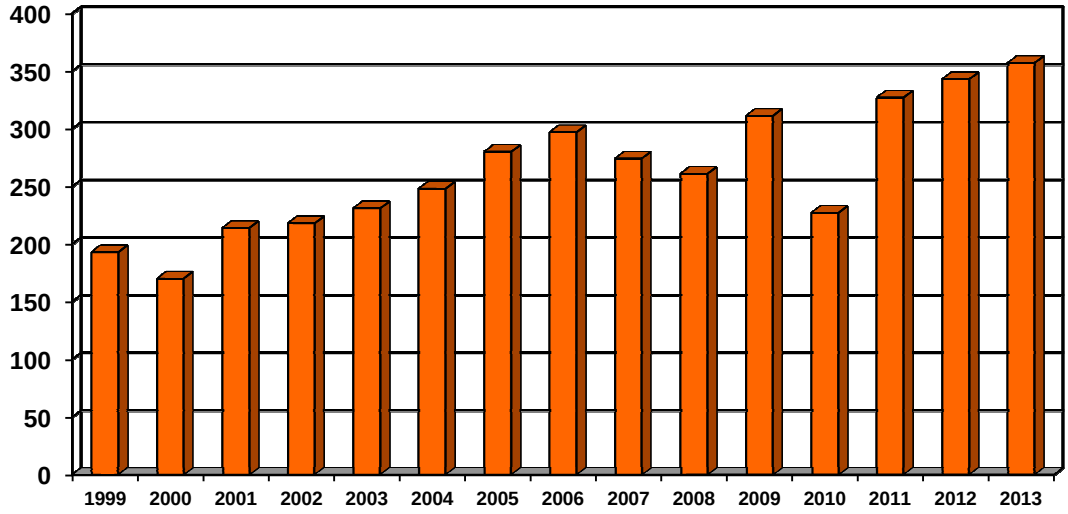
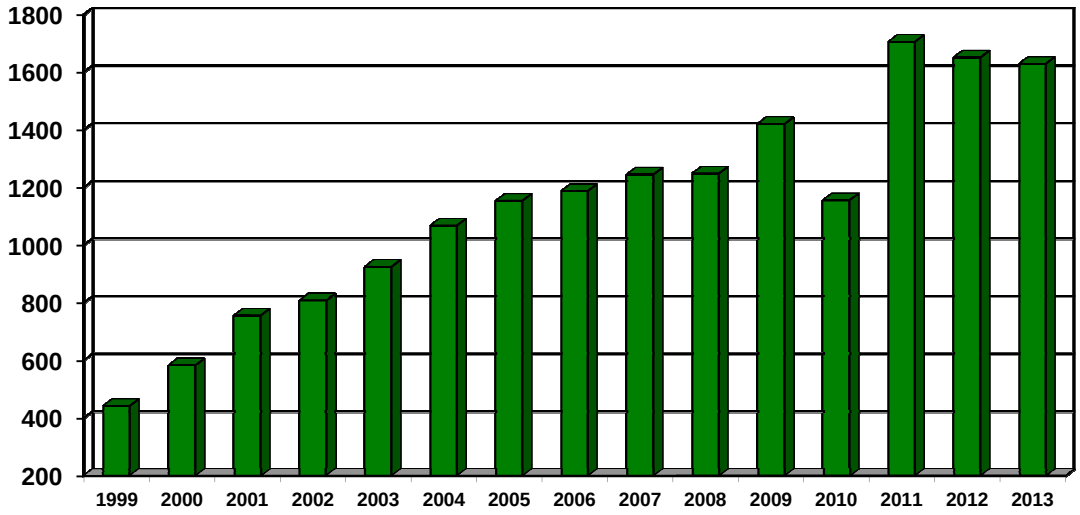


Figure 3 - Impact Factor



RESEARCH LINES AND PUBLICATIONS 2013

Research line 1
Innovative diagnostic strategies

Title
Clinical, molecular, and functional studies for the development and optimization of new diagnostic and therapeutic approaches

Coordinators
Prof. Roberto Ravazzolo, Dr. Luigi Varesio

Project description (outline and objectives)
The inspiring principle of this research line is the study of disease pathogenetic mechanisms as the basis for translation into the clinical practice in terms of development of new diagnostic and therapeutic strategies. Research projects are carried out through different approaches in the units involved in the implementation of this research line and are focused on the following areas:

- use of new sequencing technologies for the development of genetic tests for genes responsible for hereditary diseases;
- new sequencing technologies for the development of molecular methods for the diagnostics of viral and bacterial diseases in the control of nosocomial infections;
- new technologies for the development of diagnostic and screening tests for chromosomal anomalies during pregnancy;
- therapeutic strategies for genetic diseases and tumors. This research area is presently in a very active phase in terms of molecular screening tests and *in vitro* tests for the identification of biological molecules (siRNA) and small chemical molecules acting at different levels of physiopathological mechanisms. In the case of cystic fibrosis, the search for molecular targets that can be involved in processing and transport of CFTR protein membrane allows the use of specific siRNA against specific targets. In the case of progressive ossifying fibrodysplasia, Alexander disease, and neuroblastoma, screening tests of chemical compounds are performed, aimed at modifying the expression of genes of interest for the pathogenetic mechanism and, in particular for neuroblastoma, the use of cyclin-dependent kinase inhibitors.

Principal investigators
Dr. Claudio Gambini/Dr. Angela Rita Sementa – Pathologic Anatomy
Dr. Luigi Varesio – Laboratory of Molecular Biology
Dr. Giovanni Melioli/Dr. Gino Tripodi – Laboratory of Clinical Chemical Analysis
Dr. Mirella Filocamo – Centre of genetic diagnostics and biochemistry of metabolic diseases
Prof. Roberto Ravazzolo – Medical Genetics

Activity year 2013
Pathologic Anatomy - *Director: Dr. Claudio Gambini/Dr. Angela Rita Sementa*
Research activity planned for 2013 has been completed or is still ongoing. Some of the scientific results obtained are reported below, namely:

- The molecular genetic study of neuroblastic tumors in adolescents belonging to the Italian case series included in the NB registry - in collaboration with the Department of Pediatric Hematology-Oncology – led to the identification of distinctive biomolecular features of this tumor type in adolescents, obtained also thanks to the participation in national and international meetings and presently in press.

A similar study on an adult series with neuroblastoma (21 patients – one of the largest published series) is in press.

- The study of Gaslini's case series of atypical Spitz tumors, including biomolecular characteristics and immunohistochemical aspects, converged in the analysis of the national case series included in the registry of rare pediatric tumors. The paper illustrating the results of this important study is in press.
- The study of minimal residual disease in patients with neuroblastoma (at onset and in different disease phases) carried out through immunocytochemical investigation with anti-GD2 antibody on bone marrow aspirates, peripheral blood, and apheretic collections, laid the foundations for an international cooperative study on minimal residual disease in neuroblastoma, to which the Italian case series represents the largest and highest quality contribution. Statistical analysis is still ongoing.
- The study on the histological correlation between biopsies at onset and samples obtained during delayed surgery of peripheral neuroblastic tumors in patients included in the Unresectable Protocol (2001 - 2006) is still ongoing.

Laboratory of Molecular Biology - *Director: Dr. Luigi Varesio*

We characterized a new murine model of glycogenosis 1a that we have recently generated in which the glucose-6-phosphatase gene was inactivated only in the liver at birth. The characteristic of these mice is to survive even without glucose supplement, thus making it possible to focus only on one of the mainly affected organs, i.e. the liver, and to evaluate the long-term consequences of liver disease. We characterized this murine model by evaluating the hepatic parameters of the animals using histochemical techniques and G6Pase function test on microsomes, we carried out metabolic tests to assay cholesterol, triglycerides, fasting and non-fasting glycemia, and histological analyses for the evaluation of liver damage. We demonstrated that these mice present all the hepatic pathological characteristics of glycogenosis 1a, including hepatomegaly, hepatic glycogen storage, fasting hypoglycemia, steatosis, and infiammation. In addition, since 10 months of life, they develop hepatic adenomas and, since 18 months, liver carcinomas. This model will allow the selective study of liver tissue alterations, the possible treatment of liver dysfunctions, and the effects of stem cell transplantation. To this end, we obtained in culture functioning hepatocytes from pluripotent stem cells derived from spermatogonial stem cells isolated in normal mice. In addition, we established the experimental conditions for infecting with recombinant lentivirus myelomonocytic cells isolated from the bone marrow of healthy mice. Both cell types will be inoculated in mice to evaluate their long-term therapeutic effect in the new murine model of glycogenosis 1a that we generated.

Laboratory of Clinical Chemical Analysis - *Director: Dr. Giovanni Melioli/Dr. Gino Tripodi*

In 2013, the staff of the Laboratory of Clinical Chemical Analysis of Gaslini continued the research activity started in previous years. Research fields mainly included molecular medicine, microbiological diagnostics, the study of new biomarkers, and the assay of therapeutic ranges of relevant drugs in pediatrics, especially focusing on the treatment of infectious diseases.

Concerning molecular medicine, two new Next Generation Sequencing instruments were implemented which, in the short term, will lead to very significant results in the fields of genetics and molecular microbiology. In the field of the analysis of the immune response at molecular level, the laboratory has reached a significant international renown in the study of IgE profiles in allergic patients. Microbiological diagnostics improved thanks to new molecular tools able to reduce dramatically response time, thus making it possible to face

with determination the problem of antibiotic resistance. Even in this field, closely related to clinical pharmacology and therapeutic drug monitoring, the laboratory has made very significant progress, to the point that it can be considered a model of efficiency at least at national level. Finally, in the field of new biomarkers, research was focused on the study of the effect of these molecules in pediatrics and on the definition of reference values for pediatric age. As a result, innovative standards were defined using age as a continuous variable for the prediction of the reference range of biomarkers and therefore going beyond the obsolete classification into age ranges.

Centre of genetic and biochemical diagnostics of metabolic diseases - *Director: Dr. Mirella Filocamo*

Research interests of the Centre include the study of molecular mechanisms underlying lisosomal diseases and some white matter disorders. Parallel research activities are related to the genetic biobank available in the centre and to the regulation of biobanking. This latter activity is carried out in collaboration with national and international working groups.

Among lisosomal diseases, Gaucher disease (GD), due to glucocerebrosidase (GBA) defect, was studied in different research projects. In particular, in collaboration with the Department of Cell Research and Immunology of the University of Tel Aviv, two parallel studies were carried out: a) the activation of unfolded protein response (UPR) was demonstrated both in fibroblasts of GD patients and in Drosophila animal model in the presence of GD mutant alleles; the same mechanism has also been hypothesized as jointly responsible with ERAD (ER associated degradation), which is responsible for the onset of Parkinson disease in GD; b) *in vitro* demonstration of the efficacy of Ambroxol, used as pharmacological chaperone in increasing the levels of the missing enzyme in a panel of fibroblasts, previously characterized at molecular level.

Concerning a second research line, the Centre with its genetic biobank services (conservation and distribution) supported internal and external (national and international) research projects and continued its activity of coordination of 10 Italian biobanks (Telethon project). In addition, it has constantly made available to national (ERIC-BBMRI; Certification Requirements-SIGU) and international (Bioresource Research Impact Factor-GEN2PHEN) working groups its specific skills acquired in the field of biobanking-related organizational, legal, and ethical aspects. In particular, within BBMRI-IT, it has actively participated in the preparation of the evaluation questionnaire for the survey of biobanks that will be part of the Italian network. Finally it continued the monitoring of the specific indicators of Biobank regulations and, in parallel, it coordinated a SIGU (Italian Society of Human Genetics) working group for preparing the final version of the "System for Quality Management of Genetic Biobanks". In order to favour the integration with the systems of management of quality, environment, safety, laboratory activity, this standard was made compatible with ISO 9001, ISO14001, OHSAS 18001, SA8000, ISO15189, ISO17025.

Medical Genetics - *Director: Prof. Roberto Ravazzolo*

The Medical Genetics unit carried out studies on different rare genetic diseases, following a research strategy based on the characterization of genes responsible for monogenic hereditary diseases. In particular, in-depth studies are carried out on disease pathogenetic mechanisms, interrelations between disease genes and functional pathways using functional genomics methods, effects of cytogenetic anomalies and genomic imbalances. These studies allowed the acquisition of new knowledge useful for the development of new diagnostic tools also through Next Generation Sequencing techniques and innovative therapeutic approaches for rare genetic diseases..

Some of the results obtained in 2013 are reported below:

- Genes and mechanisms associated with the pathogenesis of Hirschsprung disease reported and described also as results of studies performed within the International Consortium for Hirschsprung disease.
- Genes and mechanisms involved in autoinflammatory diseases with description of new forms and new responsible genes.
- Genes and mechanisms involved in Alexander disease and Congenital Central Hypoventilation Syndrome.
- Further characterization of genes coding for proteins of the TMEM16 family: TMEM16A, TMEM16B, and TMEM16E.
- Advances in the strategies of drug therapy of cystic fibrosis.
- Animal model for drug therapy of Spinocerebellar Ataxia type 1.
- Mechanisms of ACVR1 gene regulation applicable to the research of chemical compounds with potential therapeutic efficacy for Progressive Ossifying Fibrodysplasia.
- Genes and mechanisms involved in EEC and ADULT syndromes and in skeletal malformations with hypergrowth.
- Genomic rearrangements in different regions of 3,2,14,15 and 22 chromosomes that include genes that can be associated with neuropsychiatric syndromes and congenital malformations.

Publications year 2013

1. **Marconi C., Brunamonti Binello P., Badiali G., Caci Emanuela, Cusano R., Garibaldi J., Pippucci T., Merlini A., Marchetti C., Rhoden KJ., Galietta Luis Juan V, Lalatta F., Balbi P., Seri M.**
   A novel missense mutation in ANO5/TMEM16E is causative for gnathodiaphyseal dysplasia in a large Italian pedigree.
   EUR J HUM GENET 2013; 21: 613-619.
   IF: 4.319 Normalized IF: 3
2. **Gimelli S., Leoni M., Di Rocco Maja, Caridi Gianluca, Porta Simona, Cuoco Cristina, Gimelli Giorgio, Tassano Elisa.**
   A rare 3q13.31 microdeletion including GAP43 and LSAMP genes.
   Mol Cytogenet. 2013; 6: 52
   IF: 2.36 Normalized IF: 2
3. **Lanzilli G., Traggiai E., Braido F., Garelli V., Folli C., Chiappori A., Riccio AM., Bazurro G., Agazzi Alessia, Magnani A., Canonica GW., Melioli Giovanni**.
   Administration of a polyvalent mechanical bacterial lysate to elderly patients with COPD: effects on circulating T, B and NK cells.
   IMMUNOL LETT 2013; 149: 62-67
   IF: 2.337 Normalized IF: 2
4. **Melchionda L., Fang M., Wang H., Fugnanesi V., Morbin M., Liu X., Li W., Ceccherini Isabella, et al.**
   Adult-onset Alexander disease, associated with a mutation in an alternative GFAP transcript, may be phenotypically modulated by a non-neutral HDAC6 variant.
   ORPHANET J RARE DIS 2013; 8: 66.
   IF: 4.315 Normalized IF: 3.
5. **Matera I., Musso M., Griseri Paola, Rusmini M., Di Duca Marco, So M., Mavillo D., Miao X., Tam PHK., Ravazzolo Roberto, Ceccherini Isabella, Garcia-Barcelo M.**

Allele-specific expression at the RET locus in blood and gut tissue of individuals carrying risk alleles for Hirschsprung disease.
HUM MUTAT 2013; 34: 754-762.
IF: 5.213 Normalized IF: 6

6. **Hinzpeter A., Aissat A., de Becdelievre A., Bieth E., Sondo E., Martin N., Costes B., Costa C., Galietta Luis Juan V, Girodon E., Fanen P.**
   Alternative splicing of in-frame exon associated with premature termination codons: implications for readthrough therapies.
   HUM MUTAT 2013; 34: 287-291.
   IF: 5.213 Normalized IF: 3
7. **Bendikov-Bar I., Maor G., Filocamo Mirella, Horowitz M.**
   Ambroxol as a pharmacological chaperone for mutant glucocerebrosidase.
   BLOOD CELL MOL DIS 2013; 50: 141-145.
   IF: 2.259 Normalized IF: 1
8. **Salsano E., Rizzo A., Bedini G., Bernard L., Dall'Olio V., Volorio S., Lazzaroni M., Ceccherini Isabella, et al.**
   An autoinflammatory neurological disease due to interleukin 6 hypersecretion.
   J NEUROINFLAMM 2013; 10: 29.
   IF: 4.351 Normalized IF: 3
9. **Bachetti Tiziana, Chiesa Sabrina, Castagnola P., Bani D., Di Zanni Eleonora, Omenetti Alessia, D'Osualdo A., Fraldi A., Ballabio A., Ravazzolo Roberto, Martini Alberto, Gattorno Marco, Ceccherini Isabella.**
   Autophagy contributes to inflammation in patients with TNFR-associated periodic syndrome (TRAPS)
   ANN RHEUM DIS 2013; 72: 1044-1052.
   IF: 9.111 Normalized IF: 8
10. **Jannot AS., Pelet A., Henrion-Caude A., Chaoui A., Masse-Morel M., Arnold S., Sanlaville D., Ceccherini Isabella, Borrego S., Hofstra RMW., Munnich A., Bondurand N., Chakravarti A., Clerget-Darpoux F., Amiel J., Lyonnet S.**
    Chromosome 21 Scan in Down Syndrome Reveals DSCAM as a Predisposing Locus in Hirschsprung Disease.
    PLOS ONE 2013; 8(5): e62519.
    IF: 3.73 Normalized IF: 3
11. **Pierobon D., Bosco Maria Carla, Blengio Fabiola, Raggi Federica, Eva Alessandra, Filippi M., Musso T., Novelli F., Cappello P., Varesio Luigi, Giovarelli M.**
    Chronic hypoxia reprograms human immature dendritic cell by inducing a proinflammatory phenotype and TREM-1 expression.
    EUR J IMMUNOL 2013; 43: 949-966.
    IF: 4.97 Normalized IF: 6
12. **Rossi PIA., Musante I., Summa M., Pittaluga A., Emionite L., Ikehata M., Rastaldi MP., Ravazzolo Roberto, Puliti Aldamaria.**
    Compensatory molecular and functional mechanisms in nervous system of the Grm1crv4 mouse lacking the mGlu1 receptor: a model for motor coordination deficits.
    CEREB CORTEX 2013; 23: 2179-2189.
    IF: 6.828 Normalized IF: 6
13. **Melioli Giovanni, Passalacqua G., Canonica GW., Baena-Cagnani CE., Matricardi P.**
    Component-resolved diagnosis in pediatric allergic rhinoconjunctivitis and asthma.

CURR OPIN ALLERGY CL 2013; 13(4): 446-451.
IF: 3.398 Normalized IF: 6

14. **Passariello A., De Brasi D., Defferrari R., Genesio R., Tufano M., Mazzocco Katia, et al.**
Constitutional 11q14-q22 chromosome deletion syndrome in a child with neuroblastoma MYCN single copy
Eur J Med Genet 2013; 56: 626-634.
IF: 1.685 Normalized IF: 1
15. **Alves MM., Sribudiani Y., Brouwer RWW., Amiel J., Antinolo G., Borrego S., Ceccherini** Isabella, Chakravarti A., Fernandez RM., Garcia-Barcelo MM., Griseri Paola, et al.
Contribution of rare and common variants determine complex disease-Hirschsprung disease as a model.
DEV BIOL 2013; 382: 320-329.
IF: 3.868 Normalized IF: 3
16. **Tassano Elisa, Di Rocco Maja, Signa S., Gimelli Giorgio.**
De novo 13q31.1-q32.1 interstitial deletion encompassing the miR-17-92 cluster in a patient with Feingold syndrome-2.
AM J MED GENET A 2013; 161A: 894-896.
IF: 2.304 Normalized IF: 2
17. **Martinoli C., Della Casa Alberighi Ornella, Di Minno G., Graziano E., Molinari Angelo C, Pasta G., Russo G., Santagostino E., Tagliaferri A., Tagliafico A., Morfini M.**
Development and definition of a simplified scanning procedure and scoring method of haemophilia early arthropathy detection with ultrasound (HEAD-US).
THROMB HAEMOSTASIS 2013; 109: 1170-1179.
IF: 6.094 Normalized IF: 6
18. **Bhatia S., Bengani H., Fish M., Brown A., Divizia Maria Teresa, De Marco R., Damante G., Grainger R., et al.**
Disruption of autoregulatory feedback by a mutation in a remote, ultraconserved PAX6 enhancer causes aniridia.
Am J Hum Genet 2013; 93: 1126-1134.
IF: 11.202 Normalized IF: 4
19. **Simon S., Grabellus F., Ferrera Loretta, Galietta Luis Juan V, Schwindenhammer B., Muhlenberg T., et al.**
DOG1 regulates growth and IGFBP5 in gastrointestinal stromal tumors.
CANCER RES 2013; 73: 3661-3670.
IF: 8.65 Normalized IF: 4
20. **Monti P., Russo D., Bocciardi Renata, Foggetti G., Menichini P., Divizia Maria Teresa, Lerone Margherita, Graziano C., Wischmeijer A., Viadiu H., Ravazzolo Roberto, Inga A., Fronza G.**
EEC- and ADULT-Associated TP63 Mutations Exhibit Functional Heterogeneity Toward P63 Responsive Sequences.
HUM MUTAT 2013; 34: 894-904.
IF: 5.213 Normalized IF: 6
21. **Coppola A., Santoro C., Franchini M., Mannucci C., Mogavero S., Molinari Angelo C, Schinco P., Tagliaferri A., Santoro RC.**
Emerging issues on comprehensive hemophilia care: preventing, identifyng, and monitoring age-related comorbidities.
SEMIN THROMB HEMOST 2013; 39: 794-802.
IF: 4.216 Normalized IF: 3

22. **Vidal E., Edefonti A., Puteo F., Chimenz R., Gianoglio B., Lavoratti G., Leozappa G., Maringhini S., Mencarelli F., Pecoraro C., Ratsch IM., Cannavò R., De Paolo T., Testa S., Murer L., Verrina Enrico.**
    Encapsulating peritoneal sclerosis in paediatric peritoneal dialysy patients: the experience of the Italian Registry of Pediatric Chronic Dialysis.
    NEPHROL DIAL TRANSPL 2013; 28: 1603-1609.
    IF: 3.371 Normalized IF: 6
23. **Gianotti Ambra, Melani R., Caci Emanuela, Sondo Elvira, Ravazzolo Roberto, Galietta Luis Juan V, Zegarra Moran Olga.**
    Epithelial sodium channel silencing as a strategy to correct the airway surface fluid deficit in cystic fibrosis.
    AM J RESP CELL MOL 2013; 49: 445-452.
    IF: 4.148 Normalized IF: 6
24. **Facco Fabio, Agazzi Alessia, Manfredini L., Dallorso Sandro, Melioli Giovanni.**
    Evaluation of a mobile clinical pathology laboratory developed for the home care of pediatric patients following transplantation of peripheral blood precursor cells.
    CLIN CHEM LAB MED 2013; 51: 1637-1642.
    IF: 3.009 Normalized IF: 6
25. **Snegireva LS., Kostik MM., Caroli Francesco, Ceccherini Isabella, Gattorno Marco, Chasnyk VG.**
    Failure of tocilizumab treatment in a CINCA patient: clinical and pathogenic implications.
    RHEUMATOLOGY 2013; 52: 1731-1732.
    IF: 4.212 Normalized IF: 3
26. **Bicocchi Maria Patrizia, Rosano C., Acquila Maura.**
    Genetic analysis in FXI deficient patients from northwestern Italy: three novel one recurrent mutation.
    EUR J HAEMATOL 2013; 90: 351-353.
    IF: 2.548 Normalized IF: 2
27. **Tassano Elisa, Buttgereit J., Bader M., Lerone Margherita, Divizia Maria Teresa, Bocciardi Renata, Napoli Flavia, Pala G., Sloan-Bena F., Gimelli S., Gimelli Giorgio.**
    Genotype-phenotype correlation of 2q37 deletions including NPPC gene associated with skeletal malformations.
    PLOS ONE 2013; 8: e66048.
    IF: 3.73 Normalized IF: 6
28. **Giribaldi F., Milanese M., Bonifacino T., Rossi PIA., Di Prisco S., Pittaluga A., Tacchetti C., Puliti Aldamaria, Usai C., Bonanno G.**
    Group I metabotropic glutamate autoreceptors induce abnormal glutamate exocytosis in a mouse model of amyotrophic lateral sclerosis.
    NEUROPHARMACOLOGY 2013; 66: 253-263.
    IF: 4.114 Normalized IF: 3
29. **Weemaes CMR., van Tol MJD., van Ostaijen-ten Dam MM., van Eggermond MCJA, Thijssen PE., Aytekin C, Brunetti-Pierri N., van der Burg M., Davies EG., Ferster A., Furthner D., Gimelli Giorgio, et al.**
    Heterogeneous clinical presentation in icf syndrome: Correlation with underlying gene defects.
    Eur J Hum Genet. 2013; 21: 1219-1225.
    IF: 4.319 Normalized IF: 3

30. **Balsamo M., Manzini C., Pietra G., Raggi Federica, Blengio Fabiola, Mingari MC., Varesio Luigi, Moretta Lorenzo, Bosco Maria Carla, Vitale M.**
Hypoxia downregulates the expression of activating receptors involved in NK-cell-mediated target cell killing without affecting ADCC.
Eur J Immunol. 2013; 43: 2756-2764.
IF: 4.97 Normalized IF: 6
31. **Giacopelli F., Cappato S., Tonachini L., Mura M., Di Lascio S., Fornasari D., Ravazzolo Roberto, Bocciardi Renata.**
Identification and characterization of regulatory elements in the promoter of ACVR1, the gene mutated in Fibrodysplasia Ossificans Progressiva.
Orphanet J Rare Dis. 2013; 8: 145.
IF: 4.315 Normalized IF: 6
32. **Rusmini M., Griseri Paola, Lantieri F., Matera Ivana, Hudspeth KL., Roberto A., Mikulak J., Avanzini S., Rossi V., Mattioli Girolamo, Jasonni Vincenzo, Ravazzolo Roberto, Pavan WJ., Pini Prato Alessio, Ceccherini Isabella, Mavillo D.**
Induction of RET dependent and independent pro-inflammatory programs in human peripheral blood mononuclear cells from Hischsprung patients.
PLOS ONE 2013; 8(3): e59066.
IF: 3.73 Normalized IF: 6
33. **Celle Maria, Cuoco Cristina, Porta Simona, Gimelli Giorgio, Tassano Elisa.**
Interstitial 2q24.3 deletion including SCN2A and SCN3A genes in a patient with autistic features, psychomotor delay, microcephaly and no history of seizures.
GENE 2013; 532: 294-296.
IF: 2.196 Normalized IF: 2
34. **Gimelli S., Cuoco Cristina, Ronchetto Patrizia, Gimelli Giorgio, Tassano Elisa.**
Interstitial deletion 14q31.1q31.3 transmitted from a mother to her daughter, both with features of hemifacial microsomia.
J APPL GENET 2013; 54: 361-365.
IF: 1.847 Normalized IF: 2
35. **Giordano P., Franchini M., Lassandro G., Faienza MF., Valente R., Molinari Angelo C.**
Issues in pediatric haemophilia care.
ITAL J PEDIATR 2013; 39: 24.
IF: 1.344 Normalized IF: 2
36. **Cangelosi Davide, Blengio Fabiola, Versteeg R., Eggert A., Garaventa Alberto, Gambini Claudio, Conte Massimo, Eva Alessandra, Muselli M., Varesio Luigi.**
Logic learning machine creates explicit and stable rules stratifying neuroblastoma patients.
BMC BIOINFORMATICS 2013; 14: S12.
IF: 3.024 Normalized IF: 6
37. **Galietta Luis Juan V.**
Managing the underlying cause of cystic fibrosis: a future role for potentiators and correctors.
PEDIATR DRUGS 2013; 15: 393-402.
IF: 1.884 Normalized IF: 4
38. **Cangemi Giuliana, Barco Sebastiano, Verrina Enrico, Scurati S., Melioli Giovanni, Della Casa Alberighi Ornella.**
Micromethod for quantification of cinacalcet in human plasma by liquid chromatography-tandem mass spectrometry using a stable isotope-labeled internal standard.

THER DRUG MONIT 2013; 35: 112-117.
IF: 2.234 Normalized IF: 4

39. **Porta F., Pagliardini V., Barbera C., Calvo P., Pagliardini S., Spada M., Lualdi Susanna, Filocamo Mirella.**
Neonatal chitotriosidase activity is not predictive for Niemann-Pick disease type A/B: Implications for newborn screening for lysosomal storage disorders.
MOL GENET METAB 2013; 108: 106.
IF: 2.834 Normalized IF: 2

40. **Donaldson SH., Galietta Luis Juan V.**
New pulmonary therapies directed at targets other than CFTR.
2013; 3: a009787.
IF: 5.5 Normalized IF: 6

41. **Sondo Elvira, Scudieri Paolo, Tomati Valeria, Caci Emanuela, Mazzone A., Farrugia G., Ravazzolo Roberto, Galietta Luis Juan V.**
Non-canonical translation start sites in the TMEM16A chloride channel.
Biochim Biophys Acta 2013; 1838: 89-97.
IF: 3.389 Normalized IF: 6.

42. **Fernandez RM., Bleda M., Luzon-Toro B., Garcia-Alonso L., Arnold S., Sribudiani Y., Besmond C., Lantieri F., Doan B., Ceccherini Isabella, Lyonnet S., et al.**
Pathways systematically associated to Hirschsprung's disease.
Orphanet J Rare Dis. 2013; 8: 187.
IF: 4.315 Normalized IF: 3

43. **Suganuma R., Wang LL., Sano H., Naranjo A., London WB., Seeger RC., Hogarty MD., Gastier-Foster JM., Look AT., Park JR., Maris JM., Cohn SL., Amann G., Beiske K., Cullinane CJ., d'Amore ESG., Gambini Claudio, et al.**
Peripheral neuroblastic tumors with genotype-phenotype discordance: a report from che Children's Oncology Group and the International Neuroblastoma Pathology Committee.
PEDIATR BLOOD CANCER 2013; 60: 363-370.
IF: 2.353 Normalized IF: 3

44. **Notartomaso S., Zappulla C., Biagioni F., Cannella M., Bucci D., Mascio G., Scarselli P., Fazio F., Weisz F., Lionetto L., Simmaco M., Gradini R., Battaglia G., Signore M., Puliti Aldamaria, Nicoletti F.**
Pharmacological enhancement of mGlu1 metabotropic glutamate receptors causes a prolonged symptomatic benefit in a mouse model of spinocerebellar ataxia type 1.
Mol Brain. 2013; 6: 48.
IF: 4.202 Normalized IF: 3

45. **Morabito R., Longo M., Rossi Andrea, Nozza Paolo, Granata F.**
Pharyngeal enterogenous cyst associated with canalis basilaris medianus in a newborn.
PEDIATR RADIOL 2013; 43: 512-515.
IF: 1.565 Normalized IF: 2

46. **Franchi A., Palomba A., Roselli G., Gambini Claudio, Beltrami G., Capanna R., Campanacci D.**
Primary juxtacortical myoepithelioma/mixed tumor of the bone: a report of 3 cases with clinicopathologic, immunohistochemical, ultrastructural, and molecular characterization.
HUM PATHOL 2013; 44: 566-577.
IF: 2.843 Normalized IF: 3

47. **Cangemi Giuliana, Storti S., Cantinotti M., Fortunato A., Emdin M., Bruschettini Matteo, Bugnone Daniela, Melioli Giovanni, Clerico A.**

Reference values for urinary neutrophil gelatinase-associated lipocalin (NGAL) In pediatric age measured with a fully automated chemiluminescent platform.
CLIN CHEM LAB MED 2013; 51(5): 1101-1105.
IF: 3.009 Normalized IF: 6

48. **Ramieri V., Basile E., Cascone NC., Arangio P., Ungari C., Gennaro P., Di Cataldo A., Sementa Angela Rita, et al.**
Surgical treatment of congenital rhabdoid tumor in a 10-day-old newborn.
J CRANIOFAC SURG 2013; 24: 523-525.
IF: 0.686 Normalized IF: 0.5
49. **Alaggio R., Turrini R., Boldrin D., Merlo A., Gambini Claudio, Ferrari A., Dall'Igna P., Coffin CM., Martines A., Banaldi L., De Salvo GL., Zanovello P., Rosato A.**
Survivin expression and prognostic significance in pediatric malignant peripheral nerve sheath tumors.
PLoS One 2013; 8: e80456.
IF: 3.73 Normalized IF: 3
50. **Passalacqua G., Melioli Giovanni, Bonifazi F., Bonini S., Maggi E., Senna G., Triggiani M., Nettis E., Rossi RE., Vacca A., Canonica GW.**
The additional values of microarray allergen assay in the management of polysensitized patients with respiratory allergy.
ALLERGY 2013; 68: 1029-1033.
IF: 5.883 Normalized IF: 6
51. **Blengio Fabiola, Raggi Federica, Pierobon D., Cappello P., Eva Alessandra, Giovarelli M., Varesio Luigi, Bosco Maria Carla.**
The hypoxic environment reprograms the cytokine/chemokine expression profile of human mature dendritic cells.
IMMUNOBIOLOGY 2013; 218: 76-89.
IF: 2.814 Normalized IF: 4
52. **Lantieri F., Caroli Francesco, Ceccherini Isabella, Griseri Paola.**
The involvement of the RET variant G691S in medullary thyroid carcinoma enlightened by a meta-analysis study.
INT J CANCER 2013; 132: 2808-2819.
IF: 6.198 Normalized IF: 6
53. **Lantieri F., Caroli Francesco, Ceccherini Isabella, Griseri Paola.**
The involvement of the RET variant G691S in medullary thyroid carcinoma: conflicting results of meta-analyses need to be reconciled.
INT J CANCER 2013; 133: 1760-1761.
IF: 6.198 Normalized IF: 6
54. **Ubby I., Bussani E., Colonna A., Stacul G., Locatelli M., Scudieri Paolo, Galietta Luis Juan V, Pagani F.**
TMEM16A alternative splicing coordination in breast cancer.
MOL CANCER 2013; 12: 75.
IF: 5.134 Normalized IF: 3
55. **Scudieri Paolo, Sondo Elvira, Caci Emanuela, Ravazzolo Roberto, Galietta Luis Juan V.**
TMEM16A-TMEM16B chimaeras to investigate the structure-function relationship of calcium-activated chloride channels.
BIOCHEM J 2013; 452: 443-455.
IF: 4.654 Normalized IF: 6

56. **Di Lascio S., Bachetti Tiziana, Saba E., Ceccherini Isabella, Benfante R., Fornasari D.**
Transcriptional dysregulation and impairment of PHOX2B auto-regulatory mechanism induced by polyalanine expansion mutations associated with congenital central hypoventilation syndrome.
NEUROBIOL DIS 2013; 50: 187-200.
IF: 5.624 Normalized IF: 6

57. **De Luca M., Calò Carducci FI., Pansini V., Coletti V., Tucci FM., Cirillo M., Acquila Maura, Bicocchi Maria Patrizia, D'Argenio P., Luciani M.**
Unusual presentation of haemophilia in two paediatric patients.
BLOOD COAGUL FIBRIN 2013; 24: 645-648.
IF: 1.248 Normalized IF: 0.5

Research line 2
Clinical Pediatrics, Perinatal Medicine, and Pediatric Surgery

Title
Clinical-translational studies of perinatal and pediatric diseases with genetic or immunological basis

Coordinators
Prof. Mohamad Maghnie, Dr. Gian Marco Ghiggeri

Project description (outline and objectives)
General objective of this research line is to create a direct correlation between basic research and clinical applicability of basic research results. The strong point is the clinical wealth of Gaslini, the multifocal approach associated with the availability of experimental and laboratory resources. In addition, the existing link among research groups makes interaction physiological. Major research areas include high impact diseases, potentialities based on the availability of technologies in the fields of molecular genetics, proteomics, and basic immunology. Other topics include the genetic characterization of high social impact diseases such as diabetes mellitus, asthma, renal and airway malformations, alterations of thyroid embryogenesis. In parallel, research pathways are proposed for the definition of the immunological bases of pulmonary and inflammatory diseases (kidney, intestine) and for the identification of the genetic causes of gestational diabetes, intrauterine growth retardation, growth hormone deficiency, hypotalamo-pituitary diseases, skeletal dysplasia and some bone diseases, neonatal diabetes. Some "multidisciplinary" rare diseases affecting the central nervous system represent an opportunity of cross-sectional research. Another priority is the study of early degenerative mechanisms affecting different organs and tissues, which are topics involving cell biology and experimental models. Finally, research in the field of solid organ transplantation will be boosted. Studies carried out within previous research projects by specific research groups on specific topics are continued: blood markers of oxidative stress predictive of acute brain damage in patients with clinical picture of acute brain distress due to hypo/anoxemia admitted to the Emergency Department; dermoscopic parameters specific of congenital nevus that can improve clinical predictivity of malignant transformation.

Coordinators:
Prof. Renata Lorini – Pediatric Clinic
Dr. Corrado Occella – Dermatology
Dr. Arrigo Barabino – Pediatric Gastroenterology with Digestive Endoscopy
Dr. Gian Marco Ghiggeri – Nephrology, Dialysis and Transplantation
Prof. Giovanni Arturo Rossi – Pediatric Pnemology and Allergology
Prof. Pasquale Di Pietro – Pediatric Emergency and Urgency
Prof. Giorgio Bentivoglio – Obstetrics and Gynecology
Dr. Luca Antonio Ramenghi – Neonatal Pathology
Dr. Gian Michele Magnano – Radiology
Dr. Pietro Tuo – PICU/NICU
Dr. Maurizio Marasini – Cardiology
Dr. Lucio Zannini – Cardiovascular Surgery
Dr. Piero Buffa – Surgery
Prof. Paolo Capris – Ophthalmology
Dr. Roberto Servetto – Dentistry

Dr. Silvio Boero – Orthopedics
Dr. Vincenzo Tarantino – Otolaryngology
Dr. Riccardo Haupt – Epidemiology, Biostatistics, and Committees
Dr. Paola Barabino – Pharmacy
Director: Dr. Ubaldo Rosati – Management Control and Quality Office

Activity year 2013

Pediatric Clinic *– Director: Prof. Renata Lorini*

Multicenter prospective randomized open with a blinded end point (PROBE) parallel-group study on treatment with biphasic insulin BIAsp70/30 and short-acting insulin or rapid-acting analogue plus glargine in comparison with short-acting insulin or rapid-acting analogue plus glargine to evaluate the metabolic control and quality of life in children and adolescents with type 1 diabetes mellitus over 12 months (AIFA FARM8MR2J7 study).

The necessary bureaucratic steps have been taken to allow the participating centres to continue patient enrolment, which to date has been carried out at the coordinating centre, where 7 children and adolescents with diabetes mellitus type 1 have been enrolled and the clinical characteristics reported in the feasibility survey. A document on IMP has been produced, aimed at standardizing the management of the experimental drug in the different centres/clusters and at having a continuous traceability of each SOP. Concerning cultural adaptation and validation in Italian language of the questionnaires on the quality of life, module specific for diabetes (PedsQoL TM 3.0- Diabetes Module), psychometric evaluation and statistical analysis of the questionnaires have been performed, including both the modules for children and adolescents and for parents. A report has been produced including the statistical analyses on a population of 169 children (age range 5-18 years) and 100 parents, from the 6 centres participating in the study (Catania, Firenze, Genova, Napoli, Roma, Torino). A paper has been submitted to a scientific journal with IF. The results of the validation study were presented in occasion of national (SIEDP) and international (ESPE) meetings as posters and oral communication, respectively.

Differential diagnosis of forms of non-autoimmune diabetes mellitus

Within this project, the activity of molecular diagnosis of the forms of non-autoimmune diabetes mellitus carried out in 2013 in the laboratory of diabetology of the Pediatric Clinic of Gaslini has been increased, in parallel with the study of genes involved in other diseases of glucide metabolism.

In particular, molecular analysis was performed by direct sequencing of the genomic DNA of 80 subjects who, after evaluation of historical, clinical, and glycometabolic data, were diagnosed clinically with hyperglycemia/diabetes mellitus/gestational diabetes with non-autoimmune etiology (documented absence of immunological markers of diabetes mellitus type 1). Patients with clinical diagnosis of MODY (Maturity Onset Diabetes of the Young) for *GCK/MODY2, HNF1a/MODY3, HNF1b/MODY5, HNF4a/MODY1* genes, of Wolfram syndrome 1 and 2 (gene *WFS1 and gene ZCD2*), of neonatal diabetes (*GCK/MODY2*, *KCNJ11, KIR6.2 ABCC8 genes*) were evaluated. Also female patients with gestational diabetes (*GCK/MODY2 gene*) were studied, as well as children with familial renal glycosuria (*SLC5A2 gene*) and newborns with congenital hyperinsulinism (*INS; KCNJ11, ABCC8, HNF4a genes*). Of the 80 studied patients, 32 were followed in the Regional Centre of Diabetology, Pediatric Clinic of Gaslini, and 48 were followed in other centres. In all cases, informed consent was obtained.

GCK gene sequencing was performed in 26 cases, 14 resulting mutated. *HNF1a* gene sequencing was performed in 4 subjects and that of *HNF1b* gene in 2 cases: none of the

patients resulted mutated. *KCNJ11* gene sequencing was performed in 6 cases, 1 resulted mutated. *SLC5A2* gene sequencing was performed in 2 cases, both resulting mutated. *WFS1* gene sequencing was performed for 22 cases; 2 patients carried a mutation in compound homozygosis/heterozygosis and 13 relatives resulted carriers of mutations in heterozygosis. *ZCD2* gene sequencing was performed in 4 cases, 1 presenting a deletion in homozygosis and the remaining ones resulted carriers. *ABCC8* gene sequencing was performed in 11 cases, 5 resulting mutated. *HNF4a* gene sequencing was performed in 2 cases, with no mutated cases. *INS* gene sequencing was performed in 1 case, not mutated.

Clinical and Experimental Endocrinology - *Director: Prof. Mohamed Maghnie*
Research activity involved some specific aspects of endocrine diseases in pediatric age, in particular:
The study of prognostic factors associated with hyperthyroidism identified that the absence of goiter, a low level of TSH anti-receptor antibodies (TRAb) at diagnosis, their normalization and their normalization velocity during medical therapy were associated with a favourable outcome.
Another important aspect concerns the etiologic diagnosis of central diabetes insipidus. In particular, research allowed a differential diagnosis in 96% of cases and the identification of markers of long-term outcome.

Dermatology – *Director: Dr. Corrado Occella*
Study of ICOS gene and of cytokeratin 17 in patients with alopecia areata
Recent studies showed the involvement of Treg lymphocytes in the development of alopecia areata. In particular, a lower suppressory functional activity of these lymphocytes present in affected patients compared to Treg in healthy subjects was found. In this context, polymorphisms in the UTR 3' region of genes coding for molecules closely involved in Treg function could alter gene expression, with an impact on Treg activity.
The results of the study showed that: a) rs4404254 (C) and rs4675379 (C) allelic variants of ICOS gene are more frequent in patients with alopecia areata than in healthy controls; b) rs4404254 (C) and rs4675379 (C) allelic variants are associated with a reduced ICOS gene expression; c) miR303 is more highly expressed in PBMC of patients, while miR27b and miR101 are more highly expressed in PBMC of healthy controls. These data suggest that a reduced expression of ICOS in patients with alopecia areata could induce a functional deficit in Treg, favouring the onset of an autoimmune reaction against some autoantigens expressed in the hair bulb and important for hair growth cycle.
This data could contribute to the therapeutic approaches developed over the last few years, based on gene therapy against hair follicle cells. Different oligonucleotides, such as antisense oligonucleotides, and small interfering RNAs mimicking or interfering with microRNA function were proposed as drug for the treatment of diseases related to hair bulb growth.

Pediatric gastroenterology with digestive endoscopy - Director: *Dr. Arrigo Barabino*
Italian multicentre approach to oesophageal varices in children (in press): medical and endoscopic therapy (ligature vs sclerosis: complications, relapses) shows a better outcome after ligature. Use of glucose breath test for the diagnosis and treatament of CIBO in cystic fibrosis (in collaboration with the Pediatric Clinic of Gaslini): diagnosis feasible in 70% of cases; with targeted treatment there is gastrointestinal and respiratory improvement. Diagnosis, treatment, and outcome of portal cavernoma (Italian multicentre study) with data being studied. Dietetic treatment of short bowel with different semi-elementary and elementary mixtures showing the non-superiority of a particular formula among tested ones in patient outcome.

Italian multicentre study (coordinated by our unit) on the evolution of esophageal stenoses according to treatment (balloon dilatations vs savary: complications, relapses) showing similarity between the two methods.. Multicentre observational study of children with Crohn's disease, mainly focusing on the intake or not of anti-TNFα: no data are available yet, since it is a very long-term study (20 years). Multicentre study on the appropriateness of colonscopy coordinated by Dr. Lombardi of Pescara: data are undergoing statistical analysis. Multicentre study on early IBD with onset at age below 5 years, with data from the new online registry (coordinated by La Sapienza University, in press) showing that this type of IBD has a phenotype similar to that of RCU, is clinically more severe, and can require early colectomy. Statistical analysis on the safety and efficacy of CyA in severe attacks not responding to cortisone (our study also included data from Meyer hospital of Firenze), where CyA avoids urgency colectomy in about 65% of cases and maintains the colon in the long term (3 years) in one third of cases. Study on the expression of eotaxin-2 in intraepithelial lymphocytes and on perineural degranulation of mast cells in order to differentiate allergic colitis from the classic forms of IBD. Allergic colitis share the space of eotaxin and IL5 with nerve endings affecting their motility and being the possible cause of clinical disorders such as diarrhoea, stipsis, or abdominal pain.

Nephrology, Dialysis and Transplantation/ **Laboratory of Uremia Physiopathology –** *Director: Dr. Gian Marco Ghiggeri*

The scientific activity of the Laboratory of Uremia Physiopathology includes three main research areas.

Genetic area including congenital renal diseases:

In 2013, different results have been obtained, including the following:

a) Identification of a new gene for nephronophthisis associated with bronchiectasis in a familial case followed in our unit;
b) Identification of new mutations in genes associated with steroid-resistant nephrotic syndrome thanks to genetic screening of patients within a specific European network;
c) Genotype-phenotype correlations in patients with Alport syndrome and validation of diagnostic tests based on Next Generation Sequencing;
d) Identification of the gene defect responsible for the spontaneous murine model of renal malformation and caudal regression (*Danforth's* short tail);
e) Identification and characterization of new mutations of the *ALB* gene associated with congenital analbuminemia;
f) Identification of the first gene associated with renal hypoplasia and urinary tract malformations.

Proteomic area:

a) Technological advances in the field of low expression protein/peptide analysis in biological fluids through capture systems for marbles and resins.

Biochemical area:

a) Advances related to structure and function of albumin in biological fluids.

Pediatric pneumology and allergology *– Director: Prof. Giovanni Arturo Rossi*

In 2013, most studies focused on the following topics:

Vitamin D and respiratory infections in children

It is still unclear which are the serum levels of 25-hydroxy vitamin D (vitD) during acute respiratory infection and whether they tend to increase spontaneously after resolution. Therefore, a prospective evaluation of the trend of vitD serum levels was performed in children on admission for acute lower airway infections (AI) and at 30 days from discharge

(Follow-up=FU). During infection, 62% of patients presented vitD levels <20 ng/ml (vitamin deficiency) and VitD levels, which did not correlate with IR severity, increased during follow-up in XX% of patients, irrespective of the levels observed during infection. No children were prescribed with VitD on discharge nor instructions on diet change were given. Children showing VitD increase during FU had had more frequently a temperature >38°C on admission, had been treated more frequently with i.v. antibiotics on admission, were more frequently allergic, were more frequently positive for pathogens on pharyngeal swab and/or blood culture. Therefore, VitD levels increase spontaneously in some patients after an acute episode of IR. Irrespective of basal values, subjects with a natural increase in Vit D values were those who had more severe diseases. For this reason: a) vit D levels on admission do not correlate with infection severity; b) the spontaneous increase in FU values in children with more severe disease seems to suggest vit. D consumption during disease acute phase.

Resistance to macrolides by Mycoplasma pneumoniae

In order to evaluate the prevalence and clinical impact of the resistance to macrolides of Mycoplasma pneumoniae, we recruited 54 children aged between 17 months and 17 years, 27 males and 27 females, with lower airway infection, ascertained on the basis of clinical and radiological evidence. Compared to the estimated sample in the statistical analysis plan, 19% of the estimated cases was reached (54 of 288). The reason for this limited numerosity could be the lack of infectious epidemics recorded to date. The prevalence of infection due to mycoplasma was 15%. To date, 2 cases of resistance to macrolides were recorded, with mutations already described in the literature: the sequence of DNA coding for V domain of rRNS 23S showed A2064G punctiform mutation. The study will be continued in 2014.

Pediatric Emergency/Urgency – *Director: Prof. Pasquale Di Pietro*

The Pediatric Emergency/Urgency unit represents a privileged observatory of complex or particular clinical cases, deserving to be reported in the literature, such as a recent case of neonatal encephalitis due to Parechovirus (HPeVs: a new family of neurotropic viruses able to cause CNS infections in the neonatal period similar to meningoencephalitides due to enterovirus) with favourable outcome. HPeVs infection is generally associated with mild respiratory or gastroenteric symptoms and the association with severe diseases, such as flaccid paralysis and encephalitis/encephalomyelitis, has been described only recently in the literature (largest case series: 10 cases of HPeVs encephalitis reported in a Dutch paper).

Critical Area – Director*: Dr. Salvatore Renna*

Within multicentre studies, we published the results of studies on complications affecting the upper gastrointestinal tract (UGIC: Upper GastroIntestinal Complications) after drug use in children, on Stevens-Johnson syndrome (SJS) associated with the use of medications and vaccines (The Italian Multicenter Study Group for Drug and Vaccine Safety in Children), and on the use of off-label antiemetic drugs (ondansetron) in the treatment of gastroenteritis (in collaboration with the Pharmacology unit of Burlo Garofalo Institute of Trieste).

The correlation between chronic use of FANS and gastrointestinal tract bleeding is well-known: in the study supported by AIFA, in all cases, mean duration of ibuprofen use resulted to be 4 days, so that it has been possible to document that UGIC can occur even after short-term therapy in children. In addition, the lower level of gastrotoxicity of paracetamol (the most frequently used medication in Italian pediatric patients) compared to the other NSAIDs has been confirmed.

Twenty-nine children with diagnosis of SJS and 1362 with neurological problems were hospitalized between November 1, 1999 and October 31, 2012 in 9 of the main Italian children's hospitals: antiepileptic drugs resulted to have the highest OR (Odds Ratio: 26,8%),

while for antibiotics OR was 3.3%, even though the limited power of the study did not make it possible to differentiate among the 3 main classes (penicillins, cephalosporins, and macrolides); concerning the other medications, a statistically significant higher risk was observed for paracetamol and corticosteroids, with OR ranging between 3.2 and 4.2. No increased risk was observed after the use of vaccines.
The study on the use of antiemetic drugs in pediatric age, carried out in the Emergency Departments of 8 main Italian cities, showed that at least 30% of prescribed antiemetic medications results to be off-label (the only antiemetic drug that can be used is domperidone, since both metoclopramide and ondansetron result off-label for age range and indications for use). In agreement with the law in force, off-label medications should be prescribed only in the presence of potential beneficial effects prevailing over potential toxic effects, with consequent legal risks for the prescribing physician in case of side effects, with compulsory request for the family's informed consent. Hence the need to start clinical trials and/or retrospective studies able to define an appropriate use of off-label antiemetics.

Obstetrics and Gynecology – *Director: Prof. Giorgio Bentivoglio*
Besides the collaboration in the fields of infectious diseases and immune diseases, thirty-year clinical research activity in early and prenatal diagnostics and for the identification and therapy of fetal diseases is continued.

Neonatal Diseases – *Director: Dr. Luca Antonio Ramenghi*
Scientific research was focused on perinatal neurology. In particular, relevant aspects of intracranial hemorrhage in preterm newborns were described, including germinal matrix hemorrhage, intraventricular hemorrhage, and cerebellar hemorrhage. The potentialities and limits of transfontanellar and mastoid US examination were studied, even for low grade hemorrhages. The level of prematurity was correlated with different risks of brain damage. In addition, lesion presence was correlated with possible long-term outcomes. Imaging diagnostic activity was continued, with the collection of brain magnetic resonance data in hundreds of newborns (this latter data has not been published yet).
Other branches of scientific research included ventilation of the preterm newborn (also through a multicentre study comparing two different techniques of neonatal resuscitation) and the characteristics of fetal-neonatal diseases such as those of the lymphatic system, yielding many publications in 2013.
Finally, about a hundred of samples have been collected for the study of hematopoietic stem cells of some cell lines present in umbilical cord blood: preliminary results will be presented at the 2014 meeting of *Pediatric American Societies.*

Radiology – Dr. Gian Michele Magnano
New imaging techniques for the evaluation of the child with chronic rheumatic disease
Concerning joint cartilages, further implementation of sequences for T2 mapping and T1 mapping (dGEMRIC) has been performed, with in vivo quantitative analysis of collagen/proteoglycans, in order to demonstrate early macromolecular alterations (i.e. without morphological equivalent). We also demonstrated that synovial CE in JIA can be quantified with both semiquantitative evaluation (synovitis scoring system) and calculation of synovial volume, and that it can be used for disease monitoring. Concerning Whole body MR in rheumatic disease: definitive validation of its use in CRMO (diagnosis and monitoring of disease) in JDM (good correlation between disease activity and alteration/distribution of the muscular signal).

MR urography with even functional evaluation of kidneys in nephrourologic disease
In 2013, about 100 complete MR urography examinations, including functional evaluations, were performed. All examinations were discussed in meetings of the uronephrologic multidisciplinary group (URANO). In collaboration with Rouen University, comparative evaluation is being performed to validate fMRU versus renal sequential scintigraphy. In collaboration with DISI UNIGE, specific software is being implemented for automatic segmentation of the renal volume, both for renal volume calculation and for a more refined analysis of contrast medium variation curves. MR with DWI sequences in UTI: at present, patients are being enrolled.

Neonatal Pediatric Intensive Care *– Director: Dr. Pietro Tuo*

Multi-site RCT comparing regional and general anaesthesia for effects on neurodevelopmental outcome in infants - The GAS study

International multicentre randomized controlled prospective open study. Patients aged below 60 weeks of postconceptional age, scheduled for inguinal hernia surgery, were randomized in two arms to receive general anesthesia with sevoflurane or regional anesthesia without narcotics. Patients are followed up at 2 and 5 years of age to evaluate whether the different anesthesias result in an equivalent neurocognitive development. Neurocognitive follow-up at 2 years of corrected age is performed with pediatric examination, Bayley scale and McArthur test. Neurocognitive follow-up at 5 years of chronological age is based on the following tools: pediatric visit, WPPSI-III Full Scale IQ (FSIQ), NEPSY-II Selected Subtests, WIAT-II Screening Test, BRIEF-P Parent Questionnaire, ABAS Parent Questionnaire, CBCL Caregiver Questionnaire. On January 31, 2013, a sample of 722 patients was reached in the 28 participating centres. 167 patients were recruited in the three Italian centres (Genova: 81; Bergamo: 38; Milano: 48), with a final contribution of 23% of cases. Data on the incidence of post-anesthesia apnea and postsurgical outcome are being analyzed and will be ready for publication at the end of 2013.

Cardiology *– Director: Dr. Maurizio Marasini*

In 2013, research activity was continued according to the clinical research lines pursued over the last few years, in particular in the following fields:

A. Fetal Cardiology: research was mainly focused on the impact of prenatal diagnosis on the outcome of congenital cardiopathies such as Tetralogy of Fallot and pulmonary atresia with intact interventricular septum. These studies should allow a better identification of fetuses that, though presenting the same cardiopathy as others, are destined to a more unfavourable perinatal evolution and therefore, in the next future, a correct selection of patients for prenatal interventions.
B) Invasive Cardiology: in particular, research was focused on the study of new transcatheter intervention techniques in complex congenital cardiopathies such as procedures of embolization of complex pulmonary vascular anomalies and perforation with radiofrequency of the pulmonary valve in newborns with pulmonary atresia with intact interventricular septum. These types of endovascular interventions allow the treatment of patients who, until few years ago, required heart surgery under extracorporeal circulation The new challenge in this field is the extension of indications to increasingly small patients and finally newborns. This will boost the miniaturization of materials, an essential requirement for the application of these techniques also in the prenatal period.
C) Pediatric cardiology: clinical research was focused on the analysis of surgical outcome in children operated for congenital cardiopathies and on the use of new drugs in pediatric cardiology. We performed a multicentre randomized double-blind event-driven study:

children aged below 92 days with cyanotic congenital cardiopathy and palliated with systemic-pulmonary shunt were randomized to receive clopidogrel or placebo. Primary efficacy end point was death or heart transplantation, shunt thrombosis, or cardiologic procedures performed because of an event considered of thrombotic nature.
Objective of our study was to evaluate the efficacy of clopidogrel vs placebo in reducing mortality due to any cause and morbidity in small children with cyanotic congenital cardiopathies palliated with a systemic-pulmonary shunt.
Our study demonstrated that supplementation of traditional aspirin therapy with clopidogrel did not reduce mortality due to any cause nor morbidity correlated to the presence of a systemic pulmonary shunt in newborns or nurslings with congenital cardiopathy palliated with systemic-pulmonary shunt.

Cardiovascular Surgery *– Director: Dr. Lucio Zannini*

Gene expression profile in advanced cardiac decompensation: identification and validation of new biomarkers

Objective of the project is to discover new biomarkers starting from the analysis of gene expression profile of the cardiac muscle in pediatric patients with cardiac decompensation in congenital cardiopathies and undergoing surgery at the Cardiovascular Surgery unit of the Istituto Gaslini.
The identification of new biomarkers showing more sensitivity and specificity is essential to improve the management of cardiac decompensation. They allow the optimization of current therapeutic approaches with beneficial effects for the patient and the reduction of hospitalizations. Pediatric patients with selected congenital cardiopathies were enrolled in the Cardiovascular Surgery unit and were submitted to surgery. In collaboration with the Laboratory of Molecular Biology, where the collected material is studied, the centralization of samples from the Gaslini's biobank-BIT is continued. The collected material is studied by analysis of the gene expression profile of the cardiac muscle through microarray technology.
Since the number of samples presently available is still insufficient, it is necessary to continue the collection of cardiac tissue during cardiovascular surgery for the study of gene expression profiles through microarray.

Surgery – Director: Dr. Piero Buffa

Characterization of phenotype variability of Hirschsprung's disease and role of the ret proto-oncogene in immune and microbial homeostasis of human and murine intestine

In 2013, the enrolment of patients with Hirschsprung's disease was continued and they were included in a complex programme of phenotype screening (abdominal US, transfontanellar US, echocardiography, cardiological examination, ECG, eye examination, and hearing test in case of surgery) and of genotype screening (screening of mutations and haplotypes of the Ret proto-oncogene). Stool was sampled from all patients for metagenomic study (ongoing at NIH laboratories – Bethesda), and intestinal tissue and peripheral DNA were sampled from those undergoing surgery for the study of the expression of Ret and other genes potentially involved in inflammation. All this was aimed at clarifying the complex correlation between genotype and phenotype of Hirschsprung's disease and to develop pathogenetic hypotheses able to explain more accurately the main complication of the disease, namely enterocolitis. Overall, until November 30, 2013, 155 patients were enrolled, 115 of them undergoing full screening and therefore included in the study aimed at the definition of the phenotype variability of Hirschsprung's disease, of genotype/phenotype correlation, and at the identification of possible risk factors for the development of enterocolitis. The results obtained in the first 106 patients were published in the international Orphanet Journal of Rare Disease.

Mini-invasive approach in pediatric surgery: clinical audits, risk management, and guidelines

In 2013, we implemented a complex database able to include all the main demographic and clinical data, intraoperative technical details, outcome measures, and complications, if present. This database, adapted for each disease, was used initially for a selected population of patients (affected by oesophageal a**tresia**) undergoing minimally invasive surgery at our Institute. The audit was extended to all units at national level in order to define the main epidemiological characteristics, surgical attitudes, and short- and medium-term outcome of this rare congenital disease. We enrolled 147 patients treated in 53 Pediatric Surgery units active at national level and representative of all eligible patients. A paper summing up the exceptional results obtained is being prepared and will be submitted to an international journal with high impact factor. Preliminary results of the study were presented in occasion of the Joint National Meeting of the Italian Society of Pediatric Surgery (Ferrara, October 2013).
The same database, adapted for another disease (ulcerative **colitis**), is presently used for collection of data concerning patients undergoing surgical treatment, even in this case extending data collection to many centres at national level.

Hirschsprung's disease as a model of neuro-immune dysfunctions in the gut: role of the ret proto-oncogene in the correct development and maintenance of microbial homeostasis

On November 30, 2013, the third year of the three-year project was concluded, but an extension of another year was granted (until Nov. 30, 2014). Since the project start on December 1, 2012, we enrolled a total of 155 patients, 48 of them undergoing sampling of bowel tissue for immunological study, 125 peripheral blood sampling for DNA extraction (63 trios = proband + both parents), and 100 peripheral blood sampling for the study of gene expression on circulating immune cells. In 2013, a paper was published in an international journal (*Plos-One)* describing the study results, focusing especially on the evaluation of the RET proto-oncogene expression on various cell lines of circulating immunity in patients with Hirschsprung's disease, and of the effect, in the same patients, of RET stimulation on up- or down-regulation of specific inflammation genes.

Ophthalmology *– Director: Prof. Paolo Capris*

From January to December 2013, we studied 3 patients with primary congenital glaucoma and 16 patients with glaucoma secondary to Sturge-Weber syndrome receiving Latanoprost. In all patients, the following diagnostic examinations were performed: corneal pachymetry, picture of anterior and posterior segments, measurement of corneal diameters, and tonometry. All patients aged > 3 years underwent measurement of thickness of peripapillary retinal nerve fibers and analysis of macular retinal thickness by optical coherence tomography (OCT), Heidelberg Spectralis, and infrared retinography of the papilla through scanning laser ophthalmoscopy. In patients aged > 7 years, we also performed computerized visual field test (programme 30-2, TOP strategy).
Topical monotherapy with Latanoprost proved effective in reducing intraocular pressure in 17% of patients, while in the remaining 83%, to reach target pressure, combined topical therapy with beta-blockers was necessary.

Dentistry – Director: Dr. Roberto Servetto

The Dentistry unit established a collaboration agreement with the University of Cagliari, Residency Course in Orthodontics. Within the framework of this collaboration in clinical, educational, and scientific fields, a Dentistry Scientific Committee was created. Prof.. Mauro Cozzani, president of this Committee, participated as speaker in many international

congresses and published many scientific papers in international journals, making Gaslini and its scientific activity known all over the world.
Moreover, an inter-hospital department was created with Galliera Hospital, Odontostomatology unit and Maxillo-facial Surgery unit, having the task of organizing scientific and educational events.

Orthopedics *– Director: Dr. Silvio Boero*

New surgical technique for the correction of flexed elbow as a sequela of obstetrical palsy

In 2013, many surgical interventions were performed and the technique was presented in occasion of many national and international meetings (Switzerland and India). A national Congress in Microsurgery chaired by Dr. Senes was organized (Spring Symposium of the Italian Society of Microsurgery) and a paper was submitted to the Journal of Hand Surgery.

Use of the guided growth technique in the correction of limb length discrepancies and in axial deviations

Even in this field, many surgical operations were performed and the technique was presented in occasion of national and international congresses (Athens, Abu Dhabi). The results of the study are being evaluated.

Vertebral tuberculosis in pediatric patients

The different possibilities of surgical treatment with and without instrumentation of vertebral deformities secondary to TBC were evaluated.

Otolaryngology *– Director: Dr. Vincenzo Tarantino*

Pediatric ENT diseases: clinical and epidemiological aspects

In the field of diagnosis and treatment of laryngeal and tracheal diseases, we continued the study on the incidence of laryngomalacia (LM) in newborns, on the number of surgically treated small patients (both absolute and relative percentages), and on the association between best anesthesiologic procedure and most effective and conservative surgical procedure.
To this end, thanks to the availability of a double laser (CO2 and diods), a prospective evaluation is being performed of the first results obtained in the treatment of a wide range airway diseases using the two techniques, on the basis of age, anatomical conditions, and applicable anesthesiology techniques.
In addition, an endoscopy-based classification of LM severity to be associated with clinical classification was proposed: the aim is to provide a more accurate LM staging, i.e. endoscopy- and symptom-based, for the identification as objective as possible of cases requiring surgical treatment.

Epidemiology, Biostatistics, and Committees *– Director: Dr. Riccardo Haupt*

In the field of epidemiology, the international exposure of Gaslini has further increased thanks to the active participation in presently ongoing European projects (PanCareSurFup and ENCCA) and in other projects approved this year by the EC (PanCareLIFE e ExPO-r-NeT). Research fields included long-term follow-up of long-term survivors of pediatric tumor with particular reference to late mortality, second tumors, and severe cardiovascular events. A prototype of the “Recovery Passport” has also been developed. In addition, we used data from the disease registries of which we are responsible for the analysis of case series, especially for neuroblastoma, infections in tumor patients, and off-therapy patients after childhood tumors.
Concerning biostatistics, we performed analyses of data from experimental studies, in particular prospective longitudinal studies a) for the evaluation of new treatments in rheumatology (juvenile dermatomyositis, juvenile idiopathic arthritis, and systemic lupus

erythematosus); b) for the validation of standardized clinical and/or radiological/echographic diagnostic tools for evaluation of joint/muscular activity and damage; c) for the development of new classification systems for diagnosis and of new standardized criteria for evaluation of outcome.
The collaboration with Cochrane International centre for the systematic review of neonatology and allergology topics is continued. In this context, 4 days were dedicated to education of the hospital staff and external professionals on the techniques of execution and reading of systematic reviews and meta-analyses.

Pharmacy – *Director: Dr. Paola Barabino*
Since 1999, a multicentre study is carried out on the safety of medications and vaccines in pediatrics. The National Centre of Epidemiology, Surveillance, and Promotion of Health of the Istituto Superiore di Sanità is the coordinator.
Active surveillance is carried out among all Emergency admissions, on some acute clinical conditions of interest. The risk of onset of events related to the use of medications or vaccines is estimated using a case-control analysis model.
To date, the study highlighted and confirmed signals of adverse reactions to some medications, making it possible to integrate data collected through spontaneous reporting of adverse reactions.
This study allowed more reliable estimates of risk for adverse reactions than those deriving from spontaneous reporting.
Overall, from September 1, 2012 to September 23, 2013, we enrolled 131 patients. Among them, 84 children were exposed to medications in the three weeks preceding hospitalization. Among neurological diseases, episodes of syncope and hyporeactivity, epilepsy, and ALTE in smaller patients were the most frequent.
The most frequent muco-cutaneous diseases were vasculitides and Henoch-Schoenlein purpura. One case of Steven- Johnson syndrome was observed.
Over the last two years, the multicentre group carried out a study on the safety and efficacy of influenza vaccination in children. Two seasons were examined, namely 2011-2012 and 2012-2013. The first phase was a pilot study, which allowed the redesign of the study criteria for the subsequent season. All enrolled patients underwent oropharyngeal swab to check positivity for influenza A and B. Typing of viral subtype was performed in all positive samples.
Overall, 773 patients were enrolled and 4% of them received influenza vaccination. Notwithstanding the low vaccination rate in children, the study showed that the vaccine is moderately effective in pediatric age.

Management control and quality office – *Director: Dr. Ubaldo Rosati*
Multicentre project for clinical risk management in children
Objectives:
1. Benchmark analysis compared to UK National Health Service hospitals.
2. Focus on risk problems related to the urgency/emergency area
3. Identification of instruments.
4. Staff education and training.

Description:
A. Development of a methodological model to be adopted for improvement of safety in pediatric age and proposal of actions to be undertaken on the basis of their efficacy, available literature evidence, and observation results, in compliance with ethical principles established by national and international bodies.
B. Definition and testing of a method for the evaluation of activities carried out to reduce clinical risk in pediatric age.

Publications year 2013

1. **Erba PA., Minichilli F., Giona F., Linari S., Dambrosia J., Pierini A., Filocamo Mirella, Di Rocco Maja, Buffoni F., Brady RO., Mariani G.**
   99mTc-Sestamibi scintigraphy to monitor the long-term efficacy of enzyme replacement therapy on bone marrow infiltration in patients with Gaucher disease.
   J NUCL MED 2013; 54: 1717-1724.
   IF: 5.774 Normalized IF: 3
2. **Parodi A., Gandolfo Carlo, Palombo D., Zannini Lucio Valerio, Ghiggeri Gian Marco.**
   A challenging case of renovascular hypertension.
   Vasc Med. 2013; 18: 318-319.
   IF: 1.617 Normalized IF: 2
3. **Santarelli F., Cassanello Michela, Enea A., Poma F., D'Onofrio V., Guala G., Garrone G., Puccinelli P., Caruso Ubaldo, Porta F., Spada M.**
   A neonatal case of 3-hydroxy-3-methylglutaric-coenzyme A lyase deficiency.
   ITAL J PEDIATR 2013; 39: 33.
   IF: 1.344 Normalized IF: 2
4. **Caridi Gianluca, Dagnino Monica, Lugani F., Shalev SA., Campagnoli M., Galliano M., Spiegel R., Minchiotti L.**
   A novel mutation in the albumin gene (c.1A>C) resulting in analbuminemia.
   EUR J CLIN INVEST 2013; 43(1): 72-78.
   IF: 3.365 Normalized IF: 6
5. **Pini Prato Alessio, Rossi V., Mosconi M., Holm C., Lantieri F., Griseri Paola, Ceccherini Isabella, Mavilio D., Jasonni Vincenzo, Tuo Giulia, Derchi Maria Elena, Marasini Maurizio Francesco, Magnano Gian Michele, Granata Claudio, Ghiggeri Gian Marco, Priolo E., Sposetti L., Porcu A., Buffa Piero, Mattioli Girolamo.**
   A prospective observational study of associated anomalies in Hirschsprung's disease.
   Orphanet J Rare Dis. 2013; 8: 184.
   IF: 4.315 Normalized IF: 6
6. **Lugani F., Arora R., Papeta N., Patel A., Zheng Z., Sterken R., Singer RA., Caridi Gianluca, Mendelsohn C., Sussel L., Papaioannou VE.**
   A retrotransposon insertion in the 5' regulatory domain of Ptf1a results in ectopic gene expression and multiple congenital defects in Danforth's short tail mouse.
   PLOS GENET 2013; 9(2): e1003206.
   IF: 8.517 Normalized IF: 4
7. **Guida E., Pini Prato Alessio, Mattioli Girolamo, Carlucci M., Avanzini Stefano, Buffa Piero, Michelazzi A., Montobbio Giovanni, Jasonni Vincenzo.**
   Abdominal wall defects: a 33-year unicentric experience.
   Minerva Pediatr. 2013; 65: 179-185.
   IF: 0.638 Normalized IF: 1
8. **Lombardi L., Bruder E., Caravaggi F., Del Rossi C., Martucciello Giuseppe.**
   Abnormalities in "low" anorectal malformations (ARMs) and functional results resecting the distal 3 cm.
   J Pediatr Surg. 2013; 48: 1294-1300.
   IF: 1.383 Normalized IF: 4
9. **Ameli F., Brocchetti F., Tosca Maria Angela, Signori A., Ciprandi G.**
   Adenoidal hypertrophy and allergic rhinitis: is there an inverse relationship?
   AM J RHINOL ALLERGY 2013; 27: e5-e10.
   IF: 1.744 Normalized IF: 3

10. **Badaloni C., Ranucci A., Cesaroni G., Zanini G., Vienneau D., Al-Aidrous F., De Hoogh K., Magnani C., Forastiere F., for the SETIL Study Group, Haupt Riccardo.**
    Air pollution and childhood leukaemia: a nationwide case-control study in Italy.
    Occup Environ Med 2013; 70: 876-883.
    IF: 3.215 Normalized IF: 1.2
11. **Bruschi Maurizio, Santucci Laura, Candiano Giovanni, Ghiggeri Gian Marco.**
    Albumin heterogeneity in low-abundance fluids. The case of urine and cerebro-spinal fluid.
    BBA-GEN SUBJECTS 2013; 1830: 5503-5508.
    IF: 3.848 Normalized IF: 6
12. **Bonthuis M., Jager KJ., Abu-Hanna A., Verrina Enrico, Schaefer F., van Stralen KJ.**
    Application of body mass index according to height-age in short and tall children.
    PLOS ONE 2013; 8: e72068.
    IF: 3.73 Normalized IF: 3
13. **Minniti Giuseppe, Lorini Renata, Veneselli Edvige, Calevo Maria Grazia, Battaglia Francesca Maria.**
    Are psychobiological markers strongly correlated with allostatic load in population with autism spectrum disorders (ASD)?
    MED HYPOTHESES 2013; 80: 505-508.
    IF: 1.054 Normalized IF: 0.5
14. **Calzia D., Candiani S., Garbarino G., Caicci F., Ravera S., Bruschi Maurizio, Manni L., Morelli A., Traverso CE., Candiano Giovanni, Tacchetti C., Panfoli I.**
    Are rod outer segment ATP-ase and ATP-synthase activity expression of the same protein?
    CELL MOL NEUROBIOL 2013; 33: 637-649.
    IF: 2.293 Normalized IF: 1
15. **Ullmann Nicola, Bossley CJ., Fleming L., Silvestri Michela, Bush A., Saglani S.**
    Blood eosinophil counts rarely reflect airway eosinophilia in children with severe asthma.
    Allergy 2013; 68: 402-406.
    IF: 5.883 Normalized IF: 6
16. **Sabatini Federica, Luppi F., Petecchia Loredana, Di Stefano A., Longo AM., Eva Alessandra, Vanni C., Hiemstra PS., Sterk PJ., Sorbello V., Fabbri LM., Rossi Giovanni A, Ricciardolo FLM.**
    Bradykinin-induced asthmatic fibroblast/myofibroblast activities via bradykinin B2 receptor and different MAPK pathways.
    EUR J PHARMACOL 2013; 710: 100-109.
    IF: 2.592 Normalized IF: 4
17. **Ciprandi G., Tosca Maria Angela, Silvestri Michela, Rossi Giovanni A.**
    Breathlessness perception in children with asthma.
    J ASTHMA 2013; 50(9): 1010.
    IF: 1.848 Normalized IF: 2
18. **Clayton P., Bonnemaire M., Dutailly P., Maisonobe P., Naudin L., Pham E., Zahang Z., Grupe A., Thiagalingam A., Denefle P., for the EPIGROW Study Group, Maghnie Mohamad.**
    Characterizing short stature by insulin-like growth factor axis status and genetic associations: results from the prospective, cross-sectional, epidemiogenetic EPIGROW study.
    J Clin Endocrinol Metab. 2013; 98(6): E1122-E1130.
    IF: 6.43 Normalized IF: 1.2
19. **Kantar A., Bernardini R., Paravati F., Minasi D., Sacco Oliviero.**
    Chronic cough in preschool children

Early Hum Dev. 2013; 89: S19-S24.
IF: 2.02 Normalized IF: 4

20. **Murtas Corrado, Landino A., Ghiggeri Gian Marco.**
Circulating antipodocyte antibodies in membranous nephropathy: new findings.
AM J KIDNEY DIS 2013; 62(1): 12-15.
IF: 5.294 Normalized IF: 6
21. **Lanari M., Silvestri Michela, Rossi Giovanni A.**
Clinical and pharmacological aspects of immunoprophylaxis for respiratory syncytial virus infection in high-risk infants.
CURR DRUG METAB 2013; 14: 216-225.
IF: 4.405 Normalized IF: 6
22. **Wessel DL., Berger F., Li JS., Dahnert I., Rakhit A., Fontecave S., Newburger JW., for the CLARINET Inestigators, Rimini Alessandro, et al.**
Clopidogrel in infants with systemic-to-pulmonary-artery shunts.
NEW ENGL J MED 2013; 213: 2277-2284.
IF: 51.658 Normalized IF: 3
23. **Averna M., Pedrazzi M., Minicucci Laura, De Tullio R., Cresta F., Salamino F., Pontremoli S., Melloni E.**
Colpain inhibition promotes the rescue of F508 del-CFTR in PBMC from cystic fibrosis patients.
PLOS ONE 2013; 8: e66089.
IF: 3.73 Normalized IF: 3
24. **Santucci Laura, Candiano Giovanni, Petretto Andrea, Lavarello Chiara, Bruschi Maurizio, Ghiggeri Gian Marco, Citterio A., Righetti PG.**
Combinatorial ligand libraries as a two-dimensional method for proteome analysis.
J CHROMATOGR A 2013; 1297: 106-112.
IF: 4.612 Normalized IF: 6
25. **Granata Claudio, Magnano Gian Michele.**
Computerized tomography in pediatric oncology.
EUR J RADIOL 2013; 82: 1098-1107.
IF: 2.512 Normalized IF: 4
26. **Minchiotti L., Galliano M., Caridi Gianluca, Kragh-Hansen U., Peters T.**
Congenital analbuminaemia: molecular defects and biochemical and clinical aspects.
BBA-GEN SUBJECTS 2013; 1830: 5494-5502.
IF: 3.848 Normalized IF: 3
27. **Olivieri A., Corbetta C., Weber G., Vigone MC, Fazzini C., Medda E., for the Italian National Registry of Infants with Congenital Hypothyroidism, Caruso Ubaldo, Gastaldi Roberto, Lorini Renata.**
Congenital hypothyroidism due to defects of thyroid development and mild increase of TSH at screening: data from the Italian National Registry of Infants with Congenital Hypothyroidism.
J CLIN ENDOCR METAB 2013; 98(4): 1403-1408.
IF: 6.43 Normalized IF: 1.2
28. **Harambat J., van Stralen KJ., Schaefer F., Granda R., Jankauskiene A., Kostic M., Macher MA., Maxwell H., Puretic Z., Raes A., Rubik J., Sorensen SS., Toots U., Topaloglu R., Tonshoff B., Verrina Enrico, Jager KJ.**
Disparities in policies, practices and rates of pediatric kidney transplantation in Europe.

AM J TRANSPLANT 2013; 13: 2066-2074.
IF: 6.192 Normalized IF: 3

29. **Esposito S., Marchese A., Tozzi AE., Rossi Giovanni A, Da Dalt L., Bona G., Pelucchi C., Schito GC.**
DNA bacterial load in children with bacteremic pneumococcal community-acquired pneumonia.
EUR J CLIN MICROBIOL 2013; 32: 877-881.
IF: 3.024 Normalized IF: 2
30. **Lotta LA., Wu HM., Cairo A., Bentivoglio Giorgio.**
Drop of residual plasmatic activity of ADAMTS13 to undetectable levels during acute disease in a patient with adult-onset congenital thrombocytopenic purpura.
BLOOD CELL MOL DIS 2013; 50: 59-60.
IF: 2.259 Normalized IF: 1
31. **Bianciotto M., Chiappini E., Raffaldi I., Gabiano C., Tovo PA., Sollai S., De Martino M., Mannelli F., Tipo V., Da Cas R., Traversa G., Menniti-Ippolito F., for the Italian Multicenter Study for Drug and Vaccine Safety in Children, Di Pietro Pasquale, Renna Salvatore, Rossi Rossella, Gamba S., et al.**
Drug use and upper gastrointestinal complications in children: a case-control study.
ARCH DIS CHILD 2013; 98: 218-211.
IF: 3.051 Normalized IF: 1.2
32. **Bllini C., Ergaz Z., Boccardo F., Bellini T., Campisi CC., Bonioli E., Ramenghi Luca Antonio.**
Dynamics of pleural fluid effusion and chylothorax in the fetus and newborn: role of the lymphatic system.
Lymphology 2013; 46: 75-84.
IF: 1.19 Normalized IF: 1
33. **Lazzerini M., Martelossi S., Magazzù G., Pellegrino S., Lucanto C., Barabino Arrigo, Calvi A., Arrigo Serena, et al.**
Effect of thalidomide on clinical remission in children and adolescents with refractory Chron disease.
JAMA 2013; 310: 2164-2173.
IF: 29.978 Normalized IF: 7.5
34. **Sannia A., Zimmermann LJI., Gavilanes WD., Vles HJ., Calevo Maria Grazia, Florio P., Gazzolo D.**
Elevated activin A urine levels are predictors of intraventricular haemorrage in preterm newborns:
ACTA PAEDIATR 2013; 102: e449-e454.
IF: 1.974 Normalized IF: 2
35. **Morcaldi G., Clementi M., Lama G., Gabrielli O., Vannelli S., Virdis R., Vivarelli R., Boero Silvio, Bonioli Eugenio.**
Evaluation of Tibial Osteopathy Occurrence in Neurofibromatosis Type 1 Italian Patients
AM J MED GENET A 2013; 161A: 927-934.
IF: 2.304 Normalized IF: 2
36. **Colombo M., Cutrona G., Reverberi D., Bruno S., Ghiotto F., Tenca C., Stamatopoulous K., Hadzidimitriou A., Ceccarelli J., Salvi S., Boccardo S., Calevo Maria Grazia, et al.**
Expression of immunoglobulin receptors with distinctive features indicating antigen selection by marginal zone B cells from human spleen.

Mol Med 2013; 19: 294-302.
IF: 4.469 Normalized IF: 3

37. **Yildiz Y., Hoffmann P., vom Dahl S., Breiden B., Sandhoff R., Niederau C., Horwitz M., Karlsson S., Filocamo Mirella, et al.**
Functional and genetic characterization of the non-lysosomal glucosylceramidase 2 as a modifier for Gaucher disease.
ORPHANET J RARE DIS 2013; 8: 151.
IF: 4.315 Normalized IF: 3

38. **Lipska BS., Iatropoulos P., Maranta L., Caridi Gianluca, Ozaltin F., Anarat A., Balat A., Gellermann J., Trautmann A., Erdogan O., Saeed B., Emre S., Bogdanovic R., Azocar M., Balasz-Chmielewska I., Ghiggeri Gian Marco, et al.**
Genetic screening in adolescents with steroid-resistant nephrotic syndrome.
KIDNEY INT 2013; 84: 206-213.
IF: 7.916 Normalized IF: 4

39. **Ciprandi G., Tosca Maria Angela, Capasso M.**
High exhaled nitric oxide levels may predict bronchial reversibility in allergic children with asthma or rhinitis.
J ASTHMA 2013; 50(1): 33-38.
IF: 1.848 Normalized IF: 2

40. **D'Annunzio Giuseppe, Marchi M., Aloi Concetta, Salina A., Lugani Francesca, Lorini Renata.**
Hyperglycaemia and ß-cell antibodies: Is it always pre-type 1 diabetes?
DIABETES RES CLIN PR 2013; 100: e20-e22.
IF: 2.741 Normalized IF: 4

41. **Occella Corrado, Bleidl Dario, Nozza Paolo, Mascelli Samantha, Raso Alessandro, Gimelli Giorgio, Gimelli S., Tassano Elisa.**
Identification of an interstitial 18p11.32-p11.31 duplication including the EMILIN2 gene in a family with porokeratosis of Mibelli.
PLOS ONE 2013; 8(4): e61311.
IF: 3.73 Normalized IF: 6

42. **Damasio Maria Beatrice, Tanturri de Horatio L., Boavida P., Lambot-Juhan K., Rosendahl K., Toma' P., Ording Muller LS.**
Imaging in juvenile idiopathic arthritis (JIA): an update with particular emphasis on MRI.
Acta Radiol. 2013; 54: 1015-1023.
IF: 1.33 Normalized IF: 2

43. **Comoli P., Cioni M., Basso S., Gagliardone C., Potenza L., Verrina Enrico, Luppi M., Zecca M., Ghiggeri Gian Marco, Ginevri Fabrizio.**
Immunity to polyomavirus BK infection: immune monitoring to regulate the balance between risk of BKV nephropathy and induction of alloimmunity.
CLIN DEV IMMUNOL 2013; ID256923: 6 pages.
IF: 3.064 Normalized IF: 4

44. **Van Stralen KJ., Verrina Enrico, Belingheri M., Dudley J., Dusek J., Grenda R., Macher MA., Puretic Z., Rubic J., Sudaitis S., Rudin C., Schaefer F., Jager KJ.**
Impact of graft loss among kidney diseases with a high risk of post-transplant recurrence in the paediatric population.
NEPHROL DIAL TRANSPL 2013; 28: 1031-1038.
IF: 3.371 Normalized IF: 6

45. **Bason C., Lorini Renata, Lunardi C., Dolcino Marzia, Giannattasio A., D'Annunzio Giuseppe, Rigo A., Pedemonte Nicoletta, Corrocher R., Puccetti Antonio.**
In type 1 diabetes a subset of anti-coxsackievirus B4 antibodies recognize autoantigens and induce apoptosis of pancreatic beta cells.
PLOS ONE 2013; 8: e57729.
IF: 3.73 Normalized IF: 6
46. **Tuo Giulia, Marasini Maurizio Francesco, Brunelli C., Zannini Lucio Valerio, Balbi M.**
Incidence and clinical relevance of primary congenital anomalies of the coronary arteries in children and a adults.
CARDIOL YOUNG 2013; 23: 381-386.
IF: 0.948 Normalized IF: 2
47. **AIRTUM Working Group., CCM., AIEOP., Haupt Riccardo.**
Italian cancer figures, report 2012: cancer in children and adolescents.
EPIDEMIOL PREV 2013; 37: 1-225.
IF: 0.919 Normalized IF: 0.2
48. **Maor G., Filocamo Mirella, Horowitz M.**
ITCH regulates degradation of mutant glucocerebrosidase: implications to Gaucher disease.
HUM MOL GENET 2013; 22(7): 1316-1327.
IF: 7.692 Normalized IF: 8
49. **Haupt Riccardo, Minkov N., Astigarraga I., Schafer E., Nanduri V., Jubran R., Egeler RM., Janka G., Micic D., Rodriguez-Galindo C., Van Gool S., Visser J., Weitzman S., Donadieu J.**
Langerhans cell histiocytosis (LCH): Guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years.
PEDIATR BLOOD CANCER 2013; 60: 175-184.
IF: 2.353 Normalized IF: 6
50. **Haupt Riccardo, Jankovic M., Hjorth L., Skinner R.**
Late effects in childhood cancer survivors and survivorship issues.
EPIDEMIOL PREV 2013; 37: 266-273.
IF: 0.919 Normalized IF: 1
51. **Keil S., Anjema K., van Srponsen FJ., Lambruschini M., Burlina A., Belanger-Quintana A., Couce ML., Feillet F., Cerone Roberto, et al.**
Long-term follow-up and outcome of phenylketonuria patients on saproterin: a retrospective study.
PEDIATRICS 2013; 131: e1881.
IF: 5.119 Normalized IF: 3
52. **Ruggiero B., Vivarelli M., Gianviti A., Benetti E., Peruzzi L., Barbano Giancarlo, Corona F., Ventura G., Pecoraro C., Murer L., Ghiggeri Gian Marco, Pennesi M., Edefonti A., Coppo R., Emma F.**
Lupus nephritis in children and adolescents: results of the Italian Collaborative Study.
NEPHROL DIAL TRANSPL 2013; 28: 1487-1496.
IF: 3.371 Normalized IF: 3
53. **Maghnie Mohamad, Lindberg A., Koltowska-Haggstrom M., Ranke MB.**
Magnetic resonance imaging of CNS in 15,043 children with GH deficiency in KIGS (Pfizer International Growth Database).
EUR J ENDOCRINOL 2013; 168: 211-217.
IF: 3.136 Normalized IF: 4

54. **Damasio Maria Beatrice, Costanzo S., Podestà E., Ghiggeri Gian Marco, Piaggio Giorgio, Faranda F., Degl'Innocenti ML., Jasonni Vincenzo, Magnano Gian Michele, Buffa Piero, Montobbio Giovanni, Mattioli Girolamo.**
Magnetic resonance urography and laparoscopy in paediatric urology: a case series.
Pediatr Radiol. 2013; 43: 1516-1527.
IF: 1.565 Normalized IF: 4

55. **Borzych-Duzalka D., Bilginer Y., Soo Ha I., Bak M., Rees L., Cano F., Munarriz RL., Chua A., Pelse S., Emre S., Urzykowska A., Quiroz L., Ruscasso JD., White C., Pape L., Ramela V., Printza N., Vogel A., Kuzmanovska D., Simkova E., Muller-Wiefel DE., Sander A., Warady BA., Schaefer F., for the International Pediatric Peritoneal Dialysis Network Registry, Verrina Enrico.**
Management of anemia in children receiving chronic peritoneal dialysis.
J AM SOC NEPHROL 2013; 24: 665-676.
IF: 8.987 Normalized IF: 1.6

56. **Lanari M., Prinelli F., Adorni F., Di Santo S., Faldella G., Silvestri Michela, Musicco M., Italian Neonatology Study Group on RSV Infections.**
Maternal milk protects infants against bronchiolitis during the first year of life. Results from an Italian cohort of newborns.
EARLY HUM DEV 2013; 89S1: S51-S57.
IF: 2.02 Normalized IF: 2

57. **Tosca Maria Angela, Silvestri Michela, D'Annunzio G., Lorini Renata, Rossi Giovanni A, Ciprandi G.**
May T1 diabetes mellitus protect from asthma?
ALLERGOL IMMUNOPATH 2013; 41(5): 288-291.
IF: 1.229 Normalized IF: 2

58. **Silvestri Michela, Rossi Giovanni A.**
Melatonin: its possible role in the management of viral infections-a brief review.
ITAL J PEDIATR 2013; 39: 61.
IF: 1.344 Normalized IF: 2

59. **Carta S., Silvestri Michela, Rossi Giovanni A.**
Modulation of airway epithelial cell functions by pidotimod: NF-kB cytoplasmatic expressio and its nuclear translocation are associated with an increased TLR-2 expression.
ITAL J PEDIATR 2013; 30: 29.
IF: 1.344 Normalized IF: 2

60. **Santorelli FM., Garavaglia B., Cardona F., Nardocci N., Della Bernardina B., Sartori S., Suppiej A., Bertini E., Claps D., Battini R., Biancheri Roberta, Filocamo Mirella, Pezzini F., Simonati A.**
Molecular epidemiology of childhood neuronal ceroid-lipofuscinosis in Italy.
ORPHANET J RARE DIS 2013; 8: 13.
IF: 4.315 Normalized IF: 3

61. **Lambot K., Boavida P., Damasio Maria Beatrice, Tanturri de Horatio L., Desgranges M., Malattia Clara, Barbuti D., Bracaglia C., Ording Muller LS., Elie C., Bader-Meunier B., Quartier P., Rosendahl K., Brunelle F.**
MRI assessment of tenosynovitis in children with juvenile idiopathic arthritis: Inter- and intra-observer variability.
PEDIATR RADIOL 2013; 43: 796-802.
IF: 1.565 Normalized IF: 2

62. **Ording Muller LS., Boavida P., Avenarius D., Damasio Maria Beatrice, Eldevik OP., Malattia Clara, Lambot-Juhan K., Tanturri L., Owens CM., Rosendahl K.**
MRI of the wrist in juvenile idiopathic arthritis: erosions or normal variants? A prospective case-control study.
PEDIATR RADIOL 2013; 43: 785-795.
IF: 1.565 Normalized IF: 2
63. **Damasio Maria Beatrice, Darge K., Riccabona M.**
Multi-detector CT in the paediatric urinary tract.
EUR J RADIOL 2013; 82: 1118-1125.
IF: 2.512 Normalized IF: 4
64. **Zampetti A., Fania L., Antuzzi D., Giurdanella F., Gnarra M., Bertola F., Lualdi Susanna, Filocamo Mirella, Morrone A., Feliciani C.**
Mutation identification of Fabry disease in families with other lysosomal storage disorders.
CLIN GENET 2013; 84: 281-285.
IF: 4.247 Normalized IF: 3
65. **Hurd TW., Otto EA., Mishima E., Gee HY., Ianoue H., Inazu M., Yamada H., Halbritter J., Seki G., Konishi M., Zhou W., Yamane T., Murakami S., Caridi Gianluca, Ghiggeri Gian Marco, Abe T., Hildebrandt F.**
Mutation of the Mg2+ transporter SLC41A1 results in a nephronophthisis-like phenotype.
J AM SOC NEPHROL 2013; 24: 967-977.
IF: 8.987 Normalized IF: 4
66. **Sanna-Cherchi S., Sampogna RV.0, Papeta N., Burgess KE., Nees SN., Perry BJ., Choi M., Bodria M., Liu Y., Weng PL., Lozanovski VJ., Verbitsky M., Lugani F., Sterken R., Paragas N., Caridi Gianluca, Carrea Alba Maria, Dagnino Monica, Materna-Kiryluk A., Santamaria G., Murtas C., Ristoska-Bojkovska N., Izzi C., Kacak N., Bianco B., Giberti S., Gigante M., Piaggio Giorgio, Gesualdo L., Ravazzolo Roberto, Ghiggeri Gian Marco, Gharavi AG.**
Mutations in DSTYK and dominant urinary tract malformations.
NEW ENGL J MED 2013; 369: 621-629.
IF: 51.658 Normalized IF: 15
67. **Salpietro C., Cuppari C., Grasso L., Tosca Maria Angela, Miraglia Del Giudice M., La Rosa M., Marseglia GL., Salpietro A., Ciprandi G.**
Nasal high-mobility group box-1 protein in children with allergic rhinitis.
INT ARCH ALLERGY IMM 2013; 161: 116-121.
IF: 2.248 Normalized IF: 2
68. **Vida VL., Padrini M., Boccuzzo G., Agnoletti G., Bondanza Sara, Butera G., Chiappa E., Marasini Maurizio Francesco, Pilati M., Pongiglione G., et al.**
Natural history and clinical outcome of "uncorrected" Scimitar syndrome patients: a multicenter study in the Italian Society of Pediatric Cardiology.
REV ESP CARDIOL 2013; 66: 556-560.
IF: 3.204 Normalized IF: 2
69. **Zanon D., Gallelli L., Rovere F., Paparazzo R., Maximova N., Lazzerini M., Reale A., Corsetti T., Renna Salvatore, Emanueli Tullia, et al.**
Off-label prescribing patterns of antiemetics in children: a multicenter study in Italy.
EUR J PEDIATR 2013; 172: 361-367.
IF: 1.907 Normalized IF: 2
70. **Bruschi Maurizio, Candiano Giovanni, Santucci Laura, Ghiggeri Gian Marco.**
Oxidized albumin. The long way of a protein of uncertain function.

BBA-GEN SUBJECTS 2013; 1830: 5473-5479.
IF: 3.848 Normalized IF: 6

71. **Tosca Maria Angela, Silvestri Michela, Rossi Giovanni A, Ciprandi G.**
Perception of bronchodilation assessed by Visual Analogue Scale in children with asthma
Allergol Immunopathol (Madr). 2013; 41: 359-363.
IF: 1.229 Normalized IF: 2

72. **De Rose P., Albamonte E., Laganà V., Sivo S., Pisoni S., Gallini F., Serrao F., Tinelli F., Purpura G., Ometto A., Sacco A.., Ramenghi Luca Antonio, et al.**
Perceptual-motor abilities in pre-school preterm children.
Early Hum Dev. 2013; 89: 809-814.
IF: 2.02 Normalized IF: 2

73. **Bernardini FP., Croxatto JO., Nozza Paolo, Rossi Andrea, Capris Paolo.**
Primary diffuse leptomeningeal gliomatosis in children: A clinical pathologic correlation.
OPHTHAL PLAST RECONS 2013; 29(29: 93-97.
IF: 0.671 Normalized IF: 1

74. **Silvestri Michela, Crimi E., Oliva S., Senarega D., Tosca Maria Angela, Rossi Giovanni A, Brusasco V.**
Pulmonary function and airway responsiveness in young competitive swimmers.
PEDIATR PULM 2013; 48: 74-80.
IF: 2.375 Normalized IF: 6

75. **Regis Stefano, Corsolini Fabio, Grossi Serena, Tappino Barbara Anna, Cooper DN., Filocamo Mirella.**
Restoration of the normal splicing pattern of the PLP1 gene by means of an antisense oligonucleotide directed against an exonic mutation.
PLOS ONE 2013; 8: e73633.
IF: 3.73 Normalized IF: 6

76. **Miligi L., Benvenuti A., Mattioli S., Salvan A., Tozzi GA., Ranucci A., Legittimo P., Rondelli R., Bisanti L., Zambon P., Cannizzaro S., Kirchmayer U., Cocco P., Celentano E., Haupt Riccardo, Acquila Maura, et al.**
Risk of childhood leukaemia and non-Hodgkin's lymphoma after parental occupational exposure to solvents and other agents: the SETIL study.
OCCUP ENVIRON MED 2013; 70: 648-655.
IF: 3.215 Normalized IF: 3

77. **Ravani P., Ponticelli A., Siciliano C., Fornoni A., Magnasco Alberto, Sica F., Bodria M., Caridi Gianluca, Wei C., Belingheri M., Ghio L., Mescher-Gomez S., Edefonti A., Pasini A., Montini G., Murtas Corrado., Ghiggeri Gian Marco.**
Rituximab is a safe and effective long-term treatment for children with steroid and calcineurin inhibitor-dependent idiopathic nephrotic syndrome.
Kidney Int. 2013; 84: 1025-1033.
IF: 7.916 Normalized IF: 8

78. **Sannia Andrea, Risso FM, Zimmermann LJI., Gavilanes AWD., Vles HJ., Gazzolo D.**
S100B urine concentrations in late preterm infants are gestational age and gender dependent.
CLIN CHIM ACTA 2013; 417: 31-34.
IF: 2.85 Normalized IF: 6

79. **Scaglione M., Ebrille E., Caponi D., Blandino A., Di Donna P., Siboldi A., Bertero G., Anselmino M., Raimondo C., Sardi D., Gabbarini F., Marasini Maurizio Francesco,**

Gaita F.
Single center experience of fluoroless AVNRT ablation guided by electroanatomic reconstruction in children and adolescents.
Pacing Clin Electrophysiol. 2013 Dec;36(12):1460-7
IF: 1.746 Normalized IF: 2

80. **Longhi S., Pasquino B., Calcagno A., Bertelli E., Olivieri I., Di Iorgi Natascia, Radetti G.**
Small metacarpal bones of low quality in obese children.
CLIN ENDOCRINOL 2013; 78: 79-85.
IF: 3.396 Normalized IF: 2
81. **Raucci U., Rossi R., Da Cas R., Rafaniello C., Mores N., Bersani G., Reale A., Pirozzi N., Minniti-Ippolito F., Traversa G., for the Italian Multicenter Study Group for Drug and Vaccine Safety in Children, Di Pietro Pasquale, Renna Salvatore, Gamba Stefania.**
Stevens-Johnson syndrome associated with drugs and vaccines in children: a case-control study.
PLoS One. 2013; 8: e68231.
IF: 3.73 Normalized IF: 1.2
82. **Basso S., Zecca M., Calafiore L., Rubert L., Fiocchi R., Paulli M., Quartuccio G.., Ginevri Fabrizio, Cugno C., Comoli P.**
Successful treatment of a classic Hodgkin lymphoma-type post-transplant lymphoproliferative disorder with tailored chemotherapy and Epstein-Barr virus-specific cytotoxic T lymphocytes in a pediatric heart transplant recipient.
Pediatr Transplant. 2013; 17: e168-e173.
IF: 1.5 Normalized IF: 2
83. **Gagliardi L., Tagliabue P., Bellù R., Corchia C., Mosca F., Zanini R., for the Network Neonatale Italiano, Risso Francesco Maria.**
Survey of neonatal respiratory support use in very preterm infants in Italy.
J Matern Fetal Neonatal Med. 2012; 25(S3): 1-5.
IF: 1.518 Normalized IF: 0.4
84. **Filocamo Mirella, Baldo C., Goldwurm S., Renieri A., Angelini C., Moggio M., Mora M., Merla G., et al.**
Telethon network of genetic biobanks: a key service for diagnosis and research on rare diseases.
ORPHANET J RARE DIS 2013; 8: 129.
IF: 4.315 Normalized IF: 6
85. **Legendre CM., Licht C., Muus P., Greenbaum LA., Babu S., Bedrosian C., Bingham C., Cohen DJ., Delmas Y., Douglas K., Eitner F., Feldkamp T., Fouque D., Furman RR., Gaber O., Herthelius M., Trivelli Antonella, et al.**
Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. NEW ENGL J MED 2013; 368: 2169-2181.
IF: 51.658 Normalized IF: 7.5
86. **Cerone Roberto, Andria G., Giovannini M., Leuzzi V., Riva E., Burlina A.**
Testing for tetrahydrobiopterin responsiveness in patients with hyperphenylalaninemia due to phenylalanine hydroxylase deficiency.
ADV THER 2013; 30: 212-228.
IF: 2.125 Normalized IF: 2
87. **Cassio A., Cobetta C., Antonozzi I., Calaciura F., Caruso Ubaldo, Cesaretti G., Gastaldi Roberto, Medda E., et al.**

The Italian screening programfor primary congenital hypothyroidism: Actions to improve screening, diagnosis, follow-up, and surveillance.
J ENDOCRINOL INVEST 2013; 36: 195-203.
IF: 1.654 Normalized IF: 1

88. **Ciprandi G., Tosca Maria Angela, Silvestri Michela, Olcese Roberta, Rossi Giovanni A.**
The possible relevance of visual analogue scale in allergic patients.
Clin Exp Allergy. 2013; 43: 1297-1298.
IF: 4.789 Normalized IF: 6
89. **Vercellino Nadia, Romanini MV, Pelegrini M., Rimini Alessandro, Occella Corrado, Dalmonte Pietro.**
The use of propranolol for complicated infantile hemangiomas.
INT J DERMATOL 2013; 52: 1140-1146.
IF: 1.342 Normalized IF: 2
90. **Wuhl E., van Stralen KJ., Verrina Enrico, Bjerre A., Wanner C., Goya Heaf J., Zurriaga O., Hoitsma A., Niaudet P., Palsson R., Ravani P., Jager KJ., Schaefer F.**
Timing and outcome of renal replacement therapy in patients with congenital malformations of the kidney and urinary tract.
CLIN J AM SOC NEPHRO 2013; 8: 67-74.
IF: 5.068 Normalized IF: 3
91. **Chellapandian DB., Das R., Zelley K., Wiener SJ., Zhao H., Teachey DT., Nichols KE., for the EBV-HLH Rituximab Study Group, Haupt Riccardo, Svahn Johanna.**
Treatment of Epstein Barr virus-induced haemophagocytic lymphohistiocytosis with rituximab-containing chemo-immunotherapeutic regimens.
BRIT J HAEMATOL 2013; 162: 376-382.
IF: 4.942 Normalized IF: 1.2].
92. **Damasio Maria Beatrice, Cittadini G., Rolla D., Massarino F., Stagnaro Nicola, Gherzi M., Paoletti E., Derchi LE.**
Ultrasound findings in dual kidney transplantation.
RADIOL MED 2013; 118: 14-22.
IF: 1.461 Normalized IF: 2
93. **Maor G., Rencus-Lazar S., Filocamo Mirella, Steller H., Segal D., Horowitz M.**
Unfolded protein response in Gaucher disease: from human to Drosophila.
ORPHANET J RARE DIS 2013; 8: 140.
IF: 4.315 Normalized IF: 3
94. **Santucci Laura, Candiano Giovanni, Bruschi Maurizio, Bodria M., Murtas Corrado, Petretto Andrea, Ghiggeri Gian Marco.**
Urinary proteome in a snapshot: Normal urine and glomerulonephritis.
J NEPHROL 2013; 26(4): 610-616.
IF: 2.015 Normalized IF: 4
95. **Risso Francesco Maria, Serpero LD., Zimmermann LJI., Gavilanes AWD., Frulio R., Michetti F., Florio P., Bashir M., et al.**
Urine S100 BB and A1B dimers are valuable predictors of adverse outcome in full-term asphyxiated infants.
Acta Paediatr. 2013; 102: e467-e472.
IF: 1.974 Normalized IF: 4
96. **Bondanza Sara, Derchi Maria Elena, Tuo Giulia, Zannini Lucio Valerio, Marasini Maurizio Francesco.**

Use of a telescopic system for transcatheter radiofrequency perforation and balloon valvotomy in infants with pulmonary atresia an intact ventricular septum.
CARDIOL YOUNG 2013; 23: 203-208.
IF: 0.948 Normalized IF: 2

97. **Ghezzi M., Guida E., Ullmann Nicola, Sacco Oliviero, Mattioli Girolamo, Jasonni Vincenzo, Rossi Giovanni A, Silvestri Michela.**
Weakly acidic gastroesophageal refluxes are frequently triggers in young children with chronic cough.
PEDIATR PULM 2013; 48: 295-302.
IF: 2.375 Normalized IF: 6

98. **Esposito C., Gheneimi AE., Yamataka A., Rothenberg S., Bailez M., Ferro M., Gamba P., Castagnetti M., Mattioli Girolamo, Delagausie P., et al.**
Work-related upper limb musculoskeletal disorders in paediatric laparoscopic surgery. A multicenter survey.
J PEDIATR SURG 2013; 48: 1750-1756.
IF: 1.383 Normalized IF: 2

Research line 3
Clinical and Experimental Immunology and Rheumatology

Title
Translational and clinical immunological aspects of tumors and autoimmune diseases in pediatric age

Coordinators
Dr. Vito Pistoia, Prof. Angelo Ravelli

Project description (outline and objectives)
General objectives of this research line include aspects of translational and clinical immunology. Concerning translational aspects, the effort to identify new receptors/ligands involved in the stimulation or inhibition of cytotoxic activity of NK lymphocytes against their targets is continued, with particular focus on tumor cells. Recent studies showed that tumors contain a small proportion of stem cells fostering tumor growth: a very interesting aspect is the study of the expression and function in these cells of ligands for citotoxicity activating receptors expressed by NK lymphocytes. Another project is focused on the inhibitory effect of tumor microenvironment on NK cell function. A related area of study is the role of NK cells from haploidentical donors in the therapy of high-risk acute leukemias in the child, which has already yielded important results of translational and clinical value. An additional field of study will be the antitumoral role of some cytokines with functions of immune response modulation but also binding to tumor cells expressing complementary receptors. These cytokines include members of the superfamily of IL-12 (IL-23, IL-27), of the superfamily of IL-6 (LIF, oncostatin-M), and of that of IL-17 (IL-17A, IL-17B, and IL-25). Experiments will be carried out especially in lymphoid and myeloid hematological tumors using in vitro and in vivo models already developed in previous studies. New modalities of experimental therapy of neuroblastoma will be developed using liposomal targeting techniques based on the identification of molecules expressed by the tumor or its associated endothelium. Clinical immunological studies will be focused on the start of new trials in pediatric patients with juvenile idiopathic arthritis using innovative biological drugs such as anti-inflammatory cytokine monoclonal antibodies. PRINTO network guarantees the recruitment of large numbers of patients and allows the achievement of conclusive results in a short time. In parallel, increasingly accurate criteria will be developed to evaluate the activity of the new tested drugs. Finally, the study of the immunologicalaspects of periodic fever will be continued in order to identify new therapeutic targets.

Principal investigators
Prof. Cristina Bottino – Laboratory of Clinical and Experimental Immunology
Prof. Alberto Martini – Pediatric Rheumatology
Dr. Vito Pistoia – Laboratory of Oncology

Activity year 2013

Laboratory of Clinical and Experimental Immunology - *Director: Prof. Cristina Bottino*
Hemopoietic stem cell transplantation from haploidentical donors (haplo-HSCT) in leukemia patients: identification of HSC optimal donor through analysis of KIR and HLA class I genotype/phenotype in potential donors and in the recipient.
Trans-endothelization of monocytes: identification of the inhibitory role of CD300a.
Characterization of dendritic cells that migrate to secondary lymphoid organs.

Autoimmune lymphoproliferative syndrome (ALPS): identification of rare variants of the UNC13D gene as risk factors for the development of ALPS.
Pelizaeus-Merzbacher leucodystrophy: in vitro correction with antisense oligonucleotides of PLP1 splicing defect.
Analysis of immunoregulatory effects of mesenchymal stem cells.
Origin of decidual NK cells: demonstration in the murine model of the migration of hemopoietic precursors in utero and decidua and of their differentiation into NK cells.
Role of infections in the pathogenesis of diabetes type I: in genetically predisposed subjects, the infection due to coxsakie B4 virus induces the production of autoantibodies that cause apoptosis of beta-pancreatic cells.
Celiac disease: we developed a test able to predict the risk of celiac disease through assay of antibodies against protein Vp7 of Rotavirus.

Pediatric Rheumatology - *Director: Prof. Alberto Martini*
In 2013, thanks to the collaboration with the pediatric rheumatology centres belonging to the Paediatric Rheumatology International Trials Organisation (PRINTO) network (www.printo.it), different academic and sponsored research projects (pharmaceutical industries or governmental bodies) were carried out. In particular, in 2013 PRINTO dealt with the implementation and management of a pharmacovigilance project (Pharmachild) for drugs used in the treatment of juvenile idiopathic arthritis (JIA) (EU grant) with over 3000 patients, the management of different phase III trials with biological drugs (tocilizumab, canakinumab, golimumab) in collaboration with pharmaceutical industries, and the updating of a website for families containing information on rheumatic diseases in over 50 languages.
Our unit was also involved in the development and validation of new parameters for quantitative evaluation of disease activity, functional ability, clinical damage, pain, and quality of life of children with rheumatic diseases, with over 9000 collected cases.
Another activity was the standardization of quantitative evaluation methods of conventional radiology, MRI, and US in rheumatic diseases
In the field of immunology, research was focused on the analysis of the role of adaptive immunity in the pathogenesis of rheumatic diseases. In particular, we started research projects on the impact of innate immunity on the development of TH17 cells, the characterization of the immunological and functional phenotype of the different populations of B cells, and the role of TLRs and purinergic receptors in the process of development of B cells.
Our unit is national reference centre for the diagnosis and treatment of autoinflammatory diseases. In addition, since 2009, our unit has been involved in a EU project (Eurofever) aimed at the creation of a registry of autoinflammatory diseases. From March 2009 to date, samples and clinical data of about 3000 patients with autoinflammatory diseases were collected. Laboratory activities were mainly focused on the pathogenesis of CIAS1-related diseases and on periodic syndromes related to TNF receptors (TRAPS).

Laboratory of Oncology - *Director: Dr. Vito Pistoia*
Two new pre-clinical therapeutic targeting approaches to human neuroblastoma were developed, both based on the use of liposomes. The first study led to the identification of five phage peptides able to react ex vivo with primary neuroblastomas; the same peptides, bound to liposomes, proved to be able to bind both tumor cells and microvessels in a preclinical model of neuroblastoma, delivering the chemotherapeutic drug (doxorubicin) to tumor site and inhibiting significantly its growth. In the second study, we developed a new liposomal formulation of fenretinide, a synthetic retinoid with antitumoral and antiangiogenic activity,

poorly water-soluble and rapidly metabolized. Thanks to this new formulation, in which liposomes containing fenretinide were coated with NGR peptides able to bind to aminopeptidase N expressed by tumor vessels, it was possible to inhibit significantly in vivo growth of human neuroblastoma through anti-angiogenic and anti-tumoral vessels.
A new prec.linical protocol of immunotherapy of immunotherapy of neuroblastoma with T γδ lymphocytes activated by zoledronic acid (ZOL) was developed. ZOL is an amino-biphosphonate used in the therapy of osteoporosis and bone metastases able to stimulate selectively the proliferation of T Vγ9δ2 lymphocytes and to sensitize tumor cells to the cytotoxic activity of these lymphocytes. In vivo infusion of T Vγ9δ2 lymphocytes with ZOL inhibited significantly neuroblastoma growth with a combination of antitumoral and antiangiogenic effects whose mechanisms have been identified.
We identified the role of BAFF, a molecule essential for survival and differentiation of B lymphocytes and characteristic, though not exclusive, in lymphoid neogenesis of cases of localized neuroblastoma associated with opsoclonus-myoclonus syndrome (OMS), a rare and invalidating paraneoplastic syndrome.
Finally, the proteome of exosomes was first characterized. Exosomes are nanovesicles derived from multivesicular bodies and secreted in the extracellular environment, isolated from some neuroblastoma cell lines; molecules as CD133, CD147, and CD276, involved in tumor growth and progression, were identified.

Publications year 2013

1) **Pistoia Vito.**
   A message from the new editor of immunology letters.
   2013; 149: A1.
   IF: 2.337 Normalized IF: 2
2) **Orecchia P., Conte R., Balza E., Petretto Andrea, Mauri PL., Mingari MC., Carnemolla B.**
   A novel human anti-syndecan-1 antibody inhibits vascular maturation and tumour growth in melanoma.
   Eur J Cancer. 2013; 49: 2022-2033.
   IF: 5.061 Normalized IF: 3
3) **Dolcino Marzia, Zanoni G., Bason C., Tinazzi E., Boccola E., Valletta E., Contreas G., Lunardi C., Puccetti Antonio.**
   A subset of anti-rotavirus antibodies directed against the viral protein VP7 predicts the onset of celiac disease in the intestinal epithelial cell line T84.
   IMMUNOL RES 2013; 56: 465-476.
   IF: 2.963 Normalized IF: 4
4) **Lovell DJ., Ruperto Nicolino, Giannini EH., Martini Alberto.**
   Advances from clinical trials in juvenile idiopathic arthritis.
   NAT REV RHEUMATOL 2013; 9: 557-563.
   IF: 9.745 Normalized IF: 8
5) **Norell H., Moretta A., Silva-Santos B., Moretta Lorenzo.**
   At the Bench: preclinical rationale for exploting NK cells and alpha delta T lymphocytes for the treatment of high-risk leukemias.
   J Leukoc Biol. 2013; 94: 1123-1139.
   IF: 4.568 Normalized IF: 6
6) **Di Prisco S., Merega E., Milanese M., Summa M., Casazza S., Raffaghello Lizzia, Pistoia Vito, Uccelli A., Pittaluga A.**

CCL5-glutamate interaction in central nervous system: early and acute presynaptic defects in EAE mice.
Neuropharmacology. 2013; 75: 337-346.
IF: 4.114 Normalized IF: 3

7) **Benelli R., Venè R., Minghelli Simona, Carlone S., Gatteschi B., Ferrari N.**
Celecoxib induces proliferation and Amphiregulin production in colon subepithelial myofibroblasts, activating erk1-2 signaling in synergy with EGFR.
CANCER LETT 2013; 328: 73-82.
IF: 4.258 Normalized IF: 3

8) **Puxeddu I., Bongiorni F., Chimenti D., Capecchi R., Bombardieri S., Moretta A., Bottino Cristina, Migliorini P.**
Cell surface expression of activating receptors and co-receptors on peripheral blood NK cells in mixed cryoglobulinemia.
JOINT BONE SPINE 2013; 80: 104-114.
IF: 2.748 Normalized IF: 2

9) **Spaggiari GM., Moretta Lorenzo.**
Cellular and molecular interactions of mesenchymal stem cells in innate immunity.
IMMUNOL CELL BIOL 2013; 91: 27-31.
IF: 3.925 Normalized IF: 6

10) **Ladenstein R., Weixler S., Baykan B., Bleeke M., Kunert R., Katinger D., Pribill I., Glander P., Bauer S., Pistoia Vito, Michon J., Garaventa Alberto, Lode HN.**
Ch14.18 antibody produced in CHO cells in relapsed or refractory stage 4 neuroblastoma patients.
MABS-AUSTIN 2013; 5: 801-809.
IF: 5.275 Normalized IF: 3

11) **Capanni C., Bruschi Maurizio, Columbaro M., Cuccarolo P., Ravera S., Dufour Carlo, Candiano Giovanni, Petretto Andrea, Degan P., Cappelli Enrico.**
Changes in vimentin, lamin A/C and mitofilin induce aberrant cell organization in fibroblasts from Fanconi anemia complementation group A (FA-A) patients.
BIOCHIMIE 2013; 95: 1838-1847.
IF: 3.142 Normalized IF: 4

12) **Morandi B., Bonaccorsi I., Mesiti M., Conte R., Carrega P., Costa G., Iemmo R., Martini S., Ferrone S., Cantoni Claudia, Mingari MC., Moretta Lorenzo, Ferlazzo G.**
Characterization of human afferent lymph dendritic cells from seroma fluids.
J Immunol. 2013; 191: 4858-4866.
IF: 5.52 Normalized IF: 3

13) **Papadopoulou C., Kostik M., Gonzalez-Fernandez MI., Bohm M., Nieto-Gonzalez JC., Pistorio Angela, Lanni Stefano, Consolaro Alessandro, Martini Alberto, Ravelli Angelo.**
Delineating the role of multiple intraarticular corticosteroid injections in the management of juvenile idiopathic arthritis in the biologic era.
ARTHRIT CARE RES 2013; 65: 1112-1120.
IF: 3.731 Normalized IF: 6

14) **Schena F., Volpi S., Faliti CE., Penco F., Santi S., Proietti M., Schenk U., Damonte G., Salis A., Bellotti M., Fais F., Tenca C., Gattorno Marco., Martini Alberto, Canossa M., Grossi F., Traggiai E.**
Dependence of immunoglobulin class switch recombination in B on vesicular release of

ATP and CD73 ectonucleotidase activity.
Cell Rep. 2013; 3: 1824-1831.
IF: 0 Normalized IF: 0.05

15) **Marigliano M., Morandi A., Maschio M., Costantini S., Contreas G., D'Annunzio Giuseppe.**
Diabetic ketoacidosis at diagnosis: role of family history and class II HLA genotypes.
Eur J Endocrinol. 2013; 168: 107-111.
IF: 3.136 Normalized IF: 2

16) **Cangemi Giuliana, Pistorio Angela, Miano Maurizio, Gattorno Marco, Acquila Maura, Bicocchi Maria Patrizia, Gastaldi Roberto, Riccardi F., Gatti C., Fioredda Francesca, Calvillo Michaela, Melioli Giovanni, Martini Alberto, Dufour Carlo.**
Diagnostic potential of hepcidin testing in pediatrics.
EUR J HAEMATOL 2013; 90: 323-330.
IF: 2.548 Normalized IF: 4

17) **Celebi-Tayfur A., Bilginer Y., Finetti M., Gattorno Marco, Ozen S.**
Different presentations in patients with tumor necrosis factor receptor-associated periodic syndrome mutations: report of two cases.
TURKISH J PEDIATR 2013; 55: 78-81.
IF: 0.558 Normalized IF: 0.5

18) **Di Paolo Daniela, Pastorino Fabio, Zuccari G., Caffa I., Loi Monica, Marimpietri Danilo, Brignole Chiara, Perri P., Cilli M., Nico B., Ribatti D., Pistoia Vito, Ponzoni Mirco, Pagnan G.**
Enhanced anti-tumor and anti-angiogenic efficacy of a novel liposomal fenretinide on human neuroblastoma.
J CONTROL RELEASE 2013; 170: 445-451.
IF: 7.633 Normalized IF: 8

19) **Solari N., Palmisani E., Consolaro Alessandro, Pistorio Angela, Viola Stefania, Buoncompagni Antonella, Gattorno Marco, Picco Paolo Pietro, Ruperto Nicolino, Malattia Clara, Martini Alberto, Ravelli Angelo.**
Factors associated with achievement of inactive disease in children with juvenile idiopathic arthritis treated with etanercept.
J RHEUMATOL 2013; 40: 192-200.
IF: 3.258 Normalized IF: 4

20) **Sechi A., Deroma L., Lapolla A., Paci S., Melis D., Burlina A., Carubbi F., Rigoldi M., Di Rocco Maja.**
Fertility and pregnancy in women affected by glycogen storage disease type I, results of a multicenter Italian study.
J INHERIT METAB DIS 2013; 36: 83-89.
IF: 4.07 Normalized IF: 6

21) **Frassoni Francesco, Locatelli F., Moretta Lorenzo.**
Foreword. New frontiers in molecular and cellular therapy.
Immunol Lett. 2013; 155: 1.
IF: 2.337 Normalized IF: 2

22) **Montaldo E., Del Zotto Genny, Della Chiesa M., Mingari MC., Moretta A., De Maria A., Moretta Lorenzo.**
Human NK cell receptors/markers: a tool to analyze NK cell development, subsets and function.

CYTOM PART A 2013; 83A: 702-713.
IF: 3.711 Normalized IF: 6

23) **Storti P., Bolzoni M., Donofrio G., Airoldi Irma, Guasco D., Toscani D., Martella E., Lazzaretti M., Mancini C., et al.**
Hypoxia-inducible factor (HIF)-1alpha suppression in myeloma cells blocks tumoral growth in vivo inhibiting angiogenesis and bone destruction.
LEUKEMIA 2013; 27: 1697-1706.
IF: 10.164 Normalized IF: 4

24) **Benelli R., Stigliani S., Minghelli Simona, Carlone S., Ferrari N.**
Impact of CXCL1 overexpression on growth and invasion of prostate cancer cell.
PROSTATE 2013; 73: 941-951.
IF: 3.843 Normalized IF: 3

25) **Ruperto Nicolino, Vesely R., Saint-Raymond A., Martini Alberto.**
Impact of the European paediatric legislation in paediatric rheumatology: past, present and future.
Ann Rheum Dis. 2013; 72: 1893-1896.
IF: 9.111 Normalized IF: 8

26) **Omenetti A., Federici S., Gattorno Marco.**
Inherited autoinflammatory diseases: a critical digest of the recent literature.
Clin Exp Rheumatol 2013; 31: S118-S126.
IF: 2.655 Normalized IF: 4

27) **Morandi Fabio, Venturi C., Rizzo R., Castellazzi M., Baldi E., Caniatti ML., Tola MR., Granieri E., Fainardi E., Uccelli A., Pistoia Vito.**
Intrathecal soluble HLA-E correlates with disease activity in patients with multiple sclerosis and may cooperate with soluble HLA-G in the resolution of neuroinflammation.
J NEUROIMMUNE PHARM 2013; 8: 944-955.
IF: 3.802 Normalized IF: 6

28) **Consolaro Alessandro, Ravelli Angelo.**
It is worth including assessment of disease activity state in juvenile arthritis clinical trials.
ARTHRIT CARE RES 2013; 65: 1207-1210.
IF: 3.731 Normalized IF: 6

29) **Falco Michela, Moretta Lorenzo, Moretta A., Bottino Cristina.**
KIR and KIR ligand polymorphism: a new area for clinical applications?
Tissue Antigens. 2013; 82: 363-373.
IF: 2.753 Normalized IF: 6

30) **Marcenaro E., Pesce S., Sivori S., Carlomagno S., Moretta Lorenzo, Moretta A.**
KIR2DS1-dependent acquisition of CCR7 and migratory properties by human NK cells interacting with allogeneic HLA-C2+ DCs or T-cell blasts.
Blood 2013; 121(17): 3396-3401.
IF: 9.06 Normalized IF: 4

31) **Di Carlo E., Bocca Paola, Emionite L., Cilli M., Cipollone G., Morandi Fabio, Raffaghello Lizzia, Pistoia Vito, Prigione Ignazia.**
Mechanisms of the antitumor activity of human Vgamma9Vdelta2 T cells in combination with zoledronic acid in a preclinical model of neuroblastoma.
MOL THER 2013; 21(5): 1034-1043.
IF: 7.041 Normalized IF: 8

32) **Papadopoulou C., Kostik M., Bohm M., Nieto-Gonzalez JC., Gonzalez-Fernandez MI., Pistorio Angela, Martini Alberto, Ravelli Angelo.**

Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis.
J PEDIATR-US 2013; 163: 879-884.
IF: 4.035 Normalized IF: 6

33) Malattia Clara, Consolaro Alessandro, Pederzoli Silvia Maria, Madeo A., Pistorio Angela, Mazzoni M., Mattiuz Chiara, Magnano Gian Michele, Viola Stefania, Buoncompagni Antonella, Palmisani E., Hasija R., Ruperto Nicolino, Ravelli Angelo, Martini Alberto.
MRI versus conventional measures of disease activity and structural demage in evaluating treatment efficacy in juvenile idiopathic arthritis.
ANN RHEUM DIS 2013; 72: 363-368.
IF: 9.111 Normalized IF: 8

34) Marras Francesco, Nicco E., Bozzano F., Di Biagio A., Dentone C., Pontali E., Boni S., Setti M., Orofino G., Mantia E., Bartolacci V., Bisio Francesca, Riva A., Biassoni Roberto, Moretta Lorenzo, De Maria A.
Natural killer cells in HIV controller patients express and activated effector phenotype and do not up-regulate NKp44 on IL-2 stimulation.
P NATL ACAD SCI USA 2013; 110: 11970-11975.
IF: 9.737 Normalized IF: 8

35) Vacca Paola, Mingari MC., Moretta Lorenzo.
Natural killer cells in human pregnancy.
J REPROD IMMUNOL 2013; 97: 14-19.
IF: 2.342 Normalized IF: 2

36) Carotenuto M., Pedone E., Diana D., De Antonellis P., Dzeroski S., Marino N., Navas L., Di Dato V., Scoppettuolo MN.., Pastorino Fabio, Ponzoni Mirco, et al.
Neuroblastoma tumorigenesis is regulated through the Nm23-H1/h-Prune C-terminal interaction.
Sci Rep. 2013; 3: 1351.
IF: 2.927 Normalized IF: 3

37) Castriconi R., Dondero A., Bellora F., Moretta Lorenzo, Catellano A., Locatelli F., Corrias Maria Valeria, Moretta A., Bottino Cristina.
Neuroblastoma-derived TGF-beta1 modulates the chemokine receptor of human resting NK cells.
J IMMUNOL 2013; 190: 5321-5328.
IF: 5.52 Normalized IF: 6

38) Frassoni Francesco, Cilloni D., Podestà M.
New possibilities to exploit the potentiality of cord blood cells in the context of transplantation.
Immunol Lett. 2013; 155: 24-26.
IF: 2.337 Normalized IF: 2].

39) Vacca P., Martini S., Garelli V., Passalacqua G., Moretta Lorenzo, Mingari MC.
NK cells from malignant pleural effusions are not anergic but produce cytokines and display strong antitumor activity on short-term IL-2 activation.
EUR J IMMUNOL 2013; 43: 550-561.
IF: 4.97 Normalized IF: 3

40) Loi Monica, Di Paolo Daniela, Soster M., Brignole Chiara, Bartolini A., Emionite L., Sun J., Becherini Pamela, Curnis F., Petretto Andrea, Sani M., Gori A., Milanese M., Gambini Claudio, Longhi R., Cilli M., Allen TM., Bussolino F., Arap W., Pasqualini R.,

Corti A., Ponzoni Mirco, Marchio S., Pastorino Fabio.
Novel phage display-derived neuroblastoma-targeting peptides potentiate the effects of drug nanocarriers in preclinical settings.
J CONTROL RELEASE 2013; 170: 233-241.
IF: 7.633 Normalized IF: 8

41) Consolaro Alessandro, Ravelli Angelo.
Paediatric Rheumatology: Juvenile idiopathic arthritis-Are biologic agents effective for pain?
NAT REV RHEUMATOL 2013; 9: 447-448.
IF: 9.745 Normalized IF: 8

42) Malattia Clara, Martini Alberto.
Paediatric-onset systemic lupus erythematous.
Best Pract Res Clin Rheumatol. 2013; 27: 351-362.
IF: 3.55 Normalized IF: 4

43) Di Rocco A., Loggini A., Di Rocco Maja, Di Rocco P., Rossi RP., Gimelli Giorgio, Bazil C.
Paradoxical worsening of seizure activity with pregabalin in an adult with isodicentric 15 syndrome involving duplications of the GABRB3, GABRA5 and GABRG3 genes.
BMC NEUROL 2013; 13: 43.
IF: 2.564 Normalized IF: 2

44) Heatley SL., Pietra G., Lin J., Widjaja JML., Harpur CM., Lester S., Rossjohn J., Szer J., Schwarer A., Bradstock K., Bardy PG., Mingari MC., Moretta Lorenzo, Sullivan LC., Brooks AG.
Polymorphism in human cytomegalovirus UL40 impacts on recognition of human leukocyte antigen-E (HLA-E) by natural killer cells.
J BIOL CHEM 2013; 288: 8679-8690.
IF: 4.651 Normalized IF: 3

45) Verazza S., Negro G., Marafon D., Consolaro Alessandro, Martini Alberto, Ravelli Angelo.
Possible discontinuation of therapies after clinical remission in juvenile idiopathic arthritis.
Clin Exp Rheumatol. 2013; 31: S98-S101.
IF: 2.655 Normalized IF: 4

46) Picco Paolo Pietro, D'Alessandro M., Leoni M., Doglio M., Martini Alberto.
Primary red ear syndrome associated with cochleo-vestibular symptomatology: A paediatric case report.
CEPHALALGIA 2013; 33(15): 1277-1280.
IF: 3.485 Normalized IF: 6

47) Marimpietri Danilo, Petretto Andrea, Raffaghello Lizzia, Pezzolo Annalisa, Gagliani C., Tacchetti C., Mauri P., Melioli Giovanni, Pistoia Vito.
Proteome profiling of neuroblastoma-derived exosomes reveal the expression of proteins potentially involved in tumor progression.
PLoS One. 2013; 8: e75054.
IF: 3.73 Normalized IF: 6

48) Marzano AV., Ishak RS., Colombo A., Caroli Francesco, Crosti C.
Pyoderma gangrenosum, acne and suppurative hidradenitis syndrome following bowel bypass surgery.
DERMATOLOGY 2012; 225: 215-219.
IF: 2.024 Normalized IF: 2

49) Picco Paolo Pietro, Naselli A., Pala G., Marsciani A., Buoncompagni Antonella, Martini Alberto.
Recurrent pericarditis in Myhre syndrome.
AM J MED GENET A 2013; 161A: 1164-1166.
IF: 2.304 Normalized IF: 2

50) Della Casa Alberighi Ornella, Barrett JS., Laer S., Meibohm B.
Response to "Physiologically based pharmacokinetic modeling at the extremes of age".
CLIN PHARMACOL THER 2013; 93(2): 149.
IF: 6.846 Normalized IF: 3

51) Gattorno Marco, Martini Alberto.
Review: Beyond the NLRP3 inflammasome.
ARTHRITIS RHEUM-US 2013; 65: 1137-1147.
IF: 7.477 Normalized IF: 8

52) Kaplan P., Baris H., De Meirleir L., Di Rocco Maja, et al.
Revised recommendations for the management of Gaucher disease in children.
EUR J PEDIATR 2013; 172: 447-458.
IF: 1.907 Normalized IF: 2

53) Raffaghello Lizzia, Fuhlhuber V., Bianchi Giovanna, Conte Massimo, Blaes F., Gambini Claudio, Pistoia Vito.
Role of BAFF in opsoclonus-myoclonus syndrome, a bridge bertween cancer and autoimmunity.
J LEUKOCYTE BIOL 2013; 94: 183-191.
IF: 4.568 Normalized IF: 6

54) Zannin ME., Birolo C., Gerloni V., Miserocchi E., Pontikaki I, Paroli MP., Bracaglia C., Shardlow A., Parentin F., Cimaz R., Simonini G., Falcini F., Corona F., Viola Stefania, et al.
Safety and efficacy of Infliximab and Adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry.
J Rheumatol. 2013; 40: 74-79.
IF: 3.258 Normalized IF: 2

55) Parodi S., Fontana V., Haupt Riccardo, Corrias Maria Valeria.
Seasonal variations of date of diagnosis and birth for neuroblastoma patients in Italy.
CANCER EPIDEMIOL 2013; 37: 575-578.
IF: 2.232 Normalized IF: 4

56) Morandi Fabio, Pistoia Vito.
Soluble HLA-G modulates miRNA-210 and miRNA-451 expression in activated CD4+T lymphocytes.
INT IMMUNOL 2013; 25(5): 279-285.
IF: 3.135 Normalized IF: 4

57) Bisio Francesca, Bozzano F., Marras Francesco, Di Biagio A., Moretta Lorenzo, De Maria A.
Successfully treated HIV-infected patients have differential expression of NK cell receptors (NKp46 and NKp30) according to AIDS status at presentation.
IMMUNOL LETT 2013; 152: 16-24.
IF: 2.337 Normalized IF: 2

58) Laurent S., Queirolo P., Boero S., Salvi S., Piccioli P., Boccardo S., Minghelli Simona, Morabito A., Fontanta V., Pietra G., Carrega P., Ferrari N., et al.

The engagement of CTLA-4 on primary melanoma cell lines induces antibody-dependent cellular cytotoxicity and TNF-alpha production.
J TRANSL MED 2013; 11: 108.
IF: 3.459 Normalized IF: 3

59) Carbotti G., Barisione G., Orengo AM., Brizzolara A., Airoldi Irma, Bagnoli M., Pinciroli P., Mezzanzanica D., Centurioni MG., Fabbi M., Ferrini S.
The IL-18 antagonist IL-18-binding protein is produced in the human ovarian cancer microenvironment.
CLIN CANCER RES 2013; 19: 4611-4620.
IF: 7.837 Normalized IF: 4

60) Fiocchi A., Annunziato F., Ass'ad A., Arshad H., Bahna SL., Boyle R., Brozek J., Bush A., Canonica W., Cicardi M., Compalati E., Dahdah L., Dupont C., Finegold I., Fineman S., Grabenhenrich L., Holgate S., Kuitunen M., Lau S., Maggi E., Martelli A., Matricardi P., et al.
The management of paediatric allergy: not everybody's cup of tea - 10-11th February 2012.
CURR OPIN ALLERGY CL 2013; 13(Suppl 1): S1-S50.
IF: 3.398 Normalized IF: 3

61) Lazarevic D., Pistorio Angela, Palmisani E., Miettunen P., Ravelli Angelo, Pilkington C., Wulffraat NM., Malattia C., Garay SM., Hofer M., Quartier P., Dolezalova P., Calvo Penades I., Ferriani VPL., Ganser G., Casapcopur O., Melo-Gomes JA., Reed Am., Wierzbowska M., Rider Mg., Martini Alberto, Ruperto Nicolino.
The PRINTO criteria for clinically inactive disease in juvenile dermatomyositis.
ANN RHEUM DIS 2013; 72: 686-693.
IF: 9.111 Normalized IF: 8

62) Caorsi R., Lepore R., Zulian F., Alessio M., Stabile A., Insalaco A., Finetti M., Battagliese A., Martini G., Bibalo C., Martini Alberto, Gattorno Marco.
The schedule of administration of canakinumab in cryopyrin associated periodic syndrome is driven by the phenotype severity rather than the age.
ARTHRITIS RES THER 2013; 15: R33.
IF: 4.302 Normalized IF: 6

63) Miettunen PM., Pistorio Angela, Palmisani E., Ravelli Angelo, Silverman E., Oliveira S., Alessio M., Cuttica R., Mihaylova D., Espada G., Pasic S., Insalaco A., Ozen S., Porras O., Sztajnbok F., Lazarevic D., Martini Alberto, Ruperto Nicolino.
Therapeutic approaches for the treatment of renal disease in juvenile systemic lupus erythemotosus: an international multicentre PRINTO study.
ANN RHEUM DIS 2013; 72: 1503-1509.
IF: 9.111 Normalized IF: 8

64) Lanni S., Wood M., Ravelli Angelo, Magni Manzoni S., Emery P., Wakefield RJ.
Towards a role of ultrasound in children with juvenile idiopathic arthritis.
RHEUMATOLOGY 2013; 52: 413-420.
IF: 4.212 Normalized IF: 3

65) Ghavampour S., Lange C., Bottino Cristina, Gerke V.
Transcriptional profiling of human monocytes identifies the inhibitory receptor CD300a as regulator of transendothelial migration.
PLOS ONE 2013; 8: e73981.
IF: 3.73 Normalized IF: 3

66) **ter Haar N., Lachmann H., Ozen S., Woo P., Uziel Y., Modesto C., Koné-Paut I., Canterini L., Insalaco A., Neven B., Hofen M., Rigante D., Al-Mayouf S., Touitou I., Gallizzi R., Papadopoulou-Alataki E., Martino S., Kuemmerle-Deschner J., Obici L., Jagaru N., Simon A., Nielsen S., 0, Ruperto Nicolino, Gattorno Marco, Frenkel J.**
Treatment of autoinflammatory diseases: results from the Eurofever Registry and literature review.
ANN RHEUM DIS 2013; 72: 678-685.
IF: 9.111 Normalized IF: 8

67) **Magni-Manzoni S., Scirè CA., Ravelli Angelo, Klersy C., Rossi S., Muratore V., et al.**
Ultrasound-detected synovial abnormalities are frequent in clinically inactive juvenile idiopathic arthritis, but do not predict a flare of synovitis.
ANN RHEUM DIS 2013; 72: 223-228.
IF: 9.111 Normalized IF: 4

68) **Montaldo E., Vacca P., Moretta Lorenzo, Mingari C.**
Understanding human NK cell differentiation: clues for improving the haploidentical hematopoietic stem cell transplantation.
Immunol Lett. 2013; 155: 2-5.
IF: 2.337 Normalized IF: 1

69) **Kallinich T., Gattorno Marco, Grattan CE., de Koning HD., Traidl-Hoffmann C., Feist E., Krause K., Lipsker D., Navarini AA., et al.**
Unexplained recurrent fever: when is autoinflammation the explanation?
Allergy 2013; 68: 285-296.
IF: 5.883 Normalized IF: 6

Research line 4
Oncohematology and cell therapies

Title
Recent advances in the diagnostics and treatment of hematologic and oncologic diseases

Coordinators
Dr. Francesco Frassoni, Dr. Alberto Garaventa

Project description (outline and objectives)
Research activity in these fields are based on the development of new diagnostic and therapeutic approaches in pediatric solid tumors (in particular the study of new antiblastic drugs in neuroblastoma and brain tumors), acute leukemias, hemophagocytic syndromes, and bone marrow failure in children, for which disease registries were implemented. In the field of HSCT, we studied in depth new immunosuppressive medications and approaches, cell manipulations (alpha/beta depletion in haploidentical transplantation, intraosseous transplantation, and positive selection of hemopoietic progenitors, extracorporeal photo-apheresis), and the production of pathogen-specific lymphocytes for therapeutic use in humans. In subjects receiving transplantation, we studied the differences in genes correlated to self-renewal in cells from patients transplanted with different sources of hematopoietic cells (bone marrow vs cord blood). Subjects undergoing chemo-radiotherapy and/or immunosuppresive treatment have a high incidence of infectious complications, that can be very severe and require intense supportive therapies for which accurate monitoring of the etiology of bacterial and fungal infections was performed, with particular focus on the emergence of drug-resistant strains. Thanks to modern treatments, the population of childhood cancer survivors is rapidly increasing, and therefore particular attention has been paid to the clinical follow-up of these off-therapy subjects and to the study of the reduction of late effects of RT for brain tumor after the introduction of high precision methods (Tomotherapy). Blood stem cells of tumor survivors undergoing or not hemopoietic progenitor cell transplantation were studied for aging markers and predisposition to second tumors, immune system, and hematologic reconstitution. Finally, we evaluated new health care modalities in patients with congenital coagulopathies and the possibility of extending new health care modalities, such as home care, to non hemato-oncologic diseases.

Principal investigators
Dr. Giorgio Dini/Dr. Francesco Frassoni – Oncology, Hematology, and Bone Marrow Transplantation
Dr. Elio Castagnola – Infectious Diseases
Dr. Gino Tripodi – Immunohematology and Transfusion Medicine
Dr. Francesco Frassoni – Laboratory of post-natal stem cells and cell therapies

Activity year 2013

Oncology, Hematology, and Bone Marrow Transplantation - *Director*: *Dr. Giorgio Dini/Dr. Francesco Frassoni*

- We continued the recruitment of candidate patients and patients undergoing allogenic HSCT from volunteer donor (total number = 260) and of patients with solid tumors (neuroblastoma, n=404; brain tumors, n=195). We also continued the recruitment in the transplant programme of patients with non-neoplastic diseases (Fanconi's anemia=27, severe bone marrow aplasia=42, congenital errors and thalassemia= 84). Patients with acute Graft versus Host Disease refractory to first line therapy were treated according to

prospective therapeutic protocols using monoclonal antibodies (anti rTNFα; 20 patients recruited in the study), lymphophotoapheresis.

- In a group of patients eligible for haploidentical HSCT, we are carrying out a project using the post-HSCT cyclophosphamide platform (in the absence of cell manipulation) (cases performed =5).
- In 2013, we passed the audit for the confirmation of JACIE accreditation obtained for our Transplantation Programme in 2011.
- We completed the European study for the prophylaxis of venoocclusive disease in pediatric patients at higher risk of this complication.
- In collaboration with the Infectious Disease unit, we completed some studies on infectious complications in subjects undergoing HSCT.
- We promoted and participated in Italian and European clinical studies on some acute and late complications in patients undergoing HSCT and we participated in the development of guidelines for the preservation of fertility.
- We promoted and managed refresher courses at Gaslini on the main critical issues in the hemato-oncologic patient undergoing HSCT.

Clinical and Experimental Hematology – *Director: Dr. Carlo Dufour*

Study of p38MAPK inhibitors in bone marrow injury in patients with Fanconi's anemia (continued).
Study on the effects of antioxidants on Fanconi's cells (continued).
Genetic study of Italian patients with Fanconi's anemia (completed).
Study on viral inclusion in the genome of patients with Fanconi's anemia (completed).
Italian registry of neutropenias (sited at Gaslini) (implemented).
Study on the outcome of Italian patients with genetic neutropenia (completed).
Study on the outcome of 537 adolescent patients with acquired bone marrow aplasia in collaboration with EBMT (completed).
Enrolment of patients with resistant acute leukemia in experimental clinical protocols (Midostaurin, Clofarabin) (implemented).

Clinical Oncology – *Director: Dr. Alberto Garaventa*

We completed the European study for the treatment of inoperable neuroblastoma and the study of the Italian neuroblastoma adult case series and on the cases of spinal compression. We also completed the study on single micturition urine markers for the diagnosis of neuroblastoma.
We participated in the DOPO project concerning patients surviving after treatment for tumor in pediatric age. It is a project for surveillance and management of medium- and long-term sequelae due to treatment. The DOPO project is still ongoing and is carried out in collaboration with the other units of the department of pediatric hematology/oncology.
We are carrying out some projects on neuroblastoma aimed at identifying new prognostic factors and innovative therapeutic modalities, and we are performing phase I and II studies on new antiblastic drugs in pediatric oncology.

Infectious Diseases - *Director*: *Dr. Elio Castagnola*

We completed and analyzed the epidemiologic study on bacteremias and invasive fungal infections in children undergoing allogenic bone marrow transplantation, showing how acute Graft versus Host Disease (aGvHD) (equivalent to transplant rejection) is an essential factor for the development of invasive fungal infection. In fact, the more severe was this complication, the higher was the incidence of fungal infections. This data was confirmed also by a cooperative prospective study of the Italian Bone Marrow Transplantation Group (BMT), in which the Istituto Gaslini participated (Infectious Disease unit, Hematology/Oncology unit,

BMT unit). Concerning bacteremias, data of the Istituto Gaslini showed that, in BMT, a lower donor-recipient compatibility was associated with a higher incidence of bacteriemias, while aGvHD did not seem to play an important role in the development of this complication. These data have an important impact on the choice of prophylactic, diagnostic, and/or therapeutic strategies in patients receiving BMT.
We continued the epidemiologic studies on antibiotic sensitivity of bacterial strains isolated from blood culture in pediatric patients at risk. The analysis of sensitivity to different drugs performed on methicillin-resistant staphylococci isolated from blood of patients with hemato-oncologic diseases, undergoing surgery, receiving pediatric or neonatal intensive care, and/or hospitalized in the Infectious Disease unit showed that strains with reduced sensitivity to vancomycin tended to increase. The analysis of the efficacy of alternative drugs showed that a considerable percentage of these strains had a reduced sensitivity also to alternative drugs such as daptomycin and linezolid. This data is important for the definition of therapeutic strategies.
Finally, we continued the collection of data on antibiotic sensitivity of Gram-negative bacteria isolated in urine culture and on the etiology and localization of yeast infections in patients hospitalized at the Istituto G. Gaslini. In addition, we continued the observational studies on invasive fungal infections, both in collaboration with the Italian Association of Pediatric Hematology-Oncology (AIEOP) and with the international study group on fungal infections (Pediatric Fungal Network, PFN). The analysis of these case series, after the recruitment of an appropriate number of subjects, is likely to yield important results for the clinical management of patients.

Immunohematology and Transfusion Medicine - *Director*: *Dr. Gino Tripodi*
The presence of high sHLA-I concentrations in many products (immunoglobulins, conserved blood components, blood put in contact with biocompatible plastic surfaces during apheretic procedures) seems to be involved in the induction of a series of modulating effects (transfusion-related immunomodulation - TRIM) when transfused/infused intravenously. There are significant differences in importance and type of documentable TRIM in patients after infusion of high amounts of sHLA-I. The CD8 soluble molecule (sCD8) is able to bind to biological membranes and to sHLA-I molecules, and therefore it could play a role in modulating sHLA-I-mediated TRIM.
We compared sCD8 levels in the plasma of patients with similar underlying disease but regularly transfused with two different blood components (pre- and post-storage unwashed leucodepleted erythrocyte concentrations with low and high sHLA-I concentrations, respectively). In addition, we studied sFasL and sHLA-I concentrations in autologous platelet concentrates (prepared for topical use using three different modalities) to evaluate whether they were able to induce TRIM via sHLA-I.
In the plasma of patients transfused with post-storage unwashed leucodepleted erythrocyte concentrates (containing significantly higher sHLA-I levels), significantly higher levels of circulating sCD8 were measured.
In autologous platelet concentrates derived from three preparation modalities, sFasL and sHLA-I levels resulted very low, much lower than those detectable in all available blood derivatives.
Though based on indirect evidence, our results describe a new role of sCD8 molecules as possible actors in sHLA-I-mediated TRIM.
In addition, the study of sFasL and sHLA-I concentrations in autologous platelet concentrates for topical use seems to exclude that these blood components can induce TRIM.

Laboratory of post-natal stem cells and cell therapies – *Director*: *Dr. Francesco Frassoni*

Evaluation of the expression of genes involved in self-renewal before and after transplantation, reconstitution of hemopoietic progenitors in adult and pediatric subjects

The principle on which HSCT is based is stem cell ability to expand and maintain stable values of WBC, RBC, and platelets throughout the recipient's lifetime. However, different scientific data (serial transplantation in the murine model, long-term reconstitution in bone marrow transplantation) show that this forced expansion leads to a limited reconstitution of the stem cell reservoir. Since transplantation leads to an about 2 log expansion of stem cells for adult bone marrow (BM) and to 3 log expansion for cord blood (CB), it is clear that stem cells undergo changes in their gene expression supporting this phenomenon. Aim of the study is to identify involved genes, type and duration of changes, whether these changes are influenced by the transplanted tissue (i.e. CB or BM) and/or by the recipient's age, and whether hemopoietic stem cells grow old after transplantation.

Basal gene expression was evaluated on selected CD34+ cells from cord blood (CB) and bone marrow (BM) of healthy adult and pediatric subjects; IPS cells were used as positive control. Our samples included CD34 cells of patients (adults and children) transplanted with BM or CB at different time intervals from transplantation (+30,+ 90, +180, +360 days). The method used was low-density TaqMan-based CARDs on which 93 genes involved in cell cycle regulation, proliferation, differentiation, and self-renewal were selected. The analysis of the corresponding proteins was performed on CD34+ cells stained with corresponding fluoresceinated antibodies; they were quantified with confocal microscopy.

Ten self-renewal genes, among which are Nanog, Oct4, and Sox2, with significantly different expression compared to hemopoietic stem cells before and after transplant, were identified. In particular, these genes result overexpressed in transplanted cord blood cells compared to their basal values, differently from the same genes that show significantly lower expression after transplantation in adult hemopoietic cells.

Surprisingly, these levels of expression are maintained over time, even when the hemopoietic system results completely reconstituted and functions according to standard maintenance levels.

Publications year 2013

1. **Cesaro S., Tintori V., Nesi F., Schiavello E., Calore E., Dallorso Sandro, Migliavacca M., Capolsini I., Desantis R., Caselli D., Fagioli F., Luksch R., Panizzolo I., Tridello G., Prete A.**
   A prospective study on the efficacy of mobilization of autologous peripheral stem cells in pediatric oncohematology patients.
   TRANSFUSION 2013; 53: 1501-1509.
   IF: 3.526 Normalized IF: 2
2. **Satgè D., Stiller CA., Rutkowski S., von Bueren AO., Lacour B., Sommelet D., Nishi, Massimino N., Garre' Maria Luisa, Moreno F., et al.**
   A very rare cancer in Down syndrome: medulloblastoma. Epidemiological data from 13 countries.
   J NEURO-ONCOL 2013; 112: 107-114.
   IF: 3.115 Normalized IF: 2
3. **Cilloni D., Carturan S., Bracco E., Campia V., Rosso V., Torti D., Calabrese C., Gaidano V.., Frassoni Francesco, Saglio G.**

Aberrant activation of ROS1 represents a new molecular defect in chronic myelomonocytic leukemia.
Leuk Res. 2013; 37: 520-530.
IF: 2.764 Normalized IF: 2

4. **Thiel U., Koscielniak E., Blaeschke F., Grunewald TGP., Badoglio M., Diaz MA., Paillard C., Prete A., Ussowicz M.., Faraci Maura.**
Allogeneic stem cell transplantation for patients with advanced rhabdomyosarcoma: a retrospective assessment.
Br J Cancer. 2013; 109: 2523-2532.
IF: 5.082 Normalized IF: 3

5. **Ha CT., Spreafico F., Graf N., Dallorso Sandro, Dome JS., Malogolowkin M., Furtwangler R., Hale JP., Moroz V., Machin D., Pritchard-Jones K.**
An international strategy to determine the role of high dose therapy in recurrent Wilms' tumour.
EUR J CANCER 2013; 49: 194-210.
IF: 5.061 Normalized IF: 3

6. **Perseghin P., Marchetti M., Messina C., Mazzoni A., Carlier P., Perotti C., Salvaneschi L., Risso Marco, Fanin R., Olivieri A., Accorsi P., Locatelli F., Bacigalupo A., Pierelli L., Bosi A.**
Best practice recommendations in: (1) peripheral clood stem cell mobilization and collection and (2) acute and chronic GvHd treatment using extracorporeal photopheresis. A joint effort from SIdEM (Società Italiana di Emaferesi e Manipolazione Cellulare).
TRANSFUS APHER SCI 2013; 48: 195-196.
IF: 1.225 Normalized IF: 0.5

7. **Buzzi E., Manzoni P., Castagnola Elio, Benjamin DK., Beghini R., Dall'Agnola A.**
Candida pneumonia in a term infant after prolonged use of inhaled corticosteroids for bronchopulmonary dysplasia.
EARLY HUM DEV 2013; 89S1: S62-S63.
IF: 2.02 Normalized IF: 2

8. **Castagnola Elio, Moroni Cristina, Bandettini Roberto, Caprino Daniela, Haupt Riccardo.**
Ciprofloxacin prophylaxis in children with acute leukemia in an era of increasing antibiotic resistence.
PEDIATR INFECT DIS J 2013; 32: 581.
IF: 3.569 Normalized IF: 3

9. **Castagnola Elio, Mikulska M., Barabino Paola, Lorenzi Ines, Haupt Riccardo, Viscoli C.**
Current research in empirical therapy for febrile neutropenia in cancer patients: what should be necessary and what is going on.
EXPERT OPIN EMERG DR 2013; 18(3): 263-278.
IF: 2.483 Normalized IF: 4

10. **Bracco E., Rosso V., Serra A., Carnuccio F., Gaidano V., Nicoli P., Musto P., Saglio G., Frassoni Francesco, Cilloni D.**
Design and application of a novel PNA probe for the detection at single cell level of JAK2 mutation in myeloproliferative neoplasms.
BMC Cancer. 2013; 13: 348.
IF: 3.333 Normalized IF: 2

11. **Lo Nigro L., Mirabile E., Tumino M., Caserta C., Cazzaniga G., Rizzari C., Silvestri D.., Micalizzi Concetta, et al.**
    Detection of PICALM-MLLT10 (CALM-AF10) and outcome in children with T-lineage acute lymphoblastic leukemia.
    Leukemia 2013; 27: 2419-2421.
    IF: 10.164 Normalized IF: 4
12. **Ma Y., Dobbins SE., Sherborne AL., Chubb D., Galbiati M., Cazzaniga G., Micalizzi Concetta, Tearle R., Lloyd A.L.O, Hain R., Houlston RS.**
    Developmental timing of mutations revealed by whole-genome sequencing of twins with acute lymphoblastic leukemia.
    P NATL ACAD SCI USA 2013; 110(18): 7429-7433.
    IF: 9.737 Normalized IF: 4
13. **Rovò A., Tichelli A., Dufour Carlo.**
    Diagnosis of acquired aplastic anemia.
    BONE MARROW TRANSPL 2013; 48: 162-167.
    IF: 3.541 Normalized IF: 4
14. **Forni GL., Podesta' Marina, Musso M., Piaggio G., Musallam KM., Balocco M., Pozzi S., Rosa A., Frassoni Francesco.**
    Differential effects of the type of iron chelator of the absolute number of hematopoietic peripheral progenitors in patients with beta-thalassemia major.
    Haematologica 2013; 98: 555-559.
    IF: 5.935 Normalized IF: 6
15. **Phillips B., Ranasinghe N., Stewart LA., for the PICNICC Collaboration, Castagnola Elio.**
    Ethical and regulatory considerations in the use of individual participant data for studies of disease prediction.
    ARCH DIS CHILD 2013; 98: 567-568.
    IF: 3.051 Normalized IF: 1.2
16. **De Ioris, Prete A., Cozza R., Podda M.1, Manzitti Carla, Pession A., Schiavello E., Contoli B., Balter R., Fagioli F., Bisogno G., Amoroso Loredana, Locatelli F., Luksch R.**
    Ewing sarcoma of the bone in children under 6 years of age.
    PLOS ONE 2013; 8: e53223.
    IF: 3.73 Normalized IF: 3
17. **Ricciardolo FLM., Sabatini Federica, Sorbello V., Benedetto S., Defilippi I., Petecchia L., Usai C., et al.**
    Expression of vascular remodelling markers in relation to bradykinin receptors in asthma and COPD.
    THORAX 2013; 68: 803-811.
    IF: 8.376 Normalized IF: 8
18. **Gouw SC., van der Bom JG., Ljung R., Escuriola C., Cid AR., Claeyssens-Donadel S., van Geet C., Kenet G., Makipernaa A., Molinari Angelo C, Muntean W., Kobelt R., Rivard G., Santagostino E., Thomas A., van der Berg HM.**
    Factor VIII products and inhibitor development in severe hemophilia A.
    NEW ENGL J MED 2013; 368: 231-239.
    IF: 51.658 Normalized IF: 7.5

19. **Comar M., Di Rocco D., Cappelli Enrico, Zanotta N., Bottega R., Svahn Johanna, Farruggia P., Misuraca A., Corsolini Fabio, Dufour Carlo, Savoia A.**
Fanconi anemia patients are more susceptible to infection with tumor virus SV40.
PLoS One 2013; 8: e79683.
IF: 3.73 Normalized IF: 6
20. **Dufour Carlo, Svahn Johanna, Bacigalupo A.**
Front-line immunosuppressive treatment of acquired aplastic anemia.
BONE MARROW TRANSPL 2013; 48: 174-177.
IF: 3.541 Normalized IF: 4
21. **Fagioli, Quarello P., Lanino Edoardo, Rognoni C., Balduzzi A., Messina C., Favre C., Foa R., Ripaldi M., et al.**
Hematopoietic stem cell transplantation for children with high-risk acute lymphoblastic leukemia in first complete remission: A report from the AIEOP registry.
HAEMATOL-HEMATOL J 2013; 98(8): 1273-1281.
IF: 5.935 Normalized IF: 3
22. **Korthof ET., Svahn Johanna, Peffault de Latour R., Terranova Maria Paola, Moins-Teisserenc H., Socié G., Soulier J., Kok M., Bredius RGM., van Tol M., Jpo-van der Zijde ECM., Pistorio Angela, Corsolini Fabio, Parodi A., Battaglia F., Pistoia Vito, Dufour Carlo, Cappelli Enrico.**
Immunological profile of Fanconi anemia: a multicentric retrospective analysis of 61 patients.
AM J HEMATOL 2013; 88: 472-476.
IF: 4.138 Normalized IF: 6
23. **Aristei C., Santucci A., Corvò R., Gardani C., Ricardi U., Scarzello G., Magrini SM., Donato V., Falcinelli L., Bacigalupo A., Locatelli F., Aversa F., Barbieri E., Italian TBI Working Group, Dini Giorgio, Faraci Maura.**
In haematopoietics SCT for acute leukemia TBI impacts on relapse but not survival: results of a multicentre observational study.
BONE MARROW TRANSPL 2013; 48: 908-914.
IF: 3.541 Normalized IF: 0.8
24. **Fioredda Francesca, Calvillo Michaela, Burlando O., Riccardi F., Caviglia Ilaria, Tucci F., Bonanomi S., Ghilardi S., Martire B., Farruggia P., Mastrodicasa E., Barone A., Castagnola Elio, Dufour Carlo.**
Infectious complications in children with severe congenital, autoimmune or idiopathic neutropenia: a retrospective study from the Italian Neutropenia Registry.
PEDIATR INFECT DIS J 2013; 32(4): 410-412.
IF: 3.569 Normalized IF: 6
25. **Cangemi Giuliana, Barco Sebastiano, Reggiardo G., Viscardi E., Di Cataldo A., Garaventa Alberto, Melioli Giovanni, Conte Massimo.**
Interchangeability between 24-hour collection and single spot urines for vanillylmandelic and homovanillic acid levels in the diagnosis of neuroblastoma.
PEDIATR BLOOD CANCER 2013; 60: E170-E172.
IF: 2.353 Normalized IF: 6
26. **Rabusin M., Snowden JA., Veys P., Quartier P., Dalle JH., Dhooge C., Di Bartolomeo P., Gonzalez-Vicent M., Gibson B., Iriondo A., Juergens H., Lisukov I., Messina C., Mialou V., Steward CG., Urban C., Renard M., Giurici N., Peters C., Badoglio M., Ronfani L., Dini Giorgio, Farge D., Saccardi R., European Group for Blood and Marrow Transplantation Autoimmune Diseases and Paediatric Disease Working Perties.**

Long-term outcomes of hematopoietic stem cell transplantation for severe treatment-resistant autoimmune cytopenia in children.
BIOL BLOOD MARROW TR 2013; 19: 661-675.
IF: 3.94 Normalized IF: 3

27. **Spreafico F., Gamba B., Mariani L., Collini P., D'Angelo P., Pession A., Di Cataldo A, Indolfi P., Nantron Marilina, Terenziani M., et al.**
Loss of heterozygosity analysis at different chromosome regions in Wilms tumor confirms 1p allelic loss as a marker of worse prognosis: a study from the Italian Association of Pediatric Hematology and Oncology.
J UROLOGY 2013; 189: 260-267.
IF: 3.696 Normalized IF: 3

28. **Ravera E., Vaccaro D., Cuccarolo P., Colulmbaro M., Capanni C., Bartolucci M., Panfoli I., Morelli A., Dufour Carlo, Degan P., Cappelli Enrico.**
Mitochondrial respiratory chain Complex I defects in Fanconi anemia complementation group A.
BIOCHIMIE 2013; 95: 1828-1837.
IF: 3.142 Normalized IF: 4

29. **Cappelli Enrico, Ravera S., Vaccaro D., Cuccarolo P., Bartolucci M., Panfoli I., Dufour Carlo, Degan P.**
Mitochondrial respiratory complex I defects in Fanconi anemia.
TRENDS MOL MED 2013; 19: 513-514.
IF: 9.571 Normalized IF: 8

30. **Ball LM., Bernardo ME., Roelofs H., van Tol MJD., Contoli B., Zwaginga JJ., Avanzini MA., Conforti A., Bertaina A., Frassoni Francesco, et al.**
Multiple infusions of mesenchymal stromal cells induce sustained remission in children with steroid-refractory, grade III-IV acute graft-versus-host disease.
Br J Haematol. 2013; 163: 501-509.
IF: 4.942 Normalized IF: 3

31. **Galbiati M., Lettieri A., Micalizzi Concetta, Songia S., Morerio Cristina, Biondi A., Dufour Carlo, Cazzaniga G.**
Natural history of acute lymphoblastic leukemia in neurofibromatosis type 1 monozygotic twins.
Leukemia 2013; 27: 1778-1781.
IF: 10.164 Normalized IF: 4

32. **Daikeler T., Labopin M., Ruggeri A., Crotta A., Abinun M., Hussein AA., Carlson K., Cornillon J., Diez-Martin J., Gandemer V., Faraci Maura, Lindemans C., O'Meara A., Mialou V., Renard M., Sedlacek P., Sirvent A., Socié G., Sora F., Varotto S., Sanz J., Voswinkel J., Vora A., Yesilipek MA., Heer AL., Gluckman E., Farge D., Rocha V.**
New autoimmune diseases after cord blood transplantation: A retrospective study of EUROCORD and the autoimmune disease working party of the European group for blood and marrow transplantation.
Blood 2013; 121(6): 1059-1064.
IF: 9.06 Normalized IF: 4

33. **Miano Maurizio, Micalizzi Concetta, Calvillo Michaela, Dufour Carlo.**
New targets in pediatric acute myeloid leukemia.
Immunol Lett. 2013; 155: 47-50.
IF: 2.337 Normalized IF: 2

34. **Maury S., Balère-Appert ML., Pollicchieni S., Oneto R., Yakoub-Agha I., Locatelli F., Dalle JH., Lanino Edoardo, Fischer A., Pession A., et al.**
Outcome of patients activating an unrelated donor serch for severe acquired aplastic anemia.
AM J HEMATOL 2013; 88: 868-873.
IF: 4.138 Normalized IF: 3
35. **Piccardo A., Lopci E., Conte Massimo, Foppiani L., Garaventa Alberto, Cabria M., Villavecchia G., Fanti S., Cistaro A.**
PET/CT imaging in neuroblastoma.
Q J NUCL MED MOL IM 2013; 57: 29-39.
IF: 1.918 Normalized IF: 2
36. **Belvini D., Salviato R., Acquila Maura, Bicocchi Maria Patrizia, Frusconi S., Garagiola I., Sanna V., Santacroce R., Rocino A., Tagariello G.**
Prenatal diagnosis of haemophilia B: the Italian experience.
Haemophilia 2013; 19: 898-903.
IF: 3.17 Normalized IF: 2
37. **Arcieri R., Molinari Angelo C, Farace S., Mazza G., Garnero A., Calizzani G., Giordano P., Oliovecchio E., Mantovani L., Manzoli L., Giangrande P.**
Present and future challenges in the treatment of haemophilia: the patient's perspective.
Blood Transfus. 2013; 11: s82-85.
IF: 1.858 Normalized IF: 2
38. **Manzoni P., De Luca D., Stronati M., Jacqz-Aigrain E., Ruffinazzi G., Luparia M., Tavella E., Boano E., Castagnola Elio, Mostert M., Farina D.**
Prevention of nosocomial infections in neonatal intensive care units.
AM J PERINAT 2013; 30: 81-88.
IF: 1.574 Normalized IF: 2
39. **Cesaro S., Pillon M., Tridello G., Aljurf M., Martino R., Schroyens W., Nozzoli C., Barba P., Faraci Maura, Fagioli F., Cappelli B., Cordonnier C., Al-Mohareb F., Floysand Y, Greil J., Panizzolo IS., Santarone S.**
Relationship between clinical and BK virological response in patients with late hemorragic cystitis treated with cidofovir: a retrospective study from the European Group for Blood and Marrow Transplantation.
BONE MARROW TRANSPL 2013; 48: 809-813.
IF: 3.541 Normalized IF: 2
40. **Branchini A., Campioni M., Mazzucconi MG., Biondo F., Mari R., Bicocchi Maria Patrizia, Bernardi F., Pinotti M.**
Replacement of the Y450 (c234) phenyl ring in the carboxyl-terminal region of coagulation factor IX causes pleiotropic effects on secretion and enzyme activity.
FEBS LETT 2013; 587: 3249-3253.
IF: 3.582 Normalized IF: 3
41. **Castagnola Elio, Ginocchio Francesca.**
Rescue therapy of difficult-to-treat indwelling central venous catheter-related bacteremias in cancer patients: A review for practical purposes.
EXPERT REV ANTI-INFE 2013; 11(2): 179-186.
IF: 3.218 Normalized IF: 6
42. **Styczynski J., Gil L., Tridello G., Ljungman P., Donnelly JP., van der Velden W., Omar H., Martino R., Halkes C., Faraci Maura, et al.**

Response to Rituximab-based therapy and risk factor analysis in Epstein Barr virus-related lymphoproliferative disorder after hematopoietic stem cell transplant in children and adults: a study from the infectious diseases working party of the European Group.
CLIN INFECT DIS 2013; 57: 794-802.
IF: 9.374 Normalized IF: 4

43. **Pession A., Masetti R., Rizzari C., Putti MC., Casale F., Fagioli F., Luciani M., Lo Nigro L., Menna G., Micalizzi Concetta, et al.**
Results of the AIEOP AML 2002/01 multicenter prospective trial for the treatment of children with acute myeloid leukemia.
Blood 2013; 122: 170-178.
IF: 9.06 Normalized IF: 4

44. **Ferrari A., De Salvo GL., Dall'Igna P., Meazza C., De Leonardis F., Manzitti Carla, De Ioris MA., Casanova M., Carli M., Bisogno G.**
Salvage rates and prognostic factors after relapse in children and adolescents with initially localised synovial sarcoma.
EUR J CANCER 2012; 48: 3448-3455.
IF: 5.061 Normalized IF: 3

45. **Molinari Angelo C.**
Screening coagulazione pre-operatori.
PEDIATRICS 2013; 5: 35-36.
IF: 5.119 Normalized IF: 6

46. **Calaminus G., Kortmann R., Worch J., Nicholson JC., Alapetite C., Garre' Maria Luisa, et al.**
SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for pat.
NEURO-ONCOLOGY 2013; 15(6): 788-796.
IF: 6.18 Normalized IF: 3

47. **Castagnola Elio, Bandettini Roberto, Ginocchio Francesca, Perotti M., La Masa D., Ciucci Antonella, Loy Anna, Caviglia Ilaria, Haupt Riccardo, Guida E., Pini Prato Alessio, Mattioli Girolamo, Buffa Piero.**
Susceptibility to antibiotics of aerobic bacteria isolated from community acquired secondary peritonitis in children: therapeutic guidelines might not always fit with and everyday experience.
J CHEMOTHERAPY 2013; 25: 213-216.
IF: 0.825 Normalized IF: 1

48. **Indolfi P., Jenkner A., Terenziani M., Crocoli A., Serra A., Collini P., Biasoni D., Gandola L., Bisogno G., Cecchetto G., Di Martino M., D'Angelo P., Bianchi M., Conte Massimo, et al.**
Synchronous bilateral Wilms tumor: A report from the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP).
CANCER-AM CANCER SOC 2013; 119: 1586-1592.
IF: 5.201 Normalized IF: 3

49. **Kohler JA., Rubie H., Castel V., Beiske K., Holmes K., Gambini Claudio, Casale F., Munzer C., Erminio G., Parodi S., Navarro S., Marquez C, Peuchmaur M., Cullinane C., Brock P., Valteau-Couanet D., Garaventa Alberto, Haupt Riccardo.**
Treatment of children over the age of one year with unresectable localised neuroblastoma without MYCN amplification: results of the SIOPEN study.

Eur J Cancer. 2013; 49: 3671-3679.
IF: 5.061 Normalized IF: 6

50. **Calafiore R., Amoroso Loredana, Della Casa Alberighi Ornella, Luksch R., Zanazzo G., Castellano A., Podda M., Dominici C., Haupt Riccardo, Corrias Maria Valeria, Garaventa Alberto.**
Two-stage phase II study of imatinib mesylate in subjects with refractory or relapsing neuroblastoma.
ANN ONCOL 2013; 24: 1406-1413.
IF: 7.384 Normalized IF: 8

51. **Rocha V., Labopin M., Ruggeri A., Podestà M., Gallamini A.., Frassoni Francesco.**
Unrelated cord blood transplantation: outcomes after single-unit intrabone injection compared with double-unit intravenous injection in patients with haematological malignancies.
TRANSPLANTATION 2013; 95: 1284-1291.
IF: 3.781 Normalized IF: 6

52. **Hasegawa D., Bugarin C., Giordan M., Bresolin S., Longoni D., Micalizzi Concetta, et al.**
Validation of flow cytometric phospho-STAT5 as a diagnostic tool for juvenile myelomonocytic leukemia.
Blood Cancer J. 2013; 3: e160.
IF: 1.4 Normalized IF: 0.5

53. **Aricò M., Boggio E., Cetica V., Melensi M., Orilieri E., Clemente N., Cappellano G., Buttini S., Soluri MF., Comi C., Dufour Carlo, Pende D., et al.**
Variations of the UNC13D gene in patients with autoimmune lymphoproliferative syndrome.
PLOS ONE 2013; 8: e68045.
IF: 3.73 Normalized IF: 3

Research line 5
Muscular and neurological diseases

Title
Genetic-functional, morphological, and clinical-rehabilitative studies in pediatric neurological and muscular diseases

Coordinators
Dr. Pasquale Striano, Dr. Claudio Bruno

Project description (outline and objectives)
General objective is the improvement of knowledge in the field of neurosciences in developmental age, in particular neuromuscular and neurodegenerative diseases of genetic origin, through a multidisciplinary approach including clinical-laboratory, neuropsychological, neuroradiological, neurosurgical, and rehabilitative aspects. This research line includes highly specialized etiopathogenetic research applied to the clinical practice and aimed at diagnostic and therapeutic outcomes. The ultimate objective of research groups is to improve the quality of life of patients and their families through an effective sociomedical care and the rationalization and reduction of direct and indirect sociomedical costs, as well as costs related to cultural, social, school, and work problems of pediatric patients. Research groups are therefore actively involved in the achievement of the following objectives:

- Integrate the different diagnostic activities (electrophysiology, neuroradiology, genetics) to improve the diagnostic ability.
- Raising of qualitative standards of the service for the management of highly complex patients in order to guarantee to Ligurian patients high health care levels and to attract patients from other regions.
- Development of guidelines on the use of pharmacologic and non pharmacologic therapies, also aimed at razionalization of costs.

Principal investigators
Prof. Carlo Minetti – Pediatric Neurology and Muscular Diseases
Dr. Armando Cama – Neurosurgery
Prof. Edvige Veneselli – Child Neuropsychiatry
Dr. Andrea Rossi – Neuroradiology
Dr. Paolo Moretti – Physical Medicine and Rehabilitation

Activity year 2013

Pediatric Neurology and Muscular Diseases - *Director: Prof. Carlo Minetti*
Study of functional molecular mechanisms in the pathogenesis of neuromuscular and neurogenetic diseases: perspectives on new therapeutic trends
General objective is the improvement of knowledge in the field of neurosciences in developmental age, in particular neuromuscular and neurodegenerative diseases of genetic origin (mainly idiopathic epilepsies), through a multidisciplinary approach including clinical-laboratory, neuropsychological, neuroradiological, neurosurgical, and rehabilitative aspects linked to applied research aspects, also based on cellular and in vivo experimental models.
This research line includes highly specialized etiopathogenetic research applied to the clinical practice and aimed at diagnostic and therapeutic outcomes, also through the identification and functional characterization of genes for rare neurodevelopmental diseases using new generation sequencing techniques.

To this end, we selected 21 families with undiagnosed or unclassified recessive diseases and we typed them with AXION 587k slide. We also analyzed a murine model of deletion of the hyccin gene, the protein identified in our laboratory and involved in hypomyelinization and congenital cataract disorder.
The ultimate objective of the research project is to improve the quality of life of patients and their families through an effective sociomedical care and the rationalization and reduction of direct and indirect sociomedical costs, as well as costs related to cultural, social, school, and work problems of pediatric patients.
Research groups are therefore actively involved in the achievement of the following objectives:

- Integrate the different diagnostic activities (electrophysiology, neuroradiology, genetics) to improve the diagnostic ability of the unit.
- Raising of qualitative standards of the service for the management of highly complex patients in order to guarantee to Ligurian patients high health care levels and to attract patients from other regions.
- Development of guidelines on the use of pharmacologic and non pharmacologic therapies, also aimed at razionalization of costs.

Translational Centre of Myology and Neurodegenerative Diseases – *Director: Dr. Claudio Bruno*
Research activity was carried out in the Laboratory di Muscular Pathology - Pediatric Neurology and Neuromuscular Disease unit (Prof. C. Minetti, Dr. F. Zara. Dr. E. Gazzerro) in collaboration with national and international centres.
We performed etiopathogenetic studies applied to the clinical practice to improve diagnosis and to provide accurate counselling and effective sociomedical care. In collaboration with national and international research centres, basic research projects are ongoing aimed at the characterization of physiopathological mechanisms of muscular dystrophies and of some metabolic myopathies, based on the use of murine and zebrafish models.
In 2013, we developed i) outcome measures for patients with muscular dystrophy and spinal muscular atrophy, within national networks, ii) guidelines on safe anesthesia in the myopathic patient and on hyperCKemia, in collaboration with the Italian Association of Myology (AIM) and the ICU of the Istituto G. Gaslini.
Dr. Bruno is responsible for the projects of therapeutic trials for patients with muscular dystrophy and spinal muscular atrophy ("Multicentre, randomized, adaptive, double blind, placebo-controlled phase II study to evaluate the safety and efficacy of olesoxime (TRO19622) in patients with spinal muscular atrophy (SMA) aged between 3 and 35 years"; "Randomized, double blind, placebo-controlled. phase III clinical study on the use of tadalafil in Duchenne muscular dystrophy").
Dr. Bruno participates in national and international clinical networks in the field of neuromuscular and metabolic diseases. He is member of the European consortium "EUROMAC", a registry of patients with muscular glycogenosis (http://euromacregistry.eu/) and is partner of the Telethon project GSP13002: "Development of an Italian Clinical Network for Spinal Muscular Atrophy".

Neurosurgery - *Director: Dr. Armando Cama*
Objectives of the project were the following: (1) sequencing of the entire exome (WES, Whole Exome Sequencing) of 7 families of patients with Neural Tube Defects (NTD) to identify rare mutations (CNVs, SNVs and InDels) that can confer susceptibility to NTD; (2) biological characterization of medulloblastoma stem cells and identification of molecular characteristics related to drug-resistance.

Concerning objective (1), in compliance with Illumina/Solexa platform, a library was prepared containing genomic DNA fragments coupled with selective enrichment of the regions, followed by generation by PCR of millions of clonal clusters sequenced by synthesis through the use of dideoxy-reversible terminators. The analysis of data includes 5 phases: 1) transformation of raw data into reads; 2) quality control of reads and their alignment on a reference genome; 3) annotation of variants and their filtering using public databases; 4) study of variant segregation within the families according to different inheritance patterns; 5) validation (gold standard methods). Phases 1-3 have been concluded and we are presently focusing on the analysis of CNVs by EXCAVATOR, a new tool suitable for the identification of CNVs from WES data.
Concerning objective (2), considering the latest advances in the field of biology of medulloblastoma with the introduction of 4 molecular groups for the classification of this tumor, the study showed the groups in which there is a higher proportion of tumor initiating cells (TICs). The result can justify the more aggressive progression of some tumor forms related to the presence of TICs, presenting higher ability to metastasize and resist to chemo/radiotherapy. In addition, the study is highlighting specific activation pathways linked to the *self-renewal* ability of these cells compared to the differentiation process. These investigations are ongoing, as well as the genetic analysis of a larger case series, in order to validate the data obtained to date.

Child Neuropsychiatry **-** *Director*: *Prof. Edvige Veneselli*
Epilepsy: we studied the outcome of seizures correlated to lesionectomy in children with epilepsy and glioneuronal tumors; we investigated epileptic encephalopathy with continuous spike-waves during slow sleep in a series of patients with periventricular leukomalacia; lymphedema was described; we collaborated to the international study "Exon-disrupting deletions of NRXN1" in idiopathic generalized epilepsy.
Neuroimmunology: concerning anti-N-methyl-D-aspartate receptor encephalitis, we described new cases to better define the study design and the diagnostic work-up and to optimize patient management and follow-up; we described the neuroradiological aspect as marker of activity in chronic demyelinating inflammatory polyradiculoneuropathy and its usefulness in the therapeutic programme. This year we also organized the congress "Inflammatory and immune-mediated diseases in child neuropsychiatry" (Genova, Nov. 8., 2013) with national and international speakers and chairmen.
Diseases of the posterior cranial fossa: innovative data were obtained from molecular analysis in patients with Joubert and J.-like syndrome, congenital cerebellar hypoplasia with involvement of anterior spinal cord horns, Dandy-Walker malformation and Wisconsin syndrome (this latter within an international cooperative study); the studies included the retrospective and prospective analysis of clinical and neuroradiological data and the correlation with genetic data.
Autistic spectrum disorders: we are analysing biological, genetic, and electroclincal data of a large series of patients to evaluate their role in pathogenesis and clinical phenotype; we also described (data not published) the presence of the interstitial deletion 2q24.3 including SCN2A and SCN3A genes in a non-epileptic autistic subject.
ADHD: a study was carried out In collaboration with the other Italian reference centres to improve the diagnostic and therapeutic procedures.
Rare neurological diseases: we also continued studies with advances in the clinical, neuroradiological, and genetic definition and phenotype-genotype correlation of different forms including some Leucoencephalopaties such as hypomyelination and congenital

cataract, Alexander disease, Pelizaeus-Merzbacher-like disease spectrum, and some poliodystrophies, such as infantile ceroidolipofuscinosis; the role of SLC2A1 (GLUT1) gene mutations in Italian cases of alternating hemiplegia was not confirmed; clinical-neuroradiological aspects in Brown-Vialetto-Van Laere syndrome were described.

Neuroradiology - *Director*: *Dr. Andrea Rossi*

The project was aimed at combining data of integrated diagnostics with 18F-DOPA PET and MR to evaluate their synergic diagnostic role and clinical impact in pediatric patients with brain tumors. Specific research fields concerned the evaluation pre- and post-treatment of diffusely infiltrating low grade and other grade gliomas.

Thirty pediatric patients were studied to date, and the analysis of functional MR data is being evaluated. As first step, comparison and merging of DOPA PET data with conventional MR data for diagnostic, therapeutic, and prognostic purposes were completed and results were published in the Journal of Nuclear Medicine (IF: 5.77). A book chapter is being published on the role of DOPA PET in pediatric brain tumors. Finally, the results of our research were presented as oral communication in occasion of the XXXVII Congress of the European Society of Neuroradiology.

Physical Medicine and Rehabilitation - *Director*: *Dr. Paolo Moretti*

Pilot study on the efficacy of olesoxime and on tests, comparison of two types of corset in spinal neurogenic atrophy, and development and evaluation of outcome measures in Duchenne muscular dystrophy in collaboration with the Department of Pediatric Neurology of the Università Cattolica of Roma and the Neuromuscular and Neurodegenerative Disease unit of the Istituto G. Gaslini.

Launch of the project for the implantation and use of infusion pumps for the intrathecal administration of baclofene in patients with generalized spasticity in collaboration with the Neurosurgery unit of the Istituto Gaslini.

Study on therapy with perception of action by eye and ear in the rehabilitation of the paretic upper limb in children with infantile cerebral palsy in collaboration with the Italian Institute of Technology.

Study on instrumental analysis of preterm newborn movement in collaboration with the Neonatal Disease unit and the Neuroradiology unit of the Istituto G. Gaslini, the Italian Institute of Technology, and the University of Hiroshima.

Study of talocrural joint modelling with the instrumental analysis of movement in juvenile rheumatoid arthritis in collaboration with the Pediatric Rheumatology unit of the Istituto Gaslini and the Rehabilitation unit of the Bambin Gesù Hospital of Roma.

Publications year 2013

1. **Mazzone ES., Pane M., Sormani MP., Scalise R., Berardinelli A., Messina S., Torrente Y., D'Amico A., Doglio Luca, Viggiano E.., Bruno Claudio, et al.**
   24 month longitudinal data in ambulant boys with Duchenne muscular dystrophy.
   PLOS ONE 2013; 8: e52512.
   IF: 3.73 Normalized IF: 3
2. **Bandettini di Poggio M., Gagliardi S., Pardini M., Marchioni E., Monti Bragadin M., Reni L., Doria Lamba Laura Maria, Roccatagliata L., Ceroni M., Schenone A., Cereda C.**
   A novel compound heterozygous mutation of C20orf54 gene associated with Brown-Vialetto-Van Laere syndrome in an Italian family.
   EUR J NEUROL 2013; 20: e94-e95.
   IF: 4.162 Normalized IF: 3

3. **Licchetta L., Pippucci T., Bisulli F., Cantalupo G., Magini P., Alvisi L., Baldassari S., Martinelli P., Naldi I., Vanni Nicola Augusto, et al.**
   A novel pedigree with familial cortical myoclonic tremor and epilepsy (FCMTE): clinical characterization, refinement of the FCMTE2 locus, and confirmation of a founder haplotype.
   Epilepsia. 2013; 54: 1298-1306.
   IF: 3.909 Normalized IF: 3
4. **Germinaro EAP., Arcieri R., Bonati M., Zuddas A., Masi G., Vella S., Chiarotti F., Panei P., for the Italian ADHD Regional Reference Centers, Veneselli Edvige.**
   Attention-deficit/hyperactivity disorder drugs and growth: an Italian prospective observational study.
   J Child Adolesc Psychopharmacol. 2013; 23: 440-447.
   IF: 2.773 Normalized IF: 1.2
5. **Siri L., Pinelli L., Giordano L., Tassi L., Striano Pasquale.**
   Atypical Sturge-Weber syndrome requires confirmation (reply to Zhou et al.).
   EUR J PAEDIATR NEURO 2013; 17: 321-322.
   IF: 1.982 Normalized IF: 2
6. **Striano Pasquale, Louis ED., Manto M.**
   Autosomal dominant cortical tremor, myoclonus, and epilepsy: is the origin in the cerebellum? Eidtorial.
   CEREBELLUM 2013; 12: 145-146.
   IF: 2.595 Normalized IF: 2
7. **Striano Pasquale, Zara Federico, Striano S., Minetti Carlo.**
   Autosomal recessive epilepsy associated with contactin 2 mutation is different from familial cortical tremor, myoclonus and epilepsy.
   Brain 2013; 136: e253.
   IF: 9.915 Normalized IF: 4
8. **Catteruccia M., Fattori F., Codemo V., Ruggiero R., Maggi L., Tasca G., Fiorillo C., Pane M., Berardinelli A., Verardo M., Bragato C., Mora M., Morandi L., Bruno Claudio, et al.**
   Centronuclear myopathy related to dynamin 2 mutations: Clinical, morphological, muscle imaging and genetic features of an Italian cohort.
   NEUROMUSCULAR DISORD 2013; 23: 229-238.
   IF: 3.464 Normalized IF: 3
9. **Rossi Daniela Paola, Doria Lamba Laura Maria, Pistorio Angela, Pedemonte Marina, Veneselli Edvige, Rossi Andrea.**
   Chronic inflammatory demyelinating polyneuropathy of childhood: clinical and neuroradiological findings.
   NEURORADIOLOGY 2013; 55: 1233-1239.
   IF: 2.7 Normalized IF: 4
10. **Agostinelli S., Accorsi P., Beccaria F., Belcastro V., Canevini MP.., Minetti Carlo, Nicita F., Parisi P., Pavone P., Pezzella M., Sesta M., Spalice A., Striano S., Tozzi E., Traverso Monica, Vari S., Vignoli A., Zamponi N., Zara Federico, Striano Pasquale, Verrotti A.**
    Clinical dissection of early onset absence epilepsy in children and prognostic implications.
    EPILEPSIA 2013; 54: 1761-1779.
    IF: 3.909 Normalized IF: 6
11. **Siri L., Giordano L., Accorsi P., Cossu M., Pinelli L., Tassi L., Striano Pasquale.**
    Clinical features of Sturge-Weber syndrome without facial nevus: five novel cases.

EUR J PAEDIATR NEURO 2013; 17: 91-96.
IF: 1.982 Normalized IF: 4

12. **Parisi P., Oliva A., Coll Vidal M., Partemi S., Campuzano O., Iglesias A., Pisani D., Pascali VL., Paolino MC., Villa MP., Zara Federico, Tassinari CA., Striano Pasquale, Brugada R.**
Coexistence of epilepsy and Brugada syndrome in a family with SCN5A mutation.
EPILEPSY RES 2013; 105: 415-418.
IF: 2.241 Normalized IF: 2
13. **Ferraris A., Bernardini L., Avramovska VS., Zanni G., Loddo S., Sukarova-Angelovska E., Parisi V., Capalbo A., Tumini S., Travaglini L., Mancini F., Duma F., Barresi S., Novelli A., Mercuri E., Tarani L., for the Italian CBCD Study Group, Biancheri Roberta, Rossi Andrea, et al.**
Dandy-Walker malformation and Wisconsin syndroma: novel cases add further insight into the genotype-phenotype correlations of 3q23q25 deletions.
ORPHANET J RARE DIS 2013; 8: 75.
IF: 4.315 Normalized IF: 1.2
14. **Suls A., Jaehn JA., Kecskes A., Weber Y., Weckhuysen S., Craiu DC., Siekierska A., Djemie T., Afrikanova T., Gormley P.., Striano Pasquale, Zara Federico, et al.**
De novo loss-of-function mutations in CHD2 cause a fever-sensitive myoclonic epileptic encephalopathy sharing features with Dravet syndrome.
Am J Hum Genet. 2013; 93: 967-975.
IF: 11.202 Normalized IF: 4
15. **Coppola A., Bagnasco I., Traverso Monica, Brusco A., Di Gregorio E., Del Gaudio L., Santulli L., Caccavale C., Vigliano P., Minetti Carlo, Striano S., Zara Federico, Striano Pasquale.**
Different electroclinical picture of generalized epilepsy in two families with I 5 q I 3.3 microdeletion.
Epilepsia. 2013; 54(5): e69-e73.
IF: 3.909 Normalized IF: 6
16. **Poretti A., Meoded A., Rossi Andrea, Raybaud C., Huisman TAGM.**
Diffusion tensor imaging and fiber tractography in brain malformations.
PEDIATR RADIOL 2013; 43: 28-54.
IF: 1.565 Normalized IF: 2
17. **Falace A., Vanni Nicola Augusto, Mallamaci A., Striano Pasquale, Zara Federico.**
Do regulatory regions matter in FOXG1 duplications?
Eur J Hum Genet. 2013; 21: 365-366.
IF: 4.319 Normalized IF: 3
18. **Bandettini di Poggio M., Nesti C., Bruno Claudio, Meschini MC., Schenone A., Santorelli FM.**
Dopamine-agonist responsive Parkinsonism in a patient with the SANDO syndrome caused by PLOG mutation.
BMC Med Genet. 2013; 14: 105.
IF: 2.536 Normalized IF: 2
19. **Pane M., Messina S., Bruno Claudio, D'Amico A., Villanova M., Brancalion B., Sivo S., Bianco F., Striano Pasquale, Battaglia D., et al.**
Duchenne muscular dystrophy and epilepsy.
Neuromuscul Disord. 2013; 23: 313-315.
IF: 3.464 Normalized IF: 3

20. **Giordano L., Vignoli A., Cusmai R., Parisi P., Mastrangelo M., Coppola G., Cordelli DM., Accorsi P., Milito G., Darra F., Pruna D., Belcastro V., Verrotti A., Striano Pasquale.**
    Early onset absence epilepsy with onset in the first year of life: a multicenter cohort study.
    Epilepsia 2013; 54(Suppl.7): 66-69.
    IF: 3.909 Normalized IF: 6
21. **Verrotti A., Striano Pasquale, Agostinelli S.**
    Early onset absence epilepsy: what changes using Panayiotopoulos's criteria?
    Epilepsia. 2013; 54: 765-766.
    IF: 3.909 Normalized IF: 3
22. **Belcastro V., Horacio Caraballo R., Romeo A., Striano Pasquale.**
    Early-onset absence epilepsy aggravated by valproic acid: a video-EEG report.
    Epileptic Disord. 2013; 15: 440-443.
    IF: 1.165 Normalized IF: 1
23. **Agostinelli S., Traverso M., Accorsi P., Beccaria F., Belcastro V., Capovilla G., Cappanera S., Coppola A., Dalla Bernardina B., Darra F., Ferretti M., Minetti Carlo, Zara Federico, Striano Pasquale, Verrotti A.**
    Early-onset absence epilepsy: SLC2A1 gene analysis and treatment evolution.
    Eur J Neurol. 2013; 20: 856-859.
    IF: 4.162 Normalized IF: 6].
24. **Verrotti A., Cusmai R., Nicita F., Pizzolorusso A., Elia M., Zamponi N., Cesaroni E., Granata T., De Giorgi I., Giordano L., Grosso S., Pavone P.., Striano Pasquale, et al.**
    Electronical features and long-term outcome of cryptogenica epilepsy in children with Down syndrome.
    J Pediatr. 2013; 163: 1754-1758.
    IF: 4.035 Normalized IF: 3
25. **Camfield CS., Striano Pasquale, Camfield PR.**
    Epidemiology of juvenile myoclonic epilepsy.
    EPILEPSY BEHAV 2013; 28: S15-S17.
    IF: 1.844 Normalized IF: 2
26. **Verrotti A., Agostinelli S., Prezioso G., Coppola G., Capovilla G., Romeo A., Striano Pasquale, Parisi P., Grosso S., et al.**
    Epilepsy in patients with Cornelia de Lange syndrome: A clinical series.
    SEIZURE-EUR J EPILEP 2013; 22: 356-359.
    IF: 2.004 Normalized IF: 2
27. **Kasperaviciute D., Catarino CB., Matarin M., Leu C., Novy J., Tostevin A., Leal B.., Robbiano Angela, Paravidino Roberta, Zara Federico, et al.**
    Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A.
    Brain 2013; 136: 3140-3150.
    IF: 9.915 Normalized IF: 8
28. **Striano Pasquale, Capovilla G.**
    Epileptic encephalopathy with continuous spikes and waves during sleep.
    CURR NEUROL NEUROSCI 2013; 13: 360.
    IF: 3.783 Normalized IF: 6
29. **Moller RS., Weber YG., Klitten LL.., for the EPICURE Consortium, Zara Federico, Striano Pasquale.**

Exon-disrupting deletions of NRXNI in idiopathic generalized epilepsy.
EPILEPSIA 2013; 54(2): 256-164.
IF: 3.909 Normalized IF: 1.2

30. **Biancheri Roberta, Cassandrini D., Pinto F., Trovato R., Di Rocco Maja, Mirabelli Badenier Marisol Elena, Pedemonte Marina, Panicucci C., Trucks H., Sander T., Zara Federico, Rossi Andrea, Striano Pasquale, Minetti Carlo, Santorelli FM.**
EXOSC3 mutations in isolated cerebellar hypoplasia and spinal anterior horn involvement.
J NEUROL 2013; 260: 1866-1870.
IF: 3.578 Normalized IF: 6

31. **Biancheri Roberta, Rosano C., Denegri L., Lamantea E., Pinto F., Lanza Federica, Severino Mariasavina, Filocamo Mirella.**
Expanded spectrum of Pelizaeus-Merzbacher-like disease: Literature revision and description of a novel GJC2 mutation in an unusually severe form.
EUR J HUM GENET 2013; 21: 34-39.
IF: 4.319 Normalized IF: 6

32. **Weckhusen S., Ivanovic V., Hendrickx R., Van Coster R., Hjalgrim H., Moller RS., Gronborg S., Schoonjans AS., Ceulemans B., Heavin SB., Eltze C.., Striano Pasquale, et al.**
Extending the KCNQ2 encephalopathy spectrum. Clinical and neuroimaging findings in 17 patients.
Neurology. 2013; 81: 1697-1703.
IF: 8.249 Normalized IF: 4

33. **Garavelli L., Simonte G., Rosato S., Wischmeijer A., Albertini E., Guareschi E., Longo C., Albertini G., Gelmini C., Greco C., Errico S., Savino G., Pavanello Marco, et al.**
Focal dermal hypoplasia (Goltz-Gorlin syndrome): a new case with a novel variant in the PORCN gene and unusual spinal anomaly.
AM J MED GENET A 2013; 161A: 1750-1754.
IF: 2.304 Normalized IF: 1

34. **Belcastro V., Striano Pasquale, Parisi P.**
From migralepsy to ictal epileptic headache: the story so far.
Neurol Sci. 2013; 34: 1805-1807.
IF: 1.412 Normalized IF: 2

35. **De Marco Patrizia, Merello Elisa, Consales Alessandro, Piatelli Gianluca, Cama Armando, Kibar Z., Capra Valeria.**
Genetic analysis of Disheveled 2 and Disheveled 3 in human neural tube defects.
J MOL NEUROSCI 2013; 49: 582-588.
IF: 2.891 Normalized IF: 4

36. **Zara Federico, Specchio N., Striano Pasquale, Robbiano Angela, Gennaro E., Paravidino R:, Vanni Nicola Augusto., Minetti Carlo.**
Genetic testing in benign familial epilepsies of the first year of life: Clinical and diagnostic significance
EPILEPSIA 2013; 54(3): 425-436.
IF: 3.909 Normalized IF: 6

37. **Consales Alessandro, Striano Pasquale, Nozza Paolo, Morana Giovanni, Ravegnani Giuseppe Marcello, Piatelli Gianluca, Pavanello Marco, Zoli ML., Baglietto Maria Giuseppina, Cama Armando.**

Glioneuronal tumors and epilepsy in children: seizure outcome related to lesionectomy.
Minerva Pediatr. 2013; 65: 609-616.
IF: 0.638 Normalized IF: 1

38. **Traverso Monica, Yuregir OO., Mimouni-Bloch A., Rossi Andrea, Aslan H., Gazzerro Elisabetta, Baldassari S., Fruscione Floriana, Minetti Carlo, Zara Federico, Biancheri Roberta.**
Hypomyelination and congenital cataract: identification of novel mutations in two unrelated families.
EUR J PAEDIATR NEURO 2013; 17: 108-111.
IF: 1.982 Normalized IF: 4
39. **Partemi S., Vidal MC., Campuzano O., Pezzella M., Paravidino R., Pascali VL., Tassinari CA., Striano S., Zara Federico, Brugada R., Striano Pasquale, Oliva A.**
Importance of post-mortem genetic testing in SUDEP patients.
2013; 4: e354-e355.
IF: 1.113 Normalized IF: 1
40. **Belcastro V., Striano Pasquale, Parisi P.**
Interictal and periictal headache in patients with epilepsy: migraine-triggered seizures or epilepsy-triggered headache?
EUR J NEUROL 2013; 20: 1333-1334.
IF: 4.162 Normalized IF: 6
41. **Belcastro V., Vidale S., Pierguidi L., Sironi L., Tancredi L., Striano Pasquale, Taborelli A., Arnaboldi M.**
Intravenous lacosamide as treatment option in post-stroke non convulsive status epilepticus in the elderly: a proof-of-concept, observational study.
Seizure. 2013; 22: 905-907.
IF: 2.004 Normalized IF: 2
42. **Belcastro V., Striano Pasquale, Parisi P.**
Is it migralepsy? No evidence yet.
NEUROL SCI 2013; 34: 1837-1838.
IF: 1.412 Normalized IF: 2].
43. **De Grandis Elisa, Stagnaro M., Biancheri Roberta, Giannotta M., Gobbi G., Traverso Monica, Veneselli Edvige, Zara Federico.**
Lack of SLC2AI (Glucose Transporter 1) mutations in 30 Italian patients with alternating hemiplegia of childhood.
J CHILD NEUROL 2013; 28(7): 863-866.
IF: 1.385 Normalized IF: 4
44. **Verrotti A., Loiacono G., Pizzolorusso A., Parisi P., Bruni O., Luchetti A., Zamponi N., Cappanera S., Grosso S.., Striano Pasquale, et al.**
Lacosamide in pediatric and adult patients: Comparison of efficacy and safety.
SEIZURE-EUR J EPILEP 2013; 22: 210-216.
IF: 2.004 Normalized IF: 2
45. **Tasca G., Moro F., Aiello C., Cassandrini D., Fiorillo C., Bertini E., Bruno Claudio, Santorelli FM., Ricci E.**
Limb-Girdle muscular systrophy with alpha-dystroglycan deficiency and mutations in the ISPD gene
NEUROLOGY 2013; 80: 963-965.
IF: 8.249 Normalized IF: 4

46. **Partemi S., Cestèle S., Pezzella M., Campuzano O., Paravidino R., Pascali VL., Zara Federico, Tassinari CA., Striano S., Oliva A., Brugada R., Mantegazza M., Striano Pasquale.**
    Loss-of-function KCNH2 mutation in a family with long QT syndrome, epilepsy, and sudden death.
    EPILEPSIA 2013; 54(8): e112-e116.
    IF: 3.909 Normalized IF: 6
47. **Michelucci R., Pasini E., Malacrida S., Striano Pasquale, Di Bonaventura C., Pulitano P., Bisulli F., et al.**
    Low penetrance of autosomal dominant lateral temporal epilepsy in Italian families without LGII mutations.
    EPILEPSIA 2013; 54(7): 1288-1297.
    IF: 3.909 Normalized IF: 3
48. **Biancheri Roberta, Rossi Andrea, Ceccherini Isabella, Pezzella M., Prato G., Striano Pasquale, Minetti Carlo.**
    Magnetic resonance imaging "tigroid pattern" in Alexander disease.
    NEUROPEDIATRICS 2013; 44: 174-176.
    IF: 1.192 Normalized IF: 2
49. **Rossi Andrea, Biancheri Roberta.**
    Magnetic resonance spectroscopy in metabolic disorders.
    NEUROIMAG CLIN N AM 2013; 23: 425-448.
    IF: 1.204 Normalized IF: 2
50. **Belcastro V., D'Egidio C., Striano Pasquale, Verrotti A.**
    Metabolic and endocrine effects of valproic acid chronic treatment.
    Epilepsy Res. 2013; 107: 1-8.
    IF: 2.241 Normalized IF: 2
51. **Natali A., Gastaldelli A., Camastra S., Baldi S., Quagliarini S., Minicocci I., Bruno Claudio, Pennisi E., Arca M.**
    Metabolic consequences of adipose triglyceride lipase deficiency in humans: an in vivo study in patients with neutral lipid storage disease with myopathy.
    J CLIN ENDOCR METAB 2013; 98: E1540-E1548.
    IF: 6.43 Normalized IF: 3
52. **Belcastro V., Striano Pasquale, Parisi P.**
    Migraine and epilepsy terminology and classification: opening Pandora's box.
    EPILEPTIC DISORD 2013; 15: 216-217.
    IF: 1.165 Normalized IF: 0.5
53. **Garone C., Donati MA., Sacchini M., Garcia-Diaz B., Bruno Claudio, Calvo S., Mootha VK., DiMauro S.**
    Mitochondrial encephalomyopathy due to a novel mutation in ACAD9.
    JAMA Neurol. 2013; 70: 1.
    IF: 7.685 Normalized IF: 4
54. **Mascelli Samantha, Barla A., Raso Alessandro, Mosci S., Nozza Paolo, Biassoni Roberto, Morana Giovanni, Huber M., Mircean C., Fasulo D., Noy K., Wittenberg G., Pignatelli S., Piatelli Gianluca, Cama Armando, Garre' Maria Luisa, Capra Valeria, Verri A.**
    Molecular fingerprinting reflects different histotypes and brain region in low grade gliomas.

BMC CANCER 2013; 13: 387.
IF: 3.333 Normalized IF: 4

55. **Morana Giovanni, Piccardo A., Garre' Maria Luisa, Nozza Paolo, Consales Alessandro, Rossi Andrea.**
Multimodal magnetic resonance imaging and 18F-L-dihydroxyphenylalanine positron emission tomography in early characterization of pseudoresponse and nonenhancing tumor progression in a pediatric patient with malignant transformation of ganglioglioma treate
J CLIN ONCOL 2013; 31: e1-e4.
IF: 18.038 Normalized IF: 15

56. **Secci F., Consales Alessandro, Merciadri P., Ravegnani Giuseppe Marcello, Piatelli Gianluca, Pavanello Marco, Cama Armando.**
Naso-ethmoidal encephalocele with bilateral orbital extension: report of a case in a western country.
CHILD NERV SYST 2013; 29: 1947-1952.
IF: 1.241 Normalized IF: 2

57. **Coppola A., Ruosi P., Santulli L., Striano S., Zara Federico, Striano Pasquale, Sisodiya SM.**
Neurological features and long-term follow-up in 15q11.2-13.1 duplication.
Eur J Med Genet.2013; 56: 614-618.
IF: 1.685 Normalized IF: 1

58. **Pappalardo A., Pitto L., Fiorillo C., Donati MA., Bruno Claudio, Santorelli FM.**
Neuromuscular disorders in zebrafish: State of the art and future perspectives.
NEUROMOL MED 2013; 15: 405-419.
IF: 4.492 Normalized IF: 3

59. **Gazzerro Elisabetta, Andreu AL., Bruno Claudio.**
Neuromuscular disorders of glycogen metabolism.
CURR NEUROL NEUROSCI 2013; 13: 333.
IF: 3.783 Normalized IF: 6

60. **Parisi P., Striano Pasquale, Belcastro V.**
New terminology for headache/migraine as the sole ictal epileptic manifestation: The down-sides. Reply to Cianchetti et al.
SEIZURE-EUR J EPILEP 2013; 22: 798-799.
IF: 2.004 Normalized IF: 2.

61. **Milh M., Falace A., Villeneuve N., Vanni Nicola Augusto, Cacciagli P., Assereto S., Nabbout R., Benfenati F., Zara Federico, et al.**
Novel compound heterozygous mutations in TBC1D24 cause familial malignant migrating partial seizures of infancy.
Hum Mutat. 2013; 34: 869-872.
IF: 5.213 Normalized IF: 3

62. **Traverso Monica, Assereto S., Gazzerro Elisabetta, Savasta S., Abdalla EM., Rossi Andrea, Baldassarri S., Fruscione Floriana, Ruffinazzi G., Fassad MR., El Beheiry A., Minetti Carlo, Zara Federico, Biancheri Roberta.**
Novel FAM126A mutations in hypomyelination and congenital caract disease.
BIOCHEM BIOPH RES CO 2013; 439: 369-372.
IF: 2.406 Normalized IF: 4

63. **Merello Elisa, De Marco Patrizia, Ravegnani Giuseppe Marcello, Riccipetitoni G., Cama Armando, Capra Valeria.**

Novel MNX1 mutations and clinical analysis of familial and sporadic Currarino cases.
Eur J Med Genet. 2013; 56: 648-654.
IF: 1.685 Normalized IF: 2

64. **Fiorillo C., Moro F., Astrea G., Morales MA., Baldacci J., Marchese M., Scapolan Sara, Bruno Claudio, Battini R., Santorelli FM.**
Novel mutations in the fukutin gene in a boy with asymptomatic hyperCKemia.
Neuromuscul Disord. 2013; 23: 1010-1015.
IF: 3.464 Normalized IF: 3
65. **Capra Valeria, Mascelli Samantha, Garre' Maria Luisa, Nozza Paolo, Vaccari C., Bricco L., Sloan-Bèna F., Gimelli S., Cuoco Cristina, Gimelli Giorgio, Tassano Elisa.**
Parental Imbalances Involving Chromosomes 15q and 22q May Predispose to the Formation of De Novo Pathogenic Microdeletions and Microduplications in the Offspring.
PLOS ONE 2013; 8: e57910.
IF: 3.73 Normalized IF: 6
66. **Conti V., Carabalona A., Pallesi-Pocachard E., Parrini E., Leventer RJ., Buhler E., McGillivray G., Michel FJ., Striano Pasquale, et al.**
Periventricular heterotopia in 6q terminal deletion syndrome: role of the C6orf70 gene.
Brain.2013; 136: 3378-3394.
IF: 9.915 Normalized IF: 4
67. **Mancuso M., Orsucci D., Angelini C., Bertini E., Carelli V., Comi PC., Minetti Carlo, Moggio M., Mongini T., Servidei S.0, Tonin P., Toscano A., Uziel G., Bruno Claudio, et al.**
Phenotypic heterogeneity of the 8344A>G mtDNA "MERRF" mutation.
NEUROLOGY 2013; 80: 2049-2054.
IF: 8.249 Normalized IF: 4
68. **Travaglini L., Brancati F., Silhavy J., Iannicelli M., Nickerson E.., for the International JSRD Study Group, Biancheri Roberta, Caridi Gianluca, Divizia Maria Teresa, Ghiggeri Gian Marco, Mirabelli Badenier Marisol Elena.**
Phenotypic spectrum and prevalence of INPP5E mutations in Joubert syndrome and related disorders.
Eur J Hum Genet. 2013; 21: 1074-1078.
IF: 4.319 Normalized IF: 1.2
69. **Cassandrini D., Cilio MR., Bianchi M., Doimo M., Blestri M., Tessa A., Rizza T., Sartori G., Meschini MC., Nesti C., Tozzi G., Petruzzella V., Piemonte F., Bisceglia L., Bruno Claudio, Dionisi-Vici C., D'Amico A., Fattori F., Carrozzo R., Salviati L., Santorelli FM., Bertini E.**
Pontocerebellar hypoplasia type 6 caused by mutations in RARS2: definition of the clinical spectrum and molecularfindings in five patients.
J INHERIT METAB DIS 2013; 36: 43-53.
IF: 4.07 Normalized IF: 3
70. **Specchio N., Terracciano A., Trivisano M., Cappelletti S., Claps D., Travaglini L., Cusmai R., Marras CE., Zara Federico, Fusco L., Bertini E., Vigevano F.**
PRRT2 is mutated in familial and non-familial benign infantile seizures.
EUR J PAEDIATR NEURO 2013; 17: 77-81.
IF: 1.982 Normalized IF: 2
71. **Becker F., Schubert J., Striano Pasquale, Anttonen AK.., Zara Federico, Lerche H., Weber YG.**

PRRT2-related disorders: further PKD and ICCA cases and review of the literature.
J NEUROL 2013; 260: 1234-1244.
IF: 3.578 Normalized IF: 3

72. **Merello Elisa, Kibar Z., Allache R., Piatelli Gianluca, Cama Armando, Capra Valeria, De Marco Patrizia.**
Rare missense variants in DVL1, one of the human counterparts of the Drosophia dishelled gene, do not confer increased risk for neural tube defects.
BIRTH DEFECTS RES A 2013; 97: 452-455.
IF: 3.146 Normalized IF: 4

73. **Verrotti A., Matricardi S., Capovilla G., D'Egidio C., Cusmai R., Romeo A., Pruna D., Pavone P., Cappanera S., Granata T., Gobbi G., Striano Pasquale, et al.**
Reflex myoclonic epilepsy in infancy: a multicenter clinical study.
EPILEPSY RES 2013; 103: 237-244.
IF: 2.241 Normalized IF: 2

74. **Fiorillo C., Brisca G., Cassandrini D., Scapolan Sara, Astrea G., Valle Maura, Scuderi F., Trucco F., Natali A., Magnano Gian Michele, Gazzerro Elisabetta, Minetti Carlo, Arca M., Santorelli FM., Bruno Claudio.**
Subclinical myopathy in a child with neutral lipid storage disease and mutations in the PNPLA2 gene.
BIOCHEM BIOPH RES CO 2013; 430: 241-244.
IF: 2.406 Normalized IF: 4

75. **Marti-Masso JF., Bergareche A., Makaraov V., Ruiz-Martinez J., Gorostidi A., Lopez de Munain A., Poza JJ., Striano Pasquale, Buxbaum JD., Paisan-Ruiz C.**
The ACMSD gene, involved in tryptophan metabolism, is mutated in a family with cortical myoclonus, epilepsy, and parkinsonism.
J Mol Med (Berl). 2013; 91: 1399-1406.
IF: 4.768 Normalized IF: 3

76. **Parisi P., Striano Pasquale, Belcastro V.**
The crossover between headache and epilepsy.
Expert Rev Neurother. 2013; 13: 231-233.
IF: 2.955 Normalized IF: 4

77. **Rossi Andrea.**
The European Diploma in Pediatric Neuroradiology sees the light of day.
Neuroradiology. 2013; 55: 1429-1430.
IF: 2.7 Normalized IF: 4

78. **Striano Pasquale, Belcastro V.**
Treating myoclonic epilepsy in children: State-of-the-art.
EXPERT OPIN PHARMACO 2013; 14(10): 1355-1361.
IF: 2.86 Normalized IF: 4

79. **Ramachandran N., Munteanu I., Wang P., Ruggieri A., Rilstone JJ., Israelian N., Naranian T., Paroutis P., Guo R., Ren ZP., Nishino I., Chabrol B., Pellissier JF., Minetti Carlo, Udd B., Fardeau M.0, Tailor CS., Mahuran DJ., Kissel JT., Kalimo H., Levy N., Manolson MF., Ackerley CA., Minassian BA.**
VMA21 deficiency prevents vacuolar ATPase assembly and cayses autophagic vacuolar myopathy.
ACTA NEUROPATHOL 2013; 125: 439-457.
IF: 9.734 Normalized IF: 4

80. Parisi P., Striano Pasquale, Verrotti A., Villa MP., Belcastro V.
What have we learned about ictal epileptic headache? A review of well-documented cases.
SEIZURE-EUR J EPILEP 2013; 22: 253-258.
IF: 2.004 Normalized IF: 4

STUDIES AND CLINICAL TRIALS YEAR 2013

Unit	Title	Year of approval
Oncology, Hematology, and BMT	LCH III: therapeutic protocol for the 3rd international study on Langerhans cell histiocytosis	2001
Oncology, Hematology, and BMT	First European cooperative study for high risk neuroblastoma	2001
Oncology, Hematology, and BMT	International registry of severe chronic neutropenias	2003
Oncology, Hematology, and BMT	A randomized phase III study on the treatment of children and adolescent with refractory or relapsed acute myeloid leukemia.	2004
Oncology, Hematology, and BMT	High risk neuroblastoma refractory to therapy or relapsed after autologous transplantation: pilot study on toxicity and antitumoral activity of allogenic transplantation from compatible or haploidentical familial donor	2004
Oncology, Hematology, and BMT	Wilms tumor 2003-11-13. Diagnostic-therapeutic protocol.	2004
Pediatric Rheumatology	Creation of a biobank for patients with pediatric rheumatic diseases.	2004
Surgery	Inoculation of botulin toxin for the treatment of achalasia of the internal anal sphincter	2005
Pediatric Clinic	The Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS)	2005
Laboratory of Oncology	Study of expression of IL-12, IL-23, IL-27 and their receptors in pediatric leukemias and lymphomas.	2005
Neurosurgery	Cooperative multicenter study for children and adolescents with low grade gliomas.	2005
Oncology, Hematology, and BMT	Protocol for patients with non metastatic rhabdomyosarcoma in pediatric age.	2005
Oncology, Hematology, and BMT	Protocol for localized non-rhabdoid soft tissue sarcoma.	2005
Pediatric Pneumology and Allergology	Use of cell material from human airway tissue for the study of the different biological activities of airway cells	2005
Pediatric Pneumology and Allergology	Cross-sectional longitudinal study of bronchial reactivity in asthmatic children and adolescents practising or starting to practise swimming	2005
Pediatric Clinic	Study of the natural history of the development of diabetes type 1	2006
Oncology, Hematology, and BMT	AIEOP LLA REC 2003: treatment of acute lymphoblastic leukemia relapse	2006

Oncology, Hematology, and BMT	AIEOP–LH 2004 therapeutic protocol	2006
Oncology, Hematology, and BMT	Use of peghylated filgrastim in severe chronic neutropenias	2006
Pediatric Rheumatology	Phase III study in juvenile dermatomyositis at onset: prednisone versus prednisone plus cyclosporine versus prednisone plus metotrexate	2006
Laboratory of Molecular Biology	Evaluation of changes of gene expression and identification of possible metabolic alterations in heart tissue during extracorporeal circulation and aortic clamping in a population of patients with congenital cardiopathies.	2007
Pediatric Clinic	Efficacy and tolerability of two substitution therapies in cases of di amenorrhea after antiblastic treatment in pediatric age	2007
Pediatric Clinic	Modifying genes in patients with cystic fibrosis and related liver disease	2007
Nephrology, Dialysis and Transplantation	Proteomic analysis of peritoneal effluents in patients treated with continuous cyclic peritoneal dialysis (CCPD).	2007
Pediatric Pneumology and Allergology	The association ipratropium bromide-salbutamol vs inhaled salbutamol in patients with bronchial asthma associated with gastroesophageal reflux	2007
Pediatric Rheumatology	Long-term, multicentre, observational study on Hunter syndrome (mucopolysaccharidosis type II) - HOS - Hunter Outcome Survey.	2007
Laboratory of Molecular Biology	Use of material of the Tissue-genomic Integrated Biobank of the Istituto Gaslini for diagnosis and research.	2008
PNICU	A multi-site RCT comparing regional and general anaesthesia for effects on neurodevelopmental outcome and apnoea in infants.	2008
Pediatric Clinic	Neonatal onset male hypogonadotropic hypogonadism	2008
Pediatric Clinic	Surveillance study after anti-pseudomonas vaccination in subjects with cystic fibrosis receiving at least one vaccination; it includes a control arm.	2008
Scientific Direction	Clinical trial: minor's awareness	2008
Epidemiology, Biostatistics and Committes	"Pensiero" project: histological centralization and activation of the national Registry of CNS tumors.	2008
Nephrology, Dialysis and Transplantation	A prospective registry study observing the safety and patterns of use of Darbepoetin Alpha in EU pediatric chronic kidney disease patients receiving or not receiving dialysis.	2008

Nefrology, Dialysis and Transplantation	Efficacy anti-CD20 monoclonal antibodies in patients with nephrotic syndrome resistant to combined therapy with steroids and calcineurin inhibitors	2008
Oncology, Hematology, and BMT	Active design of open randomized multicentre two-phase study on the association of bevacizumab with conventional chemotherapy in minors with rhabdosarcoma, non-rhabdomyosarcoma of soft tissues or Ewing's sarcoma/metastatic primary neuroectodermal tumors of soft tissues	2008
Oncology, Hematology, and BMT	Active design of open randomized multicentre two-phase study on the association of bevacizumab with conventional chemotherapy in minors with rhabdosarcoma, non-rhabdomyosarcoma of soft tissues or Ewing's sarcoma/metastatic primary neuroectodermal tumors of soft tissues	2008
Neurosurgery	Active design of open randomized multicentre two-phase study on the association of bevacizumab with conventional chemotherapy in minors with rhabdosarcoma, non-rhabdomyosarcoma of soft tissues or Ewing's sarcoma/metastatic primary neuroectodermal tumors of soft tissues	
Oncology, Hematology and BMT	Interfant 2006 for the treatament of children aged < 1 year with acute lymphoblastic leukemia	2008
Oncology, Hematology and BMT	Rules for the management of biological material and for its use for diagnostic and research purposes in neuroblastoma.	2008
Oncology, Hematology and BMT	Associated Clofarabine with Vepeside and Cyclophosphamide (CLOVE) salvage protocol for the treatement of resistant or second relapse acute leukemias in pediatric age	2008
Pediatric Rheumatology	Randomized double blind placebo-controlled parallel group 2-arm 12-week study to evaluate the efficacy and safety of tocilizumab in patients with active systemic juvenile idiopathic arthritis (sJIA), with 92 week extension of single arm open study the evaluate the long-term use of tocilizumab	2008
Pediatric Rheumatology	Randomized controlled study to evaluate the efficacy and tolerability of intraarticular injections of corticosteroids as monotherapy or in association with methotrexate in juvenile idiopathic arthritis	2008

Cardiovascular surgery	Efficacy of fenoldopam mesylate in the control of splancnic ischemia during extracorporeal circulation in pediatric patients.	2009
Pediatric Clinic	Anti-adrenal autoimmunity in pediatric subjects with diabetes mellitus type 1 and/or celiac disease.	2009
Pediatric Clinic	Bone density, body composition, glucide homeostasis in preterms.	2009
Infectious Diseases	International observational study on fungal infections in pediatric age ("International Pediatric Fungal Network").	2009
Nephrology, Dialysis and BMT	Pediatric chronic kidney disease and cardiovascular complications.	2009
Nephrology, Dialysis and BMT	Multicentre, controlled, intrapatient (retrospective-prospective) 12-month phase II/III open study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of cinacalcet hydrochloride in the treatment of secondary hyperparathyroidism in pediatric subjects with chronic renal failure on dialysis, with extension to further 6 months of observation	2009
Nephrology, Dialysis and BMT	Treatment of the child with previous acute pyelonephritis or recurrent urinary tract infections and prevention of renal damage: prospective randomized clinical study	2009
Oncology, Hematology, and BMT	Anti-TNF monoclonal antibody (Etanercept) for the treatment of acute GvHD refractory to first line steroid therapy	2009
Oncology, Hematology, and BMT	European prospective observational study for the evaluation of quality of life as related to the health conditions and to identify the situations and events impacting on the quality of life in patients with moderate or severe hemophilia A treated with Helixate NexGen	2009
Oncology, Hematology, and BMT	Immunosuppressive therapy with antilymphocyte serum, anti-TNF alpha, and cyclosporine for acquired aplastic anemia (AAA)	2009
Oncology, Hematology, and BMT	Treatment study for children and adolescents with acute Promyelocitic Leukemia	2009
Oncology, Hematology, and BMT	Preclinical evaluation of small molecules as potential therapeutic agents in Fanconi's anemia	2009
Pediatric Pneumology and Allergology	Acid and non-acid gastroesophageal reflux and respiratory disorders in pediatric age	2009
Pediatric Rheumatology	EUROFEVER. EULAR/PReS European network for the creation of a registry for the classification of autoinflammatory diseases in pediatric age	2009

Pediatric Rheumatology	Randomized, double blind, placebo-controlled study on the prevention of new acute phases with canakinumab (ACZ885) in patients with systemic juvenile idiopathic arthritis (SjIA) with active systemic manifestations	2009
Pediatric Rheumatology	MR ultrastructural evaluation of the joint cartilage in subjects with joints lacking pathogenic damage and comparison with subjects affected by juvenile idiopathic arthritis	2009
PNICU	Comparison between stereofundin (and glucose 1%) and physiological solution (and glucose 1%) for intraoperative maintenance fluid therapy in patients undergoing major and medium surgery chirurgia aged below 36 years	2010
PNICU	European network for central hypoventilation syndromes: optimizing health care to patients.	2010
Pediatric Clinic	Kuvan® Adult Maternal Paediatric European Registry	2010
Pediatric Clinic	Multicenter prospective randomized open with a blinded end point (PROBE) parallel-group study on treatment with biphasic insulin BIAsp70/30 and short-acting insulin or rapid-acting analogue plus glargine in comparison with short-acting insulin or rapid-acting analogue plus glargine to evaluate the metabolic control and quality of life in children and adolescent with type 1 diabetes mellitus over 12 months.	2010
Pediatric Clinic	Prevalence of metabolic syndrome in off-therapy patients after pediatric tumor. Analysis of risk factors and biochemical markers of the syndrome	2010
Pediatric Clinic	Study of bone mass and body composition in newborns and nurslings with different types of intrauterine growth	2010
Medical Genetics	Study of ion transport systems in human bronchial epithelium	2010
Nephrology, Dialysis and Transplantation	Therapy of post-Rituximab relapse of the nephrotic syndrome in short-mid and lasting remittent patients. Comparison of different therapeutic schemes	2010
Child Neuropsychiatry	Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as adjunctive therapy of refractory partial epileptic seizures in children: multicentre, parallel group, placebo-controlled, randomized, double blind clinical study	2010
Child Neuropsychiatry	Metallothionein in Rett syndrome	2010

Child Neuropsychiatry	Proinflammatory role of CC chemokines in the physiopathology of West syndrome and other epileptic encephalopathies	2010
Child Neuropsychiatry	Parallel group, placebo-controlled, double blind, multicentre, randomized clinical study on the effects of eslicarbazepine acetate (BIA 2-093) as adjunctive therapy on cognitive function in children with partial refractory epilepsy	2010
Child Neuropsychiatry	Botulin toxin A (BT-A) in the treatment of spasticity in developmental age	2010
Oncology, Hematology, and BMT	Clinical data collection in comprehensive diagnostics of Fanconi's anemia: creation of a clinical-biological database	2010
Oncology, Hematology, and BMT	Evoltra European Registry (Clofarabine)	2010
Oncology, Hematology, and BMT	Search for glucane in CSF in a population of subjects treated for acute lymphoblastic leukemia/non Hodgkin lymphoma	2010
Oncology, Hematology, and BMT	Single-dose pilot study of oral rivaroxaban in pediatric subjects with venous Thromboembolism	2010
Oncology, Hematology, and BMT	Randomized, open, dose definition comparative phase 1/2 combined study for the evaluation of efficacy and safety of plerixafor in addition to standard therapeutic regiments of mobilization of hemopoietic stem cells in peripheral blood and subsequent apheretic collection as compared to sole standard therapeutic regimens of mobilization in pediatric patients aged 2 to 18 years with solid tumors and suitable for autologous transplantation	2010
Oncology, Hematology, and BMT	Multicentre open study on the safety and phrmacokinetics of progressive doses of a recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in subjects with hemophilia B	2010
Pediatric Pneumology and Allergology	Applicability of the "Visual Analogic Scale" to a pediatric population with asthma and/or rhinitis as screening instrument for the evaluation of respiratory function	2010
Pediatric Pneumology and Allergology	Blood levels of vitamin D and respiratory infections in the preschool child	2010
Pediatric Rheumatology	A long term, multi-center, longitudinal post-marketing, observational registry to assess long term safety and effectiveness of HUMIRA (Adalimumab) in children with moderate to severe active polyarrticular or polyarticular course juvenile idiopathic arthritis (JIA)-STRIVE.	2010

Pediatric Rheumatology	An open-label, multicenter, efficacy and safety study of 4-month canakinumab treatment with 6-month follow-up in patients with active recurrent or chronic TNF-receptor associated periodic syndrome (TRAPS).	2010
Pediatric Rheumatology	Development of diagnostic criteria for macrophage activation syndrome (MAS) in systemic onset juvenile idiopathic arthritis (SJIA).	2010
Pediatric Rheumatology	NMR evaluation of early damage to joint cartilage in patients with juvenile idiopathic arthritis	2010
Pediatric gastroenterology with digestive endoscopy	A multicentre, prospective, long-term, registry of pediatric patients with Crohn's disease.	2010
Pediatric Emergency/Urgency	Multicentre randomized controlled trial for comparative evaluation of ondansetron versus domperidone for the symptomatic treatment of acute vomiting due to gastroenteritis in the child	2010
PNICU	Regional multicentre study on the risk of hospitalization for lower airway RSV infections in preterms: incidence and risk factors	2011
Cardiology	An open label, long term extension study for treatment of pulmonary arterial hypertension in paediatric patients aged 8 years up to 18 years who have participated in AMB112529 and in whom continued treatment with ambrisentan is desired.	2011
Pediatric Clinic	A randomized double-blind, placebo-controlled parallel group dose-finding study of linagliptin (1mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents, from 10 to 17 years of age, with type 2 diabetes and insufficient glycaemic control despite with diet and exercise alone.	2011
Pediatric Clinic	Database of the European forum on increlex® growth (injection of mecasermin [origin rdna]): European registry for monitoring of long-term safety and efficacy of increlex®	2011
Pediatric Clinic	Influence of aerobic training vs interval training on the activity of antioxidant enzymes and on glycometabolic parameters in children and adolescents with diabetes mellitus type 1	2011
Pediatric Clinic	Participation of the Cystic Fibrosis Centre of Genova in the Italian Cystic Fibrosis Registry at the Istituto Superiore di Sanità.	2011

Pediatric Clinic	Descriptive epidemiologic study on the identification of the methylation status of the genome in children with idiopathic short stature	2011
Pediatric Clinic	National multicentre observational study to evaluate compliance and long-term outcome of therapy in pediatric subjects using EasypodTM, an electromechanical device for the administration of growth hormone	2011
Pediatric Clinic	Radiological study of anomalies of the male reproductive system in cystic fibrosis	2011
Pediatric Clinic	Use of metformin in obese pediatric patients	2011
Pediatric Clinic	Evaluation of long-term risk-benefit profile of levothyroxin therapy in children with congenital hypothyroidism: influence of initial levothyroxin dose on neurological development, growth, cardiovascular and skeletal systems.	2011
Pediatric Clinic	Evaluation of adherence to aerosol antibiotic therapy with Promixin and I-neb in patients with cystic fibrosis: Italian multicentre observational study	2011
Pediatric Clinic	Evaluation of the effect of the diagnosis of cystic fibrosis as a result of neonatal screening on the communication relationship between mother and child and possible impact on nutritional behaviour and/or growth in the first five years of life	2011
Medical Genetics	Molecular study of genetic disorders associated with RET gene alterations.	2011
Laboratory of Oncology	Validation, characterization and selective targeting of new tumor markers in patients with neuroblastoma	2011
Nephrology, Dialysis and BMT	Multicentre, randomized, controlled, open, 12-month study to evaluate the efficacy, tolerability, and safety of the early administration of everolimus in association with reduced dose of calcineurin inhibitor (CNI) and with early steroid elimination as compared to therapy with standard dose of CNI, mycophenolate mofetil and steroid in pediatric patients undergoing renal transplantation, with further safety follow-up at 24 months	2011
Nephrology, Dialysis and BMT	Validation of assay of circulating antibodies versus glomerular neo-autoantigens (SOD2, AR, PLA2r) as surrogate biomarker of the evolution of membranous glomerulonephritis	2011
Neuropsychiatry	Multicentre, expanded access, open study with RAD001 in patients with subependymal giant cell (SEGA) associated with tuberous sclerosis (TSC).	2011

Pediatric Neurology and Muscular Diseases	Pharmacogenetic study on focal and generalized epilepsies: clinical predictive criteria of pharmacoresistance and search for predisposing genetic factors	2011
Pediatric Neurology and Muscular Diseases	Randomized, placebo-controlled, double blind study for the evaluation of safety and efficacy of intransal Midazolam (USL261) in the treatment of cluster epileptic seizures in outpatients-ARTEMIS1.	2011
Pediatric Neurology and Muscular Diseases	Multicentre, randomized, adaptive, double blind, placebo-controlled phase II study to evaluate safety and efficacy of olesoxime (TRO19622) in patients with spinal muscular atrophy (SMA) between 3 and 25 years of age	2011
Child Neuropsychiatry	A randomized, double-blind, placebo-controlled, parallel group study to evaluate AFQ056 in adult patients with Fragile X Syndrome.	2011
Child Neuropsychiatry	A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of AFQ056 in adolescent patients with Fragile X Syndrome.	2011
Child Neuropsychiatry	Open study to evaluate safety, tolerability, and long-term efficacy of AFQ056 in adult patients with Fragile X syndrome	2011
Child Neuropsychiatry	Multicentre, open, expanded access study with RAD001 in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TSC)	2011
Oncology, Hematology and BMT	A SIOPEN Study – Phase I-II study for dose and schedule of anti GD2 ch14.18/CHO monoclonal antibody in continuous infusion associated with Aldesleukin (IL2) in patients with refractory or relapsed neuroblastoma. Study of the International Society of Pediatric Oncology-Europe Neuroblastoma (SIOPEN).	2011
Oncology, Hematology and BMT	An open-label, multicenter, single-arm, Phase I dose-escalation with efficacy tail extension study of RO5185426 in pediatric patients with surgically incurable and unresectable Stage IIIC or Stage IV melanoma harboring BRAFV600 mutations.	2011
Oncology, Hematology and BMT	Expression of ABCB1/P-glycoprotein as factor for biological stratification of non metastatic osteosarcoma of extremities: a prospective study	2011
Oncology, Hematology and BMT	Follow-up of patients at risk for bronchiolitis obliterans after allogenic stem cell transplantation	2011

Oncology, Hematology and BMT	International cooperative protocol for the treatment of children and adolescents with acute lymphoblastic leukemia	2011
Oncology, Hematology and BMT	Multicentre pediatric registry in essential thrombocytemia (ET).	2011
Oncology, Hematology and BMT	Randomized, double blind, active drug-controlled, internal blind phase II study to evaluate the efficacy and safety of Aprepitant in the prevention of nausea and vomiting induced by chemotherapy (CINV) in pediatric patients	2011
Oncology, Hematology and BMT	Multicentre pharmacokinetic open study on oral nilotinib in pediatric patients with chronic phase (CP) or accelerated phase (AP) Ph+ CML resistant/intolerant to Gleevec (imatinib) or with Ph+ refractory/relapsing ALL	2011
Oncology, Hematology and BMT	International multicentre randomized phase II study on combined vincristine and Irinotecan, with or without Temozolomide, in patients with refractory or relapsed rhabdomyosarcoma	2011
Oncology, Hematology and BMT	Evaluation of the metabolomic profile in serum and urine of patients with Fanconi's anemia	2011
Neonatal Disease	Sli study: respiratory assistance in delivery room with sustained lung inflation in the extremely preterm newborn at risk for RDS. A controlled randomized study	2011
Neonatal Disease	Validation of the "champs" instrument for the evaluation of the risk of fall of the underage patient in a children's hospital	2011
Pediatric Rheumatology	Cross-cultural adaptation and validation of the parents' and patients' version of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR).	2011
Pediatric Rheumatology	Pharmacovigilance in patients with juvenile idiopathic arthritis (Pharmachild). A registry of PRINTO (Paediatric Rheumatology International Trials Organisation) and PRES (Pediatric Rheumatology European Society)	2011
Pediatric Rheumatology	International, observational , non-interventional, volunteer study programme on lisosomal storage diseases	2011
Pediatric Rheumatology	Registry for patients with Niemann-Pick Type C Disease	2011
PNICU	Monitoring of abstinence syndrome in PIC through use of WAT1 scale	2012
PNICU	International point prevalence study on volemic reintegration with resuscitation manoeuver in intensive care pediatric patients	2012

Cardiology	Hemodynamic effects of mechanical ventilation and nCPAP on the preterm newborn	2012
Pediatric Clinic	A single arm, open-label, multicenter, Phase IV trial to assess long term safety of tobramycin inhalation powder (TIP) in patients with Cystic Fibrosis.	2012
Pediatric Clinic	Glycemic control and quality of life in children, adolescents and young adults with type 1 diabetes mellitus descirbed in a world-wide cross-sectional study in 2012: Impact of age-patient-related, treatment-related, behaviour and structure of care-related variables – TEENs study	2012
Pediatric Clinic	Small intestine bacterial colonization syndrome in cystic fibrosis: epidemiology, clinical impact, and experimentation of a therapeutic protocol	2012
Pediatric Clinic	Multicentre, randomized, double blind, placebo- and metformin-controlled phase III clinical study to evaluate the safety and efficacy of sitagliptin in poorly compensated pediatric patients with diabetes mellitus type II	2012
Pediatric Clinic	European study on modifying genes in cystic fibrosis. Italian network.	2012
Pediatric Clinic	Investigation of cystic fibrosis airway microbiome in patients showing a severe decline in lung function and not responding to conventional antimicrobial therapy	2012
Laboratory of Molecular Genetics and Service of Cytogenetics	Identification of the genetic bases of Poland anomaly.	2012
Laboratory of Molecular Genetics and Service of Cytogenetics	Molecular study of genetic disorders associated with PHOX2B gene alterations	2012
Laboratory of Oncology	Study of the role of IL-27 in the progression of leukemias and in the regulation of normal and leukemic hemopoietic stem cell compartment	2012
Nephrology, Dialysis and Transplantation	International Pediatric Peritoneal Biopsy Study in Children.	2012
Nephrology, Dialysis and Transplantation	Prospective study protocol of renal parenchyma with DWI-MR sequence in upper urinary tract infections for the detection of parenchymal focuses	2012
Neurosurgery	Sequencing of the whole genome and/or exome in familial and sporadic cases of neural tube defects by massive new generation sequencing (NGS)	2012

Pediatric Neurology and Muscular Diseases	Evaluation of upper limb function in patients with limited mobility affected by Duchenne muscular dystrophy	2012
Child Neuropsychiatry	Open study to evaluate safety and long-term tolerability of AFQ056 in adolescent patients with fragile X syndrome	2012
Oncology, Hematology and BMT	European low and intermediate risk neuroblastoma - SIOPEN study	2012
Oncology, Hematology and BMT	Reinduction protocol for patients with first relapse of high risk neuroblastoma	2012
Oncology, Hematology and BMT	Multicentre, historical data-controlled phase II clinical study with Dasatinib added to standard chemotherapy in children and adolescents with new diagnosis of Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL)	2012
Oncology, Hematology and BMT	Phase II multicentre study to evaluate the activity and toxicity of liposomal cytarabine in the treatment of acute lymphoblastic leukemia and resistant or relapsing meningeal localization after systemic and intrarachidian treatment	2012
Oncology, Hematology and BMT	Multicentre, single-arm, open, pilot study to explore safety, tolerability, pharmacokinetics, and efficacy of multiple intravenous administrations of NI-0501, an anti-gamma interferon monoclonal antibody (anti-IFNγ), in pediatric patients with reactivated primary hemophagocytic lymphohistiocytosis (HLH)	2012
Oncology, Hematology and BMT	International trial for children and adolescents with B cell LNH or ALL-B: evaluation of efficacy and safety of Rituximab in high risk patients	2012
Pediatric Pneumology and Allergology	Prevalence of resistance to macrolides in Mycoplasma pneumoniae in a pediatric population with lower airway infections	2012
Pediatric Rheumatology	A long-term, open-label follow-up study of CP-690,550 for treatment of juvenile idiopathic artnritis (JIA)	2012
Pediatric Rheumatology	An open-label multiple dose study to evaluate the pharmacokinetics, safety and tolerability of CP-690,550 in pediatric patients from 2 to less than 18 years of age with juvenile idiopathic arthritis (JIA)	2012
Pediatric Rheumatology	Standardization of joint US examination in patients with juvenile idiopathic arthritis	2012
Pediatric Rheumatology	International, multicentre, non-controlled, open phase IIa study to evaluate the safety and pharmacokinetics of 4 i.v. infusions of rituximab 375 mg/m2 each in pediatric patients with severe granulomatosis with polyangitis (Wegener's) or microscopic polyangitis	2012

Pediatric Rheumatology	Phase IV study to evaluate the reduction of the frequency of tocilizumab administration in patients with systemic juvenile idiopathic arthritis (sJIA) showing anomalies of laboratory parameters during treatment with tocilizumab	2012
Pediatric Rheumatology	Multicentre, randomized, double blind, placebo-controlled, parallel group study to evaluate the safety, efficacy, and pharmacokinetics of belimumab, an anti-Blys monoclonal antibody, in addition to standard therapy in pediatric patients with systemic lupus erythematosus (LES)	2012
Pediatric Rheumatology	Validation of the multidimensional questionnaire for Juvenile Dermatomyositis Multidimensional Assessment Report (JDMAR)	2012
Pediatric Rheumatology	Ultrastructural evaluation of the joint cartilage by MR in patients with cryopyrinopathies	2012
Pediatric Emergency/Urgency	Monitoring of safety and evaluation of appropriateness of antibiotic use in children with bronchopneumonia, pharyngotonsillitis and acute otitis media in Liguria region	2012
Surgery	Comparison between sensory saturation and oral glucose during lumbar puncture for subarachnoid anesthesia in the newborn. A randomized, controlled, open study	2012
Cardiology	Retrospective study on the incidence of respiratory diseases in the first two years of life in children with hemodynamically significant congenital cardiopathies: the Italian experience (SINERGY)	2013
Cardiology	Double blind study on the efficacy and safety of tadalafil type 5 phosphodiesterase in pediatric patients with pulmonary arterial hypertension	2013
Pediatric Clinic	A phase III, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous for the F508del-CFTR Mutation"	2013
Pediatric Clinic	Quality of life in the young with short stature	2013
Dermatology	Observational study on the therapeutic approach to atopic dermatitis and on the role of corticophobia in determining compliance to treatment	2013
Infectious Diseases	Co-trimoxazole plasma dosage in pediatric patients	2013

Nephrology, Dialysis and Transplantation	Prospective randomized study to optimize prednisone therapy in relapses of idiopathic nephrotic syndrome in children (PROPINE study)	2013
Pediatric Neurology and Muscular Diseases	Randomized, double blind, placebo-controlled, phase III study on the use of tadalafil in Duchenne muscular dystrophy.	2013
Child Neuropsychiatry	A three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures	2013
Child Neuropsychiatry	Role of attachment as protection factor in somatoform and disruptive behaviour: a clinical study	2013
Child Neuropsychiatry	Multicentre, randomized, double blind, placebo-controlled study for the evaluation of safety and efficacy of a dose of aripiprazole administered orally once a day in children and adolescents with Tourette syndrome.	2013
Child Neuropsychiatry	Treatment with BOTOX in pediatric patients with lower limb spasticity: a double blind study	2013
Oncology, Hematology and BMT	Diagnostic efficacy and prognostic implications of 18F-DOPAPET/CT method in the study of high risk neuroblastoma: comparison with I-123-MIBG scintigraphy	2013
Oncology, Hematology and BMT	MD-Paedigree – Integration of data and processes in juvenile idiopathic arthritis	2013
Oncology, Hematology and BMT	Multinational European Trial Children with Opsoclonus Myoclonus Syndrome/ Dancing Eye Syndrome	2013
Oncology, Hematology and BMT	Randomized, partially blind, active comparative, controlled phase IIb study to evaluate pharmacokinetics/pharmacodynamics, safety and tolerability of fosaprepitant in pediatric patients for the prevention of nausea and vomiting associated with emetogenic chemotherapy	2013
Oncology, Hematology and BMT	Multicentre, open, dose definition, phase I/II study for evaluation of safety and tolerability and preliminary evaluation of effectiveness of nab-paclitaxel in pediatric subjects with relapsed or refractory solid tumors	2013
Oncology, Hematology and BMT	Multicentre, single arm, phase II study of Moxetumomab Pasudotox in pediatric subjects with relapsing or refractory pediatric acute lymphoblastic leukemia or B cell lymphoblastic lymphoma	2013

Oncology, Hematology and BMT	Multicentre, non controlled phase II study to evaluate the efficacy and safety of oral nilotinib in pediatric patients with newly diagnosed Ph+ chronic myeloid leukemia during chronic phase or with Ph+ chronic myeloid leukemia during chronic or accelerated phase resistant or intolerant to imatinib or dasatinib	2013
Oncology, Hematology and BMT	Multicentre study for long-term monitoring of patients with HLH receiving treatment with NI-0501, an anti-interferon gamma monoclonal antibody (anti-IFNy)	2013
Oncology, Hematology and BMT	Use of cyclophosphamide after non t-depleted haploidentical stem cell transplantation	2013
Pediatric Pneumology and Allergology	Allergy to house dust mites and viral respiratory infections in pediatric age	2013
Pediatric Pneumology and Allergology	Definition of new inflammatory markers of severity and etiology in the child with community acquired pneumonia (CAP) and their correlation with clinical and lung US parameters	2013
Pediatric Rheumatology	An observational registry of abatacept in patients with juvenile idiopathic arthritis	2013
Pediatric Rheumatology	Comparison between US and MR examinations in patients with juvenile idiopathic arthritis	2013
Pediatric Rheumatology	Anti-biopharmaceutical immunization: predictors and analysis of clinical relevance to minimize the risk of immunization in rheumatoid arthritis and in juvenile idiopathic arthritis (substudy of Pharmachild – Pharmacovigilance in patients with juvenile idiopathic arthritis)	2013
Pediatric Rheumatology	Multicentre, open phase Ib study for the evaluation of pharmacokinetics, pharmacodynamics and safety of tocilizumab administered subcutaneously in patients with systemic juvenile idiopathic arthritis	2013
Pediatric Rheumatology	Multicentre, open phase Ib study for the evaluation of pharmacokinetics, pharmacodynamics, and safety of tocilizumab administered subcutaneously in patients with juvenile idiopathic arthritis with polyarticular course	2013
Pediatric Rheumatology	Multinational, multicentre open study to evaluate the safety, efficacy, and pharmacokinetics of asfotase alpha (recombinant human non tissue-specific alkaline phosphatase fusion protein) in newborns and children aged ≤ 5 years with hypophosphatasia (HPP)	2013

Pediatric Rheumatology	Multicentre, randomized, placebo-controlled study of SBC-102 in patients with lack of lisosomal acid lipase	2013
Pediatric Rheumatology	Treatment of recurrent idiopathic pericarditis with anakinra	2013

SEMINARS

DATE	PROPOSING UNIT(S)	SPEAKER	TITLE
31/01/13	Scientific Direction - Library	Fabio Di Bello	Presentation of new bibliographic resources
15/02/13	Scientific Direction	Giuseppe Poli	Oxidized lipids during the development of Alzheimer disease
21/02/13	Scientific Direction	Leticia Huergo	Epithelial-mesenchymal transition induces an anti-tumor immune response mediated by NKG2D receptor
18/02/13	Airway Team	Philippe Monnier	1) Oesophageal and laryngeal stenosis due to caustics: clinical and reconstructive aspects; 2) Tracheotomy: techniques, pros and cons
26/02/13	Laboratory of Oncology	Elena Adinolfi	P2X7 receptor as new oncogene and potential target in neuroblastoma
01/03/13	High intensity care and Birth pathway	Rinaldo Zanini Danilo Celleno	Evidence Based Medicine of clinical risk management in delivery room: a research analysis of recent outcomes
14/03/13	Scientific Direction Rare Diseases Medical Genetics	Maja Di Rocco Roberto Ravazzolo	**RESEARCH AT GASLINI** 1) Open clinical issues in progressive ossifying fibrodysplasia; 2) Progressive ossifying fibrodysplasia: aspects of molecular genetics and studies on the regulation of ACVR1 gene expression
15/03/13	Scientific Direction	Daniel Olive	Interaction of BTLA-HVEM in the regulation of Vg9Vd2 T cells in lymphoma
03/04/13	Scientific Direction Clinical Hematology Laboratory of Clinical and Experimental Immunology	Concetta Micalizzi Stefania Mercenaro	**RESEARCH AT GASLINI** Hemophagocytic histiocytosis: a challenge for the clinician and the laboratorist
22/04/13	Scientific Direction	Claudio Lunardi	Role of Endothelin-1 in the pathogenesis of systemic sclerosis (and of its complications)
24/04/13	Scientific Direction Muscular Diseases	Federico Zara Pasquale Striano	**RESEARCH AT GASLINI** From Hippocrates to the age of "next generation sequencing": successes of genetics and impact on the clinical practice

08/05/13	Medical Genetics	Giambattista Bonanno Giorgio Casari	1) Group I metabotropic glutamate receptors, abnormal glutamate release and excitotoxicity: role in amniotrophic lateral sclerosis 2) Spinocerebellar ataxia type 28, from molecular hypothesis to preclinical treatment
10/05/13	Scientific Direction Neurosurgery	Valeria Capra Patrizia De Marco	**RESEARCH AT GASLINI** Update on genetics of Neural Tube Defects
17/05/13	Laboratory of Molecular Genetics	Andres Stutzin	TRPM4, hydrogen peroxide and necrotic cell death
22/05/13	Translational Centre of Myology and Neurodegenerative Diseases	Ester Zito	Scurvy is the cost to pay for a defective oxidative protein folding
22/05/13	Scientific Direction Nephrology, Dialysis and Transplantation	Gian Marco Ghiggeri Maurizio Bruschi	**RESEARCH AT GASLINI:** Autoimmune nephropathies: from basic research to routine diagnostics
23/05/13	Scientific Direction	Alberto Diaspro	Breaking news in imaging - Talking about superresolution
28/05/13	Scientific Direction	Francesco Di Virgilio	The split personality of adenosine triphosphate (ATP): an energy currency as well as a signl of danger
30/05/13	Scientific Direction	Claudio Ortolani	Cytometry and statistics: positive and negative aspects of a love match
06/05/13	Scientific Direction	Franco Locatelli	Pediatric hematology/oncology, a model for translational clinical research
07/06/13	Scientific Direction Cystic Fibrosis Centre – Pediatric Clinic Medical Genetics	Laura Minicucci Luis Galietta	**RESEARCH AT GASLINI** Cystic fibrosis: from gene identification to correction of underlying defect
10/06/13	Scientific Direction	Roberto M. Lemoli	Bone marrow stem cells detect danger through purinergic signaling
19/06/13	Scientific Direction Medical Genetics Pediatric Rheumatology	Isabella Ceccherini Marco Gattorno	**RESEARCH AT GASLINI:** When infiammation lights up by itself: positive and negative aspects of next generation sequencing in autoinflammatory syndromes
04/07/13	Scientific Direction Clinical and Experimental Oncology Laboratory of Oncology	Alberto Garaventa Ignazia Progione	**RESEARCH AT GASLINI** Immunological studies and immunotherapy in neuroblastoma

08/07/13	Neuroradiology Neurosurgery	Martin Catala	Gastrulation and neurulation: the actual facts and a need for a new classification of spinal cord malformations
09/07/13	Scientific Direction	Gioacchino Natoli	Macrophage specialization and plasticity: what can we learn from genomic approaches
10/07/13	Pediatric Rheumatology	Pierre Miossec	Cytokine interactions in chronic joint inflammation
18/07/13	Medical Genetics	Alessio Accardi	Ion and lipid transport in an ion channel of TMEM16 family
13/09/13	Scientific Direction	Stefano Papa	Study of cell communication in flow cytometry
09/10/13	Scientific Direction Laboratory of Clinical and Experimental Immunology Department of Experimental Medicine, University of Genova	Cristina Bottino Roberta Castriconi	**RESEARCH AT GASLINI** Virtues and vices of the immune system
23/10/13	Scientific Direction	Max D. Cooper	A Darwinian View of Adaptive Immunity
05/11/13	Scientific Direction Laboratory of Molecular Biology Clinical Oncology	Luigi Varesio Massimo Conte	**RESEARCH AT GASLINI** Neuroblastoma risk factors: from biology to therapy
21/11/13	Scientific Direction Clinical and Experimental Hematology	Carlo Dufour Johanna Svahn	**RESEARCH AT GASLINI** Fanconi's anemia. Positive and negative aspects of a rare pre-neoplastic disease
26/11/13	Core Facilities	Jörg Schlegel	Amnis quantitative imaging flow cytometry: statistical microscopy of thousands of cells in flow for science-driven conclusions backed up by statistics
04/12/13	Scientific Direction Core Facilities Laboratory of Mass Spectrometry and Proteomics Laboratory of Oncology	Andrea Petretto Lizzia Raffaghello	**RESEARCH AT GASLINI** Proteomics as an instrument for the study of tumor metabolism
05/12/13	Hematology-Oncology	Roberto Maggi	Obtaining cancer stem cells from a human neuroblastoma cell line (SK-N-AS)

MINISTRY OF HEALTH-FUNDED PROJECTS

"Role of protein misfolding in the pathogenesis of Niemann-Pick type C disease: a possible therapeutic target".
In collaboration with "Santa Maria della Misericordia" Hospital of Udine.
Principal investigator: Dr. Mirella Filocamo.
Grant: € 42,500.00

"Search for novel genes involved in heterogeneous Cryopyrin associated periodic syndromes (CAPS)- like autoinflammatory disorders".
Principal investigator: Dr. Silvia Borghini
Grant: € 281,800.00

"Interleukin-27 in the control of pediatric acute leukemia cell growth in NOD/SCID/Il2rg-/-mice with human immune system".
Principal investigator: Dr. Irma Airoldi
Grant: € 274,840.00

"Congenital anomalies of the kidney and urinary tract (CAKUT): definition of genetic and structural backgrounds based on high through-put innovative approaches".
Principal investigator: Dr. Gian Marco Ghiggeri
Grant: € 244,100.00

"Identification of genes for rare developmental disorders by next generation sequencing".
Principal investigator: Dr. Federico Zara
Grant: € 451,500.00

"Childhood Histiocytoses: getting deeper in pathogenesis and exploring novel therapeutic approaches".
In collaboration with Meyer Hospital of Firenze.
Principal investigator: Prof. Lorenzo Moretta
Grant: € 60,000.00

"Optimization of alloreactive natural killer (NK) cell- and invariant NKT (iNKT) cell-mediated anti-leukemia effect in children with hematological malignancies given a T-cell depleted hematopoietic stem cell transplantation (HSCT) from an HLA-disparate relative".
In collaboration with "Bambino Gesù" Children's Hospital of Roma.
Principal investigator: Prof. Lorenzo Moretta
Grant: € 75,000.00

***"*Congenital Myopathies: genetic screening starting from a new diagnostic algorithm".**
In collaboration with "Bambino Gesù" Children's Hospital of Roma.
Principal Investigator: Dr. Claudio Bruno
Grant: € 26,400.00

"Definition of mechanisms controlling processing and secretion of IL-1beta in health and autoinflammatory diseases, search for novel therapeutic strategies".
In collaboration with "San Martino/IST" hospital of Genova.
Principal Investigator : Dr. Sabrina Chiesa
Grant: € 190,700.00

"A multidisciplinary study to investigate the molecular bases of hereditary tubulointerstitial nephritis".
In collaboration with "Ospedale San Raffaele S.r.l." of Milano.
Principal Investigator : Dr. Gian Marco Ghiggeri
Grant: € 25,500.00

"Creation of a database of MR studies in normal children and in children with rare neurological diseases".
In collaboration with "Associazione La Nostra Famiglia – Eugenio Medea" of Milano.
Principal Investigator: Dr. Andrea Rossi
Grant: € 30,000.00

"Implementation and optimization of T-cell therapy for EBV-related tumors".
In collaboration with San Matteo hospital of Pavia.
Principal Investigator : Dr. Gian Marco Ghiggeri
Grant: € 45,000.00

"Analysis of lymphoid cells with effector or regulatory function in children with solid tumors or high-risk leukemias".
Principal Investigator: Prof. Lorenzo Moretta
Grant for acquisition of equipment: € 540,000.00

"Acquisition and implementation of a high field 3 tesla MRI tomograph"
Principal Investigator: Dr. Andrea Rossi
Grant for acquisition of equipment: € 1,360,000.00

"Integrated system of biological images"
Principal Investigator: Dr. Gino Tripodi
Grant for acquisition of equipment: € 400,000.00

Additional grant for further research projects: € 8.211,691.41

EU-FUNDED RESEARCH PROJECTS

"Model Driven European Digital Repository – MD PAEDIGREE".
In collaboration with "Bambino Gesù" Children's Hospital of Roma.
Principal Investigator: Dr. Alberto Martini
Grant: € 307,960.00

"European registry of patients with McArdle disease and very rare muscle glycogenolytic disorders (MGD) with exercise intolerance as the major symptom (PR-MDMGD) – EUROMAC".
In collaboration with "Fundacio' Hospital Universitari Vall d'Hebron – Institut de Recerca".
Principal Investigator: Dr. Claudio Bruno
Grant: € 39,945.00

"PanCare Studies in fertility and ototoxicity to improve quality of life after cancer during childhood, adolescence and young adulthood. PanCare LIFE".
In collaboration with "Universitaetsmedezin der Joahannes Gutemberg – Universitat Mainz".
Principal Investigator: Dr. Riccardo Haupt
Grant: € 200,819.00

"GAbapentin in Paediatric Pain. GAPP".
In collaboration with the "Consortium for Biological and Pharmacological Evaluations" of Bari.
Principal Investigator: Dr. Luca Manfredini
Grant: € 148,791.25

RESEARCH PROJECTS FUNDED BY ITALIAN ASSOCIATION FOR CANCER RESEARCH - ASSOCIAZIONE ITALIANA PER LA RICERCA SUL CANCRO (AIRC)

"Post-transcriptional control of RET gene expression: implications in thyroid cancer". 2nd year.
Principal Investigator: Dr. Isabella Ceccherini
Grant: € 65,000.00

"PH0X2B overexpression and pathogenetic interactions as targets for a pharmacological approach to Neuroblastoma". 3rd year.
Principal Investigator: Dr. Tiziana Bachetti
Grant: € 50,000.00

"Interleukin-27 in the control of pediatric acute leukemia cell growth in humanized mice". 2nd year.
Principal Investigator: Dr. Irma Airoldi
Grant: € 140,000.00

"MicroRNA replacement and RNAi-mediated silencing of ALK as combined targeted therapies for Neuroblastoma". 2nd year.
Principal Investigator: Dr. Patrizia Perri
Grant: € 55,000.00

"NK cell subsets in germinal center B cell lymphoma microenvironment: cellular and molecular characterization". 2nd year.
Principal Investigator: Dr. Vito Pistoia
Grant: € 90,000.00

RESEARCH PROJECTS FUNDED BY PRIVATE INSTITUTIONS OR COMPANIES

"Sax 2012, Lm Int. Leinbniz Research Cluster Immunomemory".
In collaboration with Deutches Rheuma Forschungszentrum Berlin.
Principal Investigator: Prof. Lorenzo Moretta
Grant: € 5,480.53

"Definition of panels for allergologic diagnostics with the use of molecular allergologic markers. Cost/benefit analysis of their daily routine use."
Project funded by Thermo fischer
Principal Investigator: Prof. Giovanni Melioli
Grant: € 20,000.00

"Characterization and isolation of tumor-derived human endothelial cells in neuroblastoma: implications for drug-resistance and immunotherapy"
Project funded by "Maria Piaggio Casarsa Foundation".
Principal Investigator: Dr. Annalisa Pezzolo
Grant: € 17,500.00

"Dietary Restriction, GH/IGF-I & Mechanisms of Differential Cellular Protection." 2nd year.

Project funded by "University of Southern California".
Principal Investigators: Drs. Vito Pistoia and Lizzia Raffaghello
Grant: € 40,420.03

Donation to support research activity in the field of lisosomal diseases and of the functional study in patients with Gaucher disease.
Project funded by Sanofi-Aventis S.p.A.
Principal Investigator: Dr. Mirella Filocamo
Grant: € 15,000.00

International project for validation criteria to determine clinical improvement in juvenile dermatomyositis and polymyositis.
Project funded by "European League Against Reumathisms (EULAR)" of Zurich.
Principal Investigator: Dr. Alberto Martini
Grant: € 20,895.00

Contribution to support the "**Eurofever Project**" by the pharmaceutical company "Swedish Orphan Biovitrum AB (SOBI)" of Stockholm.
Principal Investigator: Dr. Alberto Martini
Grant: € 14,000.00

"Role of the novel presynaptic protein PRRT in neuronal physiology and in the pathogenesis of paroxysmal neurological disorders".
Project funded by Telethon Foundation.
Principal Investigator: Dr. Federico Zara
Grant: € 136,000.00

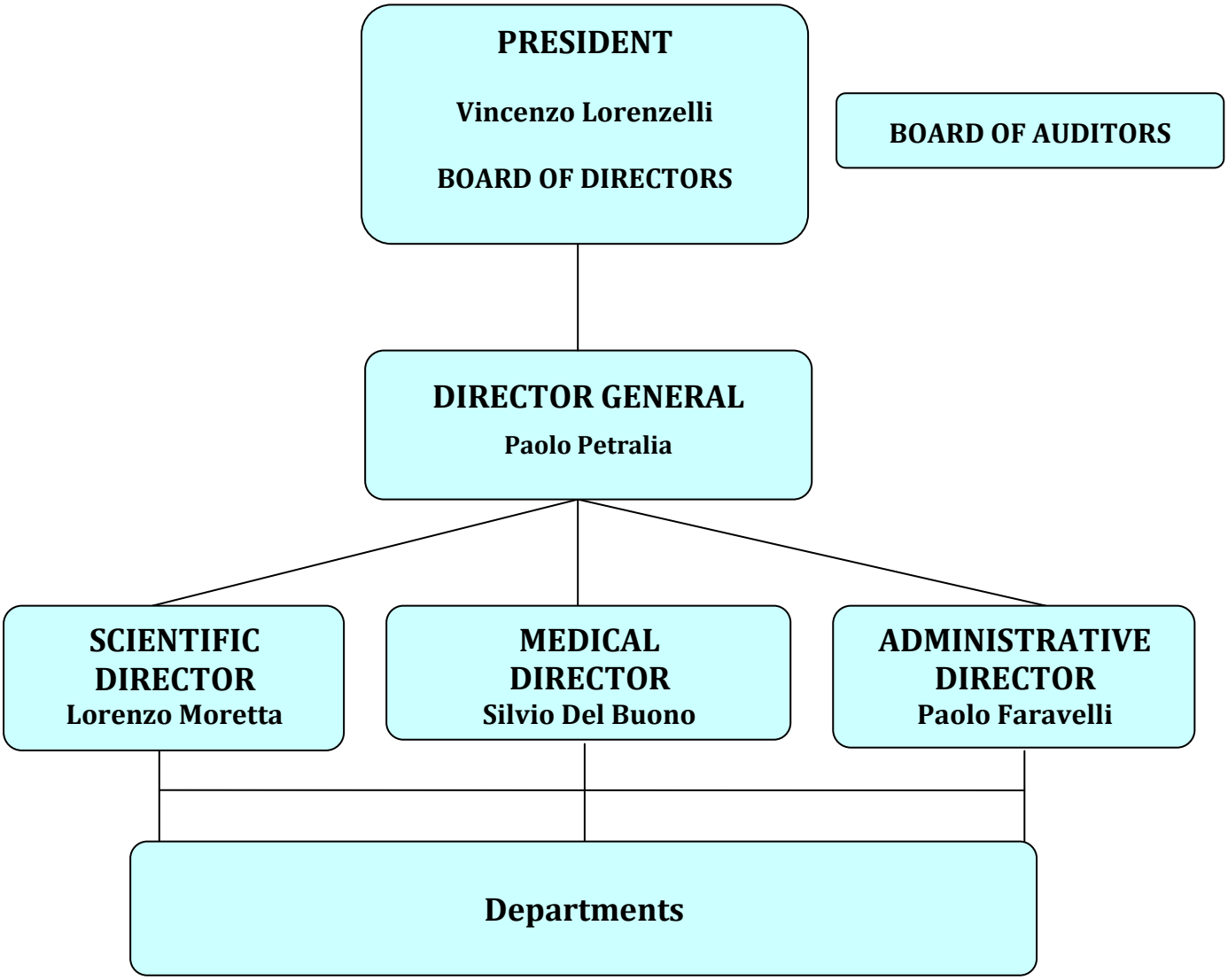
Donation by the pharmaceutical company ChanTest Corporation of Cleveland, USA for the acquisition of equipment to be used to carry out research projects.
Principal Investigator: Dr. Luis Galietta
Grant: € 12,000.00

Contribution by "Umberto Veronesi Foundation" aimed at co-funding Dr. Tiziana Bachetti's contract of excellence for collaboration to the research project: **"High throughput drug screening approaches to identify molecules able to oppose the pathogenetic effects of PHOX2B overexpression in neuroblastoma".**
Grant: € 27,000.00

RESEARCH PROJECTS FUNDED BY PUBLIC INSTITUTIONS

"Randomized study for optimization of steroid treatment of corticosensitive idiopathic nephrosic syndrome (PROPINE Study), funded by the "Agenzia Italiana del Farmaco".
In collaboration with "Bambino Gesù" Hospital of Roma.
Principal Investigator: Dr. Gian Marco Ghiggeri
Grant: € 3,300.00

"Twenty four month, multi center, prospective, randomized, double-blind, placebo controller, parallel-group study to evaluate the efficacy, safety, tolerability, and cost-effectiveness of allergen specific sublingual immunotherapy (SLIT) in combination with standard of care (SoC) in pediatric allergic asthma", funded by the "Agenzia Italiana del Farmaco". In collaboration with the"Associazione per la Ricerca sull'Allergia e l'Asma Infantili – ALLEGRIA Onlus".
Principal Investigator: Dr. Mariangela Tosca
Grant: € 98,500.00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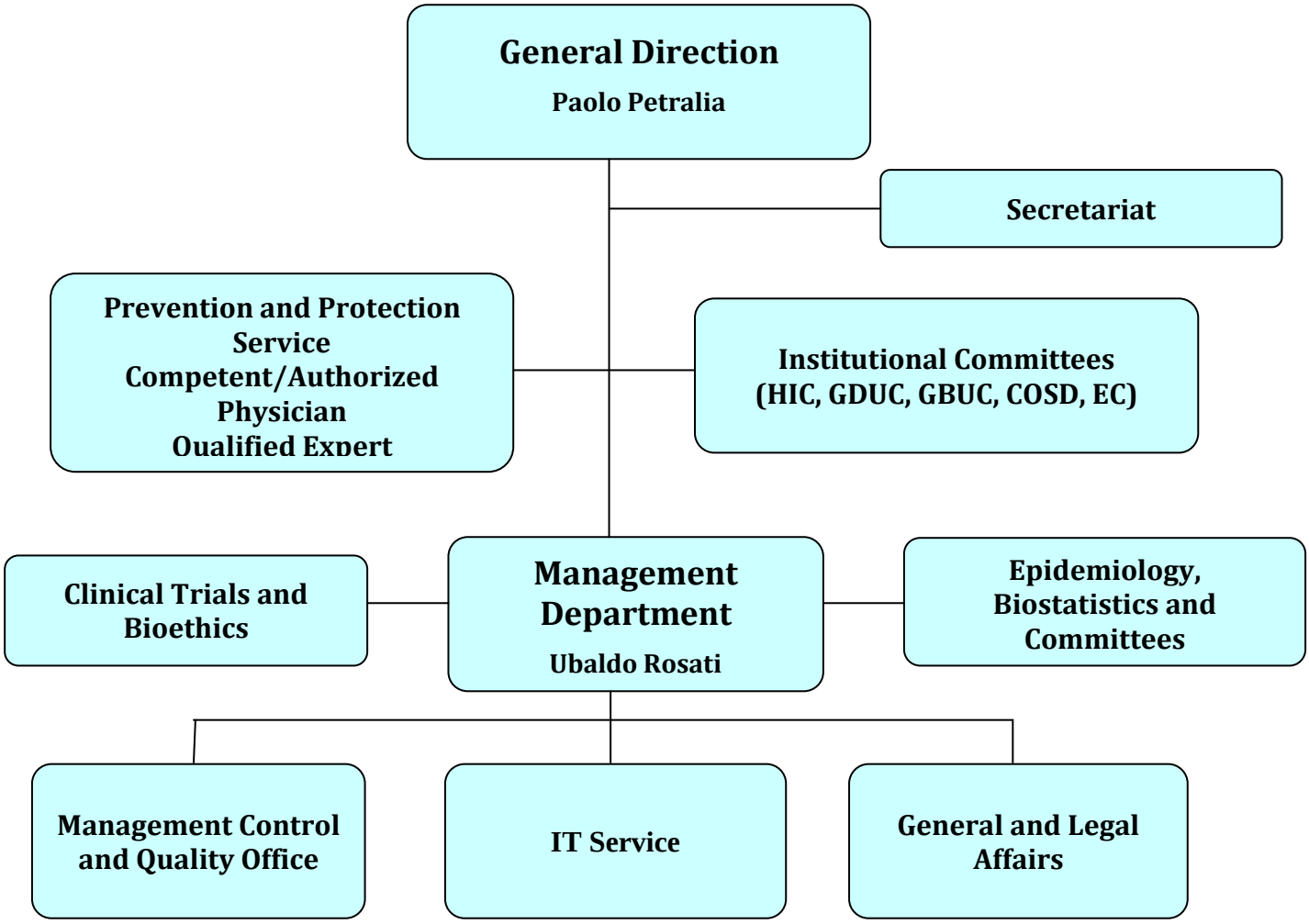
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Management Control and Quality Office
IT Service
General and Legal Affairs

Management Control and Quality Office

Director: Ubaldo Rosati

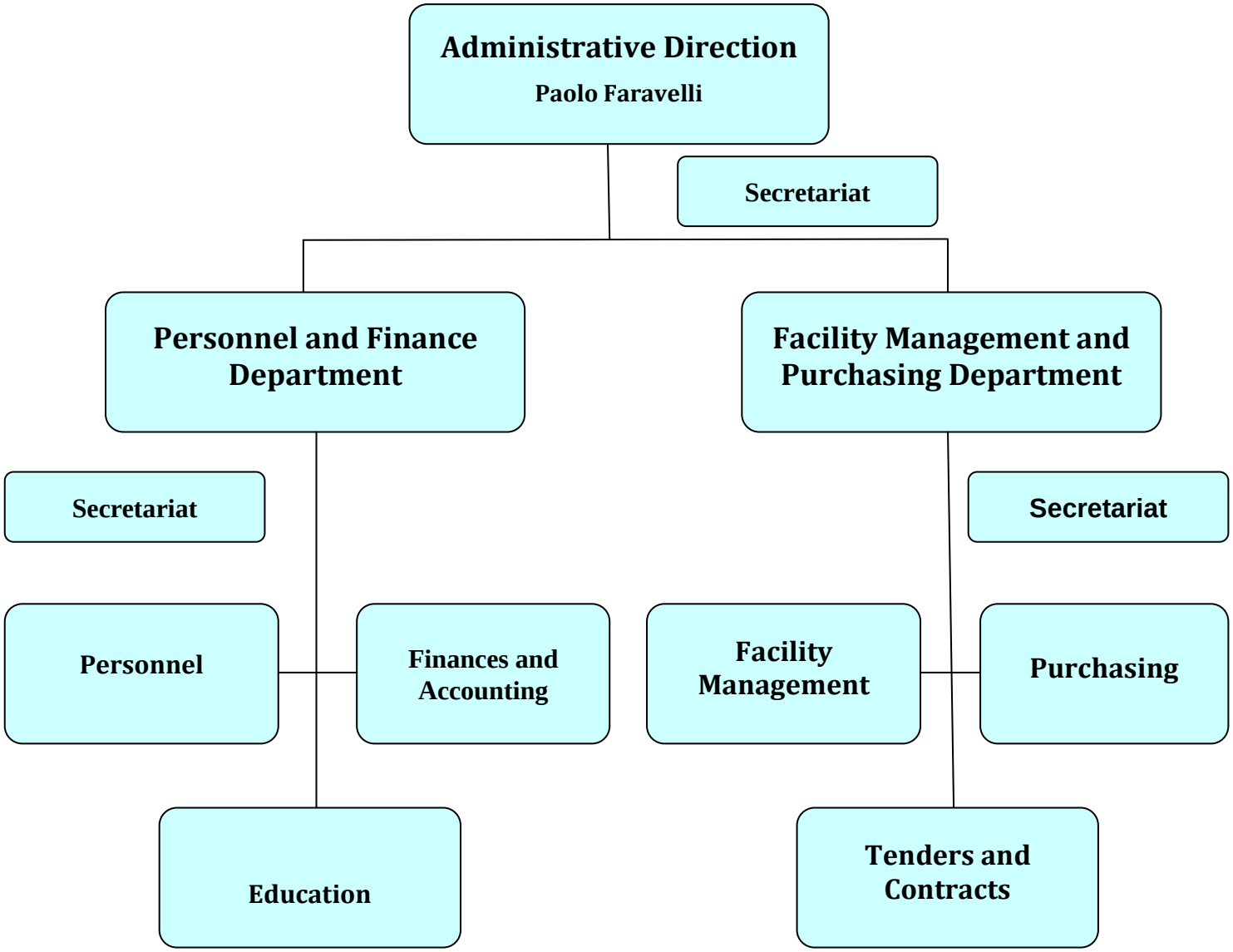
Staff

Elena Battistini Fulvia Cavanenghi Chiara Giuliano Pierina Santini

Multicentre project for clinical risk management in pediatrics

Objective: 1) Benchmark analysis comparing Gaslini Institute with National Health Service (UK) hospitals; 2) Focus on risk problems in the urgency/emergency area 3) Identification of instruments 4) Staff training.

Description: A. development of the methodological model to adopt for the improvement of safety in pediatric age and proposal of actions to undertake according to their efficacy, on the basis of evidence available in the literature and evaluation results, in compliance with ethical principles established by national and international organisms; B. definition and testing of a method for evaluation of activities carried out to reduce clinical risk in pediatric age.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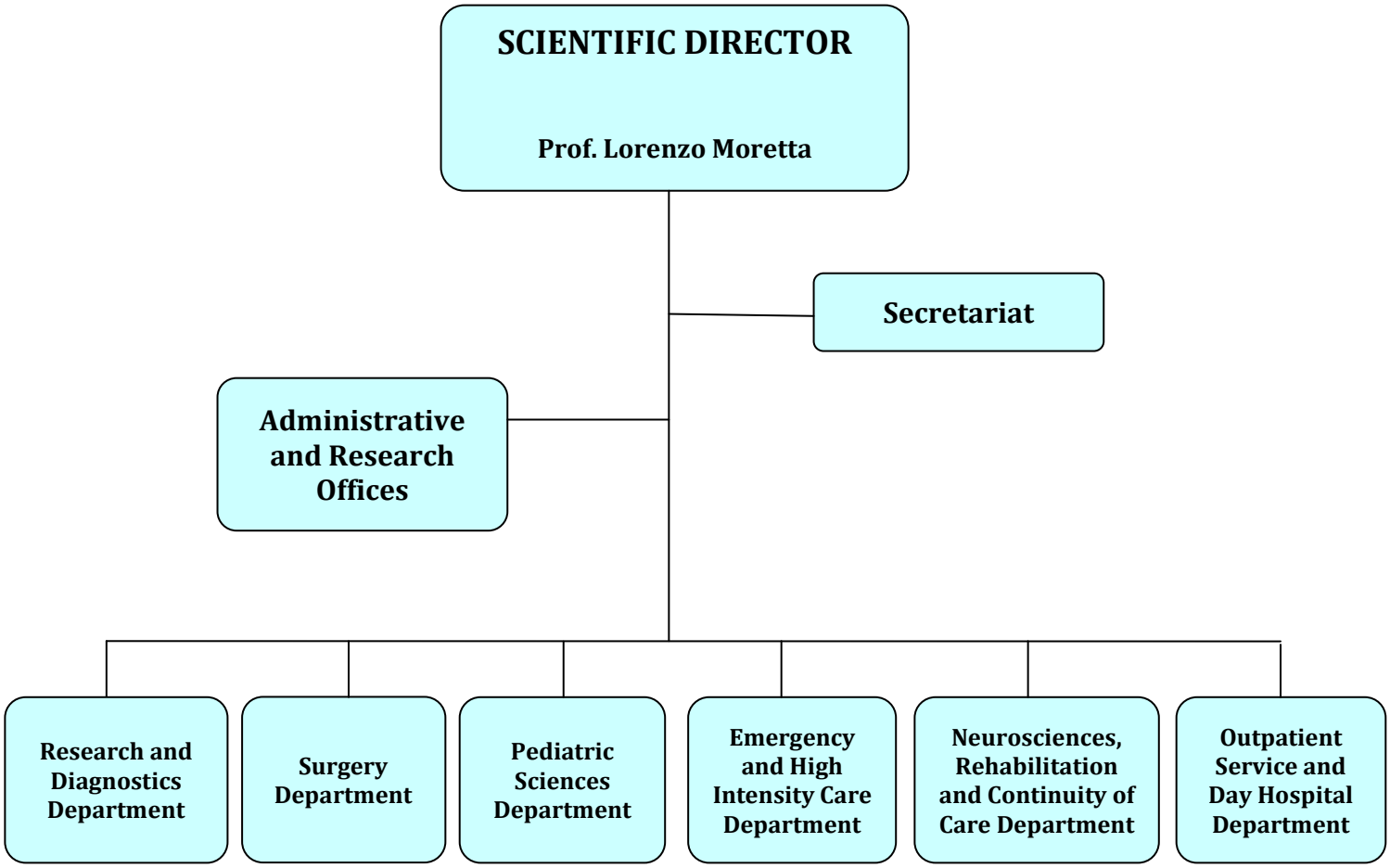
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Howard Hughes Medical Institute Research Laboratories, University of Alabama at Birmingham, Birmingham, Alabama, USA

Alain **Fischer**
Groupe Hospitalier Necker- Enfants Malades, Parigi, Francia

Sergio **Romagnani**
Istituto di Clinica Medica III, Servizio di Immuno - Allergologia, Università di Firenze

Ethics Committee Liguria Region Section III (pediatric) since Sept. 23, 2013

Members (mandatory to form the quorum):

Scientific Director	Lorenzo Moretta
Medical Director	Silvio del Buono
n. 3 clinicians	Vincenzo Jasonni
	Giorgio Dini
	Angelo Ravelli
	Vito Pistoia (deputy)
n. 1 general practitioner	Maria A.Dufour
	Paola Maria Bini (deputy)
n. 1 pediatrician	Federico Freschi
	Aldo Iester (deputy)
n. 1 biostatistician	Riccardo Haupt
	Maria Grazia Calevo (deputy)
n. 1 pharmacologist	Giovan B.Bonanno
	Ornella Della Casa (deputy)
n. 1 pharmacist of RHS	Paola Barabino
	Chiara Intra (deputy)
n. 1 legal and insurance expert or medical examiner	Francesco De Stefano - **President**
	Anna Banchero (deputy)
n. 1 bioethics expert	Adele Comelli
	Paola Oreste (deputy)
n.1 representative of health care professionals interested in experimentation	Marina Picconi
	Ivana Carpanelli (deputy)
n. 1 representative of volunteers or associations for patient protection	Rino Tortorelli
	Giovanni Foti (deputy)

n. 1 expert of medical devices	Maurizio Marasini Carlo Gandolfo (deputy)

<u>Members appointed as experts:</u>

1 clinical engineer (clinical-surgical area, medical devices)	Gino Spada Franca Foppiano (deputy)
1 nutrional expert (study of food products)	Paolo Fiore Fabrizio Gallo (deputy)
1 clinical expert (new technical Diagnostic-therapeutic procedures)	Giovanni Melioli Gino Tripodi (deputy)
1 genetics expert (genetic studies)	Roberto Ravazzolo Emilio Di Maria (deputy)

Curriculum Vitae et Studiorum of Professor Lorenzo Moretta

Prof. Lorenzo Moretta Born in Genoa on September 26, 1948 Married, two children		
Education	1966	Maturità classica, Genoa
	1972	Degree in Medicine and Surgery with honors, University of Genoa
Board certifications	1974	Medical Microbiology
	1982	Clinical Immunology and Allergology
Positions held	1972-80	Assistant, Institute of Microbiology, University of Genoa
	1976-77	Visiting Scientist, Dept. of Pediatrics and Microbiology, Cancer Center, University of Alabama, Birmingham, USA
	1980-84	Director Clinical Immunology Laboratories, Ludwig Institute for Cancer Research, Lausanne, Switzerland
	1984-90	Associate Professor of Immunopathology, University of Genoa. Director of Immunopathology Laboratories, Cancer Research Institute, Genoa
	1990-1991	Temporary Professor of General Pathology, University of L'Aquila
	1991-1994	Temporary Professor of Immunology, University of Turin, Novara
	1994-to date	Professor of General Pathology, University of Genoa
	1994-2000	Director of Immunopathology Laboratories, Cancer Research Institute, Advanced Biotechnology Centre, Genoa
	1996-97	President of the Italian Society of Immunology and Immunopathology
	1998-2000	Vice-Scientific Director of Cancer Research Institute, Genoa
	Nov 1, 2000 to date	Scientific Director, Istituto Giannina Gaslini, Genoa
	2009-2012	President Elect, European Federation of Immunological Societies (EFIS)
	2012 – to date	President, European Federation of Immunological Societies (EFIS)
Awards	1989	Lyon's Prize for the best Italian contribution to Immunology/Oncology (co-winner Robin Foà) (Giardini Naxos, Italy)
	1998	Cancer Research Institute W.B. Coley Award for Distinguished Research in Basic and Tumor Immunology (co-winners K. Kärre and R. Steinman) (New York, USA)

	1998	Biotec Award for outstanding contribution to biotechnology-oriented research in Italy (co-winners A. Mantovani and E. Pinna) (Siena, Italy)
	1999	The 2nd PISO International Prize for Research (co-winner A.S. Fauci) (Cagliari, Italy)
	2000	Invernizzi Prize for major advances in Medicina (Milan, Italy)
	2000	San Salvatore Prize 2000 for excellence in biomedical research in Immunology and Oncology (Lugano, Switzerland)
	2001	Yvette Mayent Prize, Institut Curie (co-winners K. Karre and A. Moretta) for their work on natural killer cells of the immune system (Paris, France)
	2001	Novartis Award for Basic Immunology (co-winners Klas Kärre and Wayne Yokoyama) (Stockholm, Sweden)
	2001	Liguria Region Prize for fundamental contribution to scientific research (Genoa, Italy)
	2002	Galeno Prize for outstanding University career (Milan, Italy)
	2003	Cristoforo Colombo Medal for scientific merits (Genoa, Italy)
	2004	Highly Cited Scientists Award, University of Genoa, Italy
	2006	"Guido Venosta" Prize for excellence in cancer research (FIRC/AIRC Foundation) (Rome, Italy)
	2011	"Delfini d'Argento" Prize (Cascina)
	2013	"Maria Vilma e Bianca Querci" Prize

Memberships (by invitation)	**2000**	Academia Europaea
	2003	European Molecular Biology Organization (EMBO)
	2003	Gruppo 2003 (highly cited scientists)
	2009	Accademia dei Lincei

Honours	**2006**	"Commendatore" of the Italian Republic for excellence in science (Rome)

International Publications in extenso	**580**
Total Impact factor	**Over 3,500**
Total number of citations	**Over 42,000 among the "Highly Cited Scientists" of ISI**
Total h-index	***112 (Google Scholar)***

Professor Lorenzo Moretta is Full Professor of General Pathology and Pathophysiology at the University of Genoa and Scientific Director of the G. Gaslini Institute.

Professor Moretta carried out research studies that are considered fundamental in immunology and in therapy of tumors and leukemias. He first identified T lymphocyte subpopulations in humans and these studies laid the foundations for understanding the diseases affecting the immune system such as immunodeficiencies and autoimmune diseases. The publication of this research was identified as "CItation Classic" in the Current Contents Life Science (vol. 28, n. 50, December 16, 1985), and it has now been cited over 1,300 times in a 7-year period. Professor Moretta is author of over 580 publications in extenso in prestigious international journals and books and has been the most cited Italian researcher in the scientific literature in a 10-year period (1977-87, as reported in "The Scientist", Current Contents, February 19, 1990).

The total number of citations is now over 42,000. Professor Moretta is in the ISI list of Highly Cited Scientists, that includes only a limited number of Italian researchers. His h-index is 112 (www.isiknowledge.com). In addition, in a recent analysis by Via Academy, Professor Moretta has been identified among the 200 authors (out of over 3 million authors in all scientific research fields) with h-index ≥ 100. Only 6 Italian scientists working in Italy belong to this category. Taken together, these data represent an important indicator of the considerable impact of the research studies carried out by Professor Moretta and his collaborators on international biomedical research.

Professor Moretta is (or was) in the Editorial Board of the following international journals: Trends in Immunology (Immunology Today), European Journal of Immunology, International Immunology, Immunology Letters, Human Immunology, The Hematology Journal, European Journal of Inflammation.

Prof. Moretta has been member of the Academia Europaea since 2000, of the Accademia dei Lincei since 2009, and of the European Molecular Biology Organization (EMBO) since 2003.

Professor Moretta is usually invited to participate in the main international and national meetings on Immunology as speaker and/or chairman of symposia and plenary sessions. He has often been invited individually to propose nominations for the Nobel prize for Medicine and Physiology and for other prestigious international prizes.

The research group coordinated by Professor Moretta carries out basic and applied research on the immunology of tumors and bone marrow transplantation for therapy of severe forms of acute leukemia. Research studies are mainly focused on human T lymphocytes and NK lymphocytes in humans.
A recent fundamental contribution of the research group coordinated by Professor Moretta, in close collaboration with the Laboratory directed by Professor Alessandro Moretta, Professor of Histology at the University of Genoa, is the definition of the mechanisms regulating NK function (tumor cell killing) with the detection of new inhibiting receptors specific to HLA class I molecules (named KIR) and of receptors responsible for NK cell activation and for induction of tumor cell killing processes. The genes coding for these new receptors were cloned in the Laboratory of Professor Moretta. Overall, over 15 new receptor molecules were identified and cloned by the research group of Professor Moretta. Knowledge acquired on NK cells and their receptors paved the way to important results in the therapy of high-risk acute leukemias based on the identification of mismatches between KIR receptors of donor NK cells and patient HLA class I alleles (typically in parent donor haploidentical transplantation). These studies were successfully carried out in children with high-risk acute leukemias by Professor Lorenzo Moretta in collaboration with Professors Alessandro Moretta and Franco Locatelli.
Overall, the discoveries of Professor Moretta and his collaborators had a considerable impact on biomedical research, also for their applications to immunotherapy of solid tumors and leukemias, and to immunodeficiencies, and won Professor Moretta prestigious international prizes (see list in table).

STAFF

Scientific Director secretary
Cinzia Miriello (University)

Scientific Director secretariat and editorial activities
Stefano Canu
Administrative activities related to the research projects carried out by the Scientific Director and to his activity as editor and/or referee for various international journals.

Scientific Direction secretariat
Roberta Fossati
Secretarial activity (supplies and maintenance work orders, correspondence)

Scientific secretariat
Laura Diamanti
Collection of publications, updating of the authors' database, and reporting on scientific production (IF monitoring).

Scientific seminars secretariat
Orietta Poggi
Administrative and organizational management of scientific seminars and cultural activities

Administrative secretariat
Maria Gabriella Marinari
Giuseppina Fabbri
Giorgio Sangalli
Anna Cesarini
Vincenza Nalbone
Eva Canepa
Administrative management of research funding by the Ministry of Health and by public and private institutions.

Computer Graphics Service
Anna Cesarini
Computer processing of images and texts for scientific presentations to national and international congresses. Preparation of images and tables for scientific publications in national and international journals. Graphic preparation (including accounting) of intermediate and final reports on Ministry of Health-funded current and targeted research programs, regional and other research programs, necessary for obtaining appopriate funding.Management of the mailing lists of the Scientific Direction.

Library
Angela Carbonaro
Orietta Poggi
Bibliosan service, document delivery for Gaslini's staff and for external users. Training and information to users for optimal use of available resources.

Translation and language consulting
Anna Capurro
Translation, writing, and revision (in English and French) of scientific papers, research projects, Gaslini's annual scientific report, presentations at congresses, contracts and agreements, guidelines and clinical protocols, various clinical documentation and informative material. Translation of documentation related to the Institute's accreditation by Joint Commission International (JCI).

Scientific relations and patents

Rosa Bellomo

Vincenza Nalbone

Maintenance of relations between the Scientific Direction and the Ministry of Health, the Regione Liguria and other national public and private bodies or institutions giving financial support to research. Support to the Scientific Director and Gaslini's researchers in planning, managing and reporting on Ministry of Health-funded targeted research programs.

Coordination of the preparation of the annual report on Gaslini's research activities as required by the Ministry of Health.

Reference person for Quality of the Scientific Direction

International Affairs

Thomas Wiley

Support and liaison services for the identification, design and planning, and management of research activity and collaborative actions financed by international funding agencies (the European Commission, the European Science Foundation, the NATO Science Program).

Consultation and assistance on the selection of international fellowship programs and mobility schemes.

Pediatric Clinical Trial Office (PCTO)

Ornella Della Casa Alberighi

Highly qualified support to the preparation and management of clinical research proposals and clinical development plans of drugs and pharmacovigilance in pediatrics. Design and conduction of collaborative clinical trials in pediatrics (from phase I to phase IV studies – pharmacovigilance) in collaboration with specialized networks of pediatric institutes of excellence, with national institutions (Istituto Superiore di Sanità) and international organizations (European Community, Orphanet), with regulatory agencies (EMEA and FDA, AIFA) and with national and international pharmaceutical companies. Continuing education of health care professionals in performing clinical trials in pediatrics.

Epidemiology, Biostatistics and Committees

Director: Riccardo Haupt

STAFF

Name	Position
Riccardo Haupt	Physician
Angela Pistorio	Physician, biostatistician
Maria Grazia Calevo	Statistician
Silvia Caruso	Biologist - data monitor
Francesca Bagnasco	Biostatistician
Giovanni Erminio	Data manager
Annarita Gigliotti	Physician
Vera Morsellino	Physician
Laura Crescini	Administrative
Stefania Gamba	Pharmacist
Serena Puiè	Administrative

RESULTS YEAR 2013

From the epidemiological perspective, Gaslini's international visibility has further increased thanks to active participation in presently ongoing European projects (PanCareSurFup and ENCCA) and in projects approved this year by the European Commission (PanCareLIFE and ExPO-r-NeT). The research area is long-term follow-up of long survivors after pediatric tumor, with focus on late mortality, second tumors, and severe cardiovascular events. A prototype of the so-called "Recovery passport" has also been developed. Furthermore, data from disease registries for which we are responsible have been used for the analysis of case series, especially with neuroblastoma, infections in oncologic patients, and off-therapy patients after pediatric tumors.

From the biostatistical perspective, data from experimental studies were analysed, in particular prospective longitudinal studies a) for the evaluation of new treatments in the field of rheumatology (juvenile dermatomyositis, juvenile idioapthic arthritis and systemic lupus erythematosus); b) for the validation of standardized clinical and/or radiological/echographic diagnostic tools for the evaluation of articular/muscular activity and damage; c) for the development of new classification systems for diagnosis and of new standardized criteria for the evaluation of outcome.

In addition, the collaboration with the Cochrane International centre is continued for the systematic review of neonatology and allergology topics. In this context, 4 days' training of internal and external staff was carried out to illustrate the techniques for performing and reading systematic reviews and meta-analyses.

MAIN COLLABORATIONS YEAR 2013

Pediatric Clinic, University of Milano-Bicocca;
CINECA (Interuniversity Centre for Automatic Calculation);
PRINTO (Paediatric Rheumatology International Trials Organization);
Cochrane Italia;
National Institute of Enviromental Health Sciences (NIEHS-NIH),
European Networks: PanCare, PanCareSurFup, ENCCA, ExPO-r-NeT

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Statistical-epidemiological methods for the analysis of clinical and laboratory data
Objective: Application of statistical-epidemiological methods for management and analysis of clinical and laboratory data from i) disease registries, ii) pharmacovigilance, iii) clinical trials, iv) validation of standardized instruments for diagnostics and classification criteria, v) planning and implementation of systematic reviews of the literature and meta-analyses. Coordination of the activity of the secretariat of the pediatric section of the regional Ethics Committee.
Description: The methods mentioned above will be applied mostly to institutional case series, national or international, in the fields of rheumatology, oncology, neonatology, infectious diseases, and endocrine and metabolic diseases.
Systematic reviews will also involve the production of guidelines in the neonatal and oncologic areas. The activity in international epidemiological projects will be continued, in particular the analysis of mortality and the risk of second malignant tumors, cardiovascular complications, or premature ovarian failure in long-term survivors after pediatric tumor.
Methodological support will be continued for the preparation and submission to the Ethics Committee of nonprofit institutional research projects.

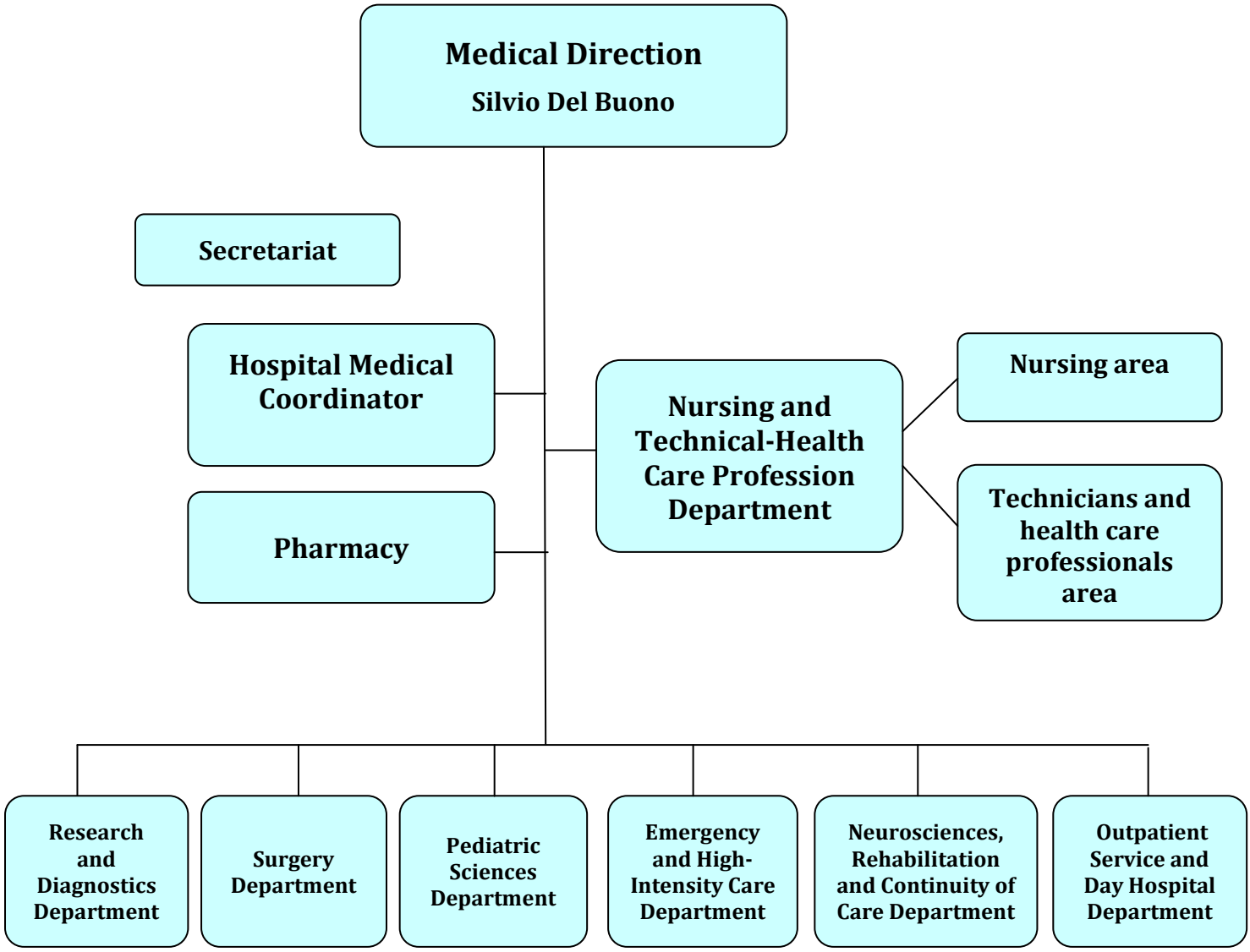
Internal collaborations:
Pediatric Hematology and Oncology unit
Infectious Disease unit
Pediatric Rheumatology unit

External collaborations:
CINECA (Interuniversity Centre for Automatic Calculation)
Cochrane Italia (Bologna),
European networks: PanCare, PanCareSurFup, ENCCA, PanCareLIFE, Ex

BEST PUBLICATIONS YEARS 2011-2013

1. Pimentel A, Haupt R, Sihelnik SA, Kimmel WB, Swierczynski SL. Focal Langerhans cell histiocytosis (LCH) coexisting with renal cell carcinoma. J Clin Oncol 2011;29(5):e107-9.
2. Malattia C, Damasio MB, Pistorio A, Ioseliani M, Vilca I, Valle M, Ruperto N, Viola S, Buoncompagni A, Magnano GM, Ravelli A, Tomà P, Martini A. Development and preliminary validation of a paediatric-targeted MRI scoring system for the assessment of disease activity and damage in juvenile idiopathic arthritis. Ann Rheum Dis 2011;70(3):440-6.
3. Pivetta E, Maule MM, Pisani P, Zugna D, Haupt R, Jankovic M, Aricò M, Casale F, Clerico A, Cordero di Montezemolo L, Kiren V, Locatelli F, Palumbo G, Pession A, Pillon M, Santoro N, Terenziani M, Valsecchi MG, Dama E, Magnani C, Merletti F, Pastore G; Italian Association of Pediatric Hematology and Oncology (AIEOP) Group. Marriage and parenthood among childhood cancer survivors: a report from the Italian AIEOP Off-Therapy Registry. Haematologica 2011;96(5):744-51.
4. Puliti A, Rossi PI, Caridi G, Corbelli A, Ikehata M, Armelloni S, Li M, Zennaro C, Conti V, Vaccari CM, Cassanello M, Calevo MG, Emionite L, Ravazzolo R, Rastaldi MP. Albuminuria and glomerular damage in mice lacking the metabotropic glutamate receptor 1. Am J Pathol 2011;178(3):1257-69.

5. Pezzolo A, Parodi F, Marimpietri D, Raffaghello L, Cocco C, Pistorio A, Mosconi M, Gambini C, Cilli M, Deaglio S, Malavasi F, Pistoia V. Oct-4+/Tenascin C+ neuroblastoma cells serve as progenitors of tumor-derived endothelial cells. Cell Res 2011;21(10):1470-86.
6. Rygg M, Pistorio A, Ravelli A, Maghnie M, Di Iorgi N, Bader-Meunier B, Da Silva C, Roldan-Molina R, Barash J, Dracou C, Laloum SG, Jarosova K, Deslandre CJ, Koné-Paut I, Garofalo F, Press J, Sengler C, Tauber T, Martini A, Ruperto N; Paediatric Rheumatology International Trials Organisation (PRINTO). A longitudinal PRINTO study on growth and puberty in juvenile systemic lupus erythematosus. Ann Rheum Dis 2012;71(4):511-7.
7. Morandi F, Scaruffi P, Gallo F, Stigliani S, Moretti S, Bonassi S, Gambini C, Mazzocco K, Fardin P, Haupt R, Arcamone G; Italian Cooperative Group for Neuroblastoma, Pistoia V, Tonini GP, Corrias MV. Bone marrow-infiltrating human neuroblastoma cells express high levels of calprotectin and HLA-G proteins. PLoS One 2012;7(1):e29922.
8. Baban A, Torre M, Costanzo S, Gimelli S, Bianca S, Divizia MT, Sénès FM, Garavelli L, Rivieri F, Lerone M, Valle M, Ravazzolo R, Calevo MG. Familial Poland anomaly revisited. Am J Med Genet A 2012;158A(1):140-9.
9. Miettunen PM, Pistorio A, Palmisani E, Ravelli A, Silverman E, Oliveira S, Alessio M, Cuttica R, Mihaylova D, Espada G, Pasic S, Insalaco A, Ozen S, Porras O, Sztajnbok F, Lazarevic D, Martini A, Ruperto N; Paediatric Rheumatology International Trials Organisation (PRINTO). Therapeutic approaches for the treatment of renal disease in juvenile systemic lupus erythematosus: an international multicentre PRINTO study. Ann Rheum Dis 2013;72(9):1503-9.
10. Calafiore L, Amoroso L, Della Casa Alberighi O, Luksch R, Zanazzo G, Castellano A, Podda M, Dominici C, Haupt R, Corrias MV, Garaventa A. Two-stage phase II study of imatinib mesylate in subjects with refractory or relapsing neuroblastoma. Ann Oncol 2013;24(5):1406-13.


Medical Direction
Silvio Del Buono
Secretariat
Hospital Medical Coordinator
Pharmacy
Nursing and Technical-Health Care Profession Department
Nursing area
Technicians and health care professionals area
Research and Diagnostics Department
Surgery Department
Pediatric Sciences Department
Emergency and High-Intensity Care Department
Neurosciences, Rehabilitation and Continuity of Care Department
Outpatient Service and Day Hospital Department

Pharmacy

Director (pro-tempore): Dr. Paola Barabino

STAFF

Name	Position
Tullia Emanueli	Pharmacist
Chiara Intra	Pharmacist
Ines Lorenzi	Pharmacist
Federica Morotti	Pharmacist
Eleonora Panetta	Pharmacist
Laura Riceputi	Pharmacist
Valentina Iurilli	Pharmacist
Antonella Missi	Nurse
De Franceschi Elisabetta	Nurse
Alessia Agazzi	Technician
Matteo Maria Di Stefano	Technician
Lucio Frondana	Technician
Giovanna Repetto	Technician
Encarnation Pardo	Orderly
Gian Marco Puppo	Orderly
Germano Fasce	Orderly
Maria Serafina Mammoliti	Orderly
Carmela Quaranta	Orderly
Alessandro Grieco	Orderly
Fabio Sanci	Orderly
Salvatore Rizzo	Orderly
Davide Ibba	Orderly

RESULTS YEAR 2013

Since 1999, the Pharmacy has been carrying out a multicentre study on the safety of drugs and vaccines in pediatrics of which the National Centre of Epidemiology, Surveillance and Promotion of Health (CNESP) of the Istituto Superiore di Sanità is the coordinator.
It is an active surveillance, in all Emergency admissions, of some acute clinical conditions of interest. The risk of onset of events associated with medication or vaccine use is estimated using a case-control analysis model.
To date, the study highlighted and confirmed signals of adverse reactions to some medications, allowing the integration of information collected by spontaneous reporting of adverse reactions.
With the data collected in this study, it was possible to perform more reliable estimates of risk of adverse reactions compared to estimates deriving from spontaneous reporting.
In the period from Sept. 1, 2012 to Sept. 23, 2013, overall 131 patients were enrolled. Of them, 84 children were exposed to medications in three weeks before hospitalization. In the group with neurologic diseases, syncope episodes and hyporeactivity, epilepsy, and ALTE in smaller patients were the most frequent occurrences.
The most frequent muco-cutaneous diseases were vasculitides, purpura, and Schoenlein-Henock syndrome. A case of Steven- Johnson syndrome was observed.
Over the last two years, the multicentre group carried out a study on safety and efficacy of

influenza vaccination in children. Influenza seasons 2011-2012 and 2012-2013 were taken into account. The first phase was a pilot study, which allowed the redesign and definition of the study criteria of the subsequent season. All enrolled patients underwent oropharyngeal swab for positivity to influenza A or B. On all positive swabs, typing of viral subtype was performed.
Overall 773 patients were enrolled, and 4% of them received influenza vaccination. Notwithstanding the low rate of vaccination in pediatric age, the study showed that the vaccine is moderately effective in pediatric age.

MAIN COLLABORATIONS YEAR 2013

- Istituto Superiore di Sanità
- Residency Program in Hospital Pharmacy of the University of Genova

PLANNED RESEARCH ACTIVITY IN 2014

Title: Surveillance of medication and vaccine safety and evaluation of efficacy of influenza vaccination in children.
Objectives: Estimate of the risk of hospital admission related to drug and/or vaccine intake for the following diseases: thrombocytopenia, esophago-gastroduodenal lesions, neurological problems , non-infectious mucocutaneous diseases, and vasculitides
Estimate of the effectiveness of seasonal vaccine in preventing hospital admission for influenza confirmed by laboratory tests.
Description of the frequency of hospital admissions for conditions different from those listed above that are considered suspected adverse reactions to medications and/or vaccines.
Description: It is an active surveillance, in all Emergency admissions to some Italian children's hospitals, of some acute clinical conditions. The risk of onset of events associated with medication or vaccine use will be estimated by adopting a case-control analysis model.
The strong point is the collection of all the events occurring in the observation period, which makes it possible to overcome the main limit of spontaneous reporting, i.e. underreporting for some medications.

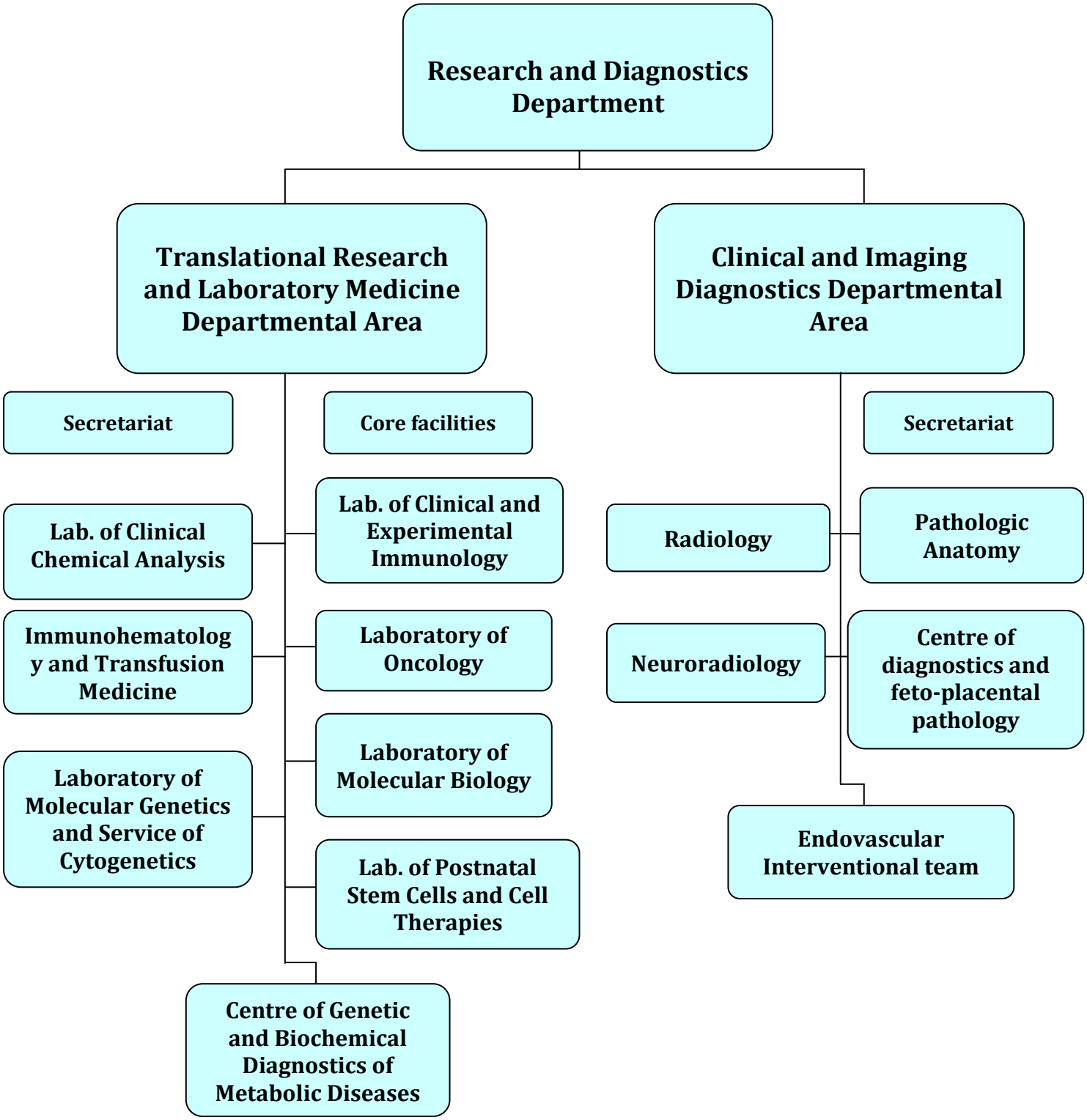
Internal collaborations:
Multicentre group composed of 10 pediatric centres participating in the study

External collaborations:
Istituto Superiore di Sanità
Residency Program in Hospital Pharmacy of the University of Genova

BEST PUBLICATIONS YEARS 2011-2013

1. Raucci U, Rossi R, Da Cas R, Rafaniello C, Mores N, Bersani G, Reale A, Pirozzi N, Menni Ippolito F, Traversa G; Italian Multicenter Study Group For Vaccine Safety In Drug Ar Children. Stevens-johnson syndrome associated with drugs and vaccines in children: case-control study. PLoS One. 2013 Jul 16, 8, 7.
2. Bianciotto M, Chiappini E, Raffaldi I, Gabiano C, Tovo PA, Sollai S, de Martino M, Mannelli F, Tipo V, Da Cas R, Traversa G, Menniti-Ippolito F; Italian Multicenter Study Group for Drug and Vaccine Safety in Children. Drug use and upper gastrointestinal complications in children: a case-control study. Arch Dis Child. 2013, 98, 3, 218-21.
3. Castagnola E, Mikulska M, Barabino P, Lorenzi I, Haupt R, Viscoli C. Current research in empirical therapy for febrile neutropenia in cancer patients: what should be necessary and what is going on. Expert Opin Emerg Drugs, 2013, 18, 3, 263-78.

4. Battaglia T, De Grandis E, Mirabelli-Badenier M, Boeri L, Morcaldi G, Barabino P, Intra C, Naselli F, Pistoia V, Veneselli E, Conte M. Response to rituximab in 3 children with opsoclonus-myoclonus syndrome resistant to conventional treatments. Eur J Paediatr Neurol, 2012, 16, 2, 192-5.
5. Mehta PA, Svahn J, Davies SM, Pang Q, Harris R, Ghezzi P, Lanza T, Ferretti E, Barabino P, Mueller R, Dufour C. Etanercept treatment in Fanconi anaemia; combined US and Italian experience. Br J Haematol, 2012, 158, 6, 809-11.


Research and Diagnostics Department
Translational Research and Laboratory Medicine Departmental Area
Clinical and Imaging Diagnostics Departmental Area
Secretariat
Core facilities
Lab. of Clinical Chemical Analysis
Lab. of Clinical and Experimental Immunology
Immunohematology and Transfusion Medicine
Laboratory of Oncology
Laboratory of Molecular Genetics and Service of Cytogenetics
Laboratory of Molecular Biology
Lab. of Postnatal Stem Cells and Cell Therapies
Centre of Genetic and Biochemical Diagnostics of Metabolic Diseases
Secretariat
Radiology
Pathologic Anatomy
Neuroradiology
Centre of diagnostics and feto-placental pathology
Endovascular Interventional team

Clinical and experimental immunology

Director: Cristina Bottino

STAFF

Name	Position
Antonio Puccetti	Associate Professor, Physician (agreement with University of Genoa)
Michela Falco	Biologist
Claudia Cantoni	Researcher, Pharmacist (agreement with University of Genoa)
Stefano Regis	Biologist
Stefania Marcenaro	Biologist
Grazia M. Spaggiari	Researcher (agreement with University of Genoa)
Laura Chiossone	Researcher
Claudia Alicata	Researcher
Fabrizio Loiacono	Researcher

RESULTS YEAR 2013

Hemopoietic stem cell transplantation from haploidentical donors (haplo-HSCT) in leukemic patients: identification of the optimal HSC donor through KIR and HLA class I genotype/phenotype analysis in potential donors and in the recipient.
Trans-endothelization of monocytes: identification of the inhibitory role of CD300a.
Characterization of dendritic cells migrating to secondary lymphoid organs.
Autoimmune lymphoproliferative syndrome (ALPS): identification of rare variants of the UNC13D gene as risk factors for the development of ALPS.
Pelizaeus-Merzbacher leucodystrophy: *in vitro* correction through antisense oligonucleotides of PLP1 splicing defect.
Analysis of the immunoregulatory effects of mesenchymal stem cells.
Origin of NK cells in the decidua: demonstration in the murine model of the migration of hemopoietic precursors into uterus and decidua and their differentiation into NK cells.
Role of infections in the pathogenesis of diabetes type I: in genetically predisposed subjects, the infection due to coxsakie B4 virus induces the production of autoantibodies inducing apoptosis of beta pancreatic cells.
Celiac disease: we developed a test able to predict the risk of celiac disease by assay of antibodies against Vp7 protein of rotavirus.

MAIN COLLABORATIONS YEAR 2013

UOC Oncologia, Diagnostica Genetica e Biochimica delle Malattie Metaboliche e Ematologia, Istituto G. Gaslini
Di.Me.S University of Genova
San Martino-IST Hospital, Genova
Bambino Gesù Children's Hospital of Roma
Meyer Children's Hospital of Firenze
University of Piemonte Est Novara
University of Verona
Institute of Medical Biochemistry, Muenster, Germany

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Role of cells of the immune system in physiology and pathology
Objective: Characterization of the molecular mechanisms responsible for immune response in humans and for the interactions among the various subpopulations of immune system cells, focusing on diseases as blood and solid tumors, immunodeficiencies, and autoimmune diseases.
Description: Natural Killer cells: analysis of molecular mechanisms involved in the development and maturation of NK cells after haploidentical transplantation, in the recognition of neoplastic and virus-infected cells, in the interaction with other cells of the immune system, and characterization of inflammatory microenvironment factors that could influence NK cell in situ function.
Immunodeficiencies: Analysis of NK cell function in X-linked lymphoproliferative disease (*XLP*, Duncan syndrome).
Systemic autoimmune diseases: Identification of damage molecular markers in diseases such as Behçet syndrome, Wegener granulomatosis, and Horton arteritis.

Internal collaborations:

Oncology/Hematology unit
Core facilities

External collaborations:

Di.Me.S University of Genova
San Martino-IST Hospital, Genova
Bambino Gesù Children's Hospital, Roma
Meyer Children's Hospital, Tuscany Cancer Institute, Firenze
University of Piemonte Est Novara
University of Verona
Università of Milano and Humanitas Institute, Milano
University of Brescia
Cambridge Institute for Medical Research, Cambridge UK.

BEST PUBLICATIONS YEARS 2011-2013

1. Falco,M. Moretta,L. Moretta, A. Bottino, C. KIR and KIR ligand polymorphism: a new area for clinical applications? Tissue Antigens 2013. 82:363-73.
2. Castriconi R, Dondero A, Bellora F, Moretta L, Castellano A, Locatelli F, Corrias MV, Moretta A, Bottino C. Neuroblastoma-derived TGF-β1 modulates the chemokine receptor repertoire of human resting NK cells. J Immunol. 2013. 190(10):5321-8.
3. Ghavampour S, Lange C, Bottino C, Gerke V. Transcriptional Profiling of Human Monocytes Identifies the Inhibitory Receptor CD300a as Regulator of Transendothelial Migration. PLoS One. 2013 Sep 18;8(9):e73981.
4. Morandi B, Bonaccorsi I, Mesiti M, Conte R, Carrega P, Costa G, Iemmo R, Martini S, Ferrone S, Cantoni C, Mingari MC, Moretta L, Ferlazzo G. Characterization of human afferent lymph dendritic cells from seroma fluids. J Immunol. 2013. 91(9):4858-66.
5. Aricò M, Boggio E, Cetica V, Melensi M, Orilieri E, Clemente N, Cappellano G, Buttini S, Soluri MF, Comi C, Dufour C, Pende D, Dianzani I, Ellis SR, Pagliano S, Marcenaro S, Ramenghi U, Chiocchetti A, Dianzani U. Variations of the UNC13D gene in patients with autoimmune lymphoproliferative syndrome. PLoS One. 2013 Jul 1;8(7):e68045.

6. Regis S, Corsolini F, Grossi S, Tappino B, Cooper DN, Filocamo M. Restoration of the normal splicing pattern of the PLP1 gene by means of an antisense oligonucleotide directed against an exonic mutation. PLoS One. 2013 Sep 3;8(9):e73633.
7. Spaggiari GM, Moretta L. Cellular and molecular interactions of mesenchymal stem cells in innate immunity.Immunol Cell Biol. 91(1):27-31. 2013
8. Chiossone L, Vacca P, Orecchia P, Croxatto D, Damonte P, Astigiano S, Barbieri O, Bottino C, Moretta L, Mingari MC. In vivo generation of decidual Natural Killer cells from resident hematopoietic progenitors. Haematologica. 2013 Oct 31. [Epub ahead of print]
9. Dolcino M, Zanoni G, Bason C, Tinazzi E, Boccola E, Valletta E, Contreas G, Lunardi C, Puccetti A. A subset of anti-rotavirus antibodies directed against the viral protein VP7 predicts the onset of celiac disease and induces typical features of the disease in the intestinal epithelial cell line T84. Immunol Res. 2013 Jul;56(2-3):465-76.
10. Bason C, Lorini R, Lunardi C, Dolcino M, Giannattasio A, d'Annunzio G, Rigo A, Pedemonte N, Corrocher R, Puccetti A. In type 1 diabetes a subset of anti-coxsackievirus B4 antibodies recognize autoantigens and induce apoptosis of pancreatic beta cells. PLoS One. 2013;8(2):e57729.

Laboratory of oncology

Director: Vito Pistoia

STAFF

Name	Position
Vito Pistoia	Director
Irma Airoldi	Biologist
Anna Corcione	Biologist
Maria Valeria Corrias	Biologist
Annalisa Pezzolo	Biologist
Mirco Ponzoni	Biologist
Ignazia Prigione	Biologist
Paola Bocca	Laboratory technician
Danilo Marimpietri	Laboratory technician
Pier Giorgio Riva	Orderly
Giulia Barbarito	Biologist
Giovanna Bianchi	Biologist
Chiara Brignole	Biologist
Barbara Carlini	Laboratory technician
Claudia Cocco	Biologist
Annarita Di Fiore	Chemist
Daniela Di Paolo	Biologist
Elisa Ferretti	Biologist
Monica Loi	Biotechnologist
Roberto Martella	Biologist
Fabio Morandi	Biologist
Gabriella Pagnan	Biologist
Fabio Pastorino	Biologist
Patrizia Perri	Biologist
Lizzia Raffaghello	Biologist
Marzia Rossi	Biotechnologist
Elisa Ventura	Biologist
Alessia Zorzoli	Biologist
Camilla Valentino	Administrative
Guendalina Zuccari	Biologist

RESULTS YEAR 2013

Two new approaches of pre-clinical therapeutic targeting of human neuroblastoma were developed, both based on the use of liposomes. The first study led to the identification of five phagic peptides able to react ex vivo with primary neuroblastomas; these peptides, bound to liposomes, proved to able to bind both tumor cells and microvessels in a preclinical model of neuroblastoma, delivering the chemotherapeutic drug doxorubicin to tumor site and inhibiting significantly tumor growth. The second study led to the development of a new liposomal formulation of fenretinide, a synthetic retinoid with antitumoral and antiangiogenic activity but poorly soluble and rapidly metabolized. Thanks to this new formulation, in which fenretinide-containing liposomes were coated with NGR peptides able to bind to

aminopeptidase N expressed by tumor vessels, it was possible to inhibit significantly in vivo growth of human neuroblastoma through antiangiogenic and antitumoral mechanisms.
A new preclinical protocol of immunotherapy of neuroblastoma with γδ T lymphocytes activated by zoledronic acid (ZOL) was developed. ZOL is an aminobisphosphonate used in the therapy of osteoporosis and bone metastases that has the property of selectively stimulating the proliferation of Vγ9δ2 T lymphocytes and of sensitizing tumor cells to the cytotoxic activity of these lymphocytes. In vivo infusion of Vγ9γ2 T lymphocytes with ZOL inhibited significantly neuroblastoma growth with a combination of antitumoral and antiangiogenic effects whose mechanisms have been identified.
We also identified the role of BAFF, an essential molecule for survival and differentiation of B lymphocytes, in lymphoid neogenesis which is typical, though not exclusive, of those cases of localized neuroblastoma associated with opsoclonus-myoclonus syndrome (OMS), a rare and disabling paraneoplastic syndrome.
Finally, we first characterized the proteome of exosomes, nanovesicles derived from multivesicular bodies and secreted in the extracellular environment, isolated from some neuroblastoma cell lines, and we identified molecules as CD133, CD147, and CD276 involved in tumor growth and progression.

MAIN COLLABORATIONS YEAR 2013

Prof. Francesco Di Virgilio, University of Ferrara
Prof. Valter Longo, University of Southern California, Los Angeles, USA
Prof. Domenico Ribatti, University of Bari
Prof. Emma Di Carlo, University of Chieti
Prof. Guido Kroemer, Institute Gustave Roussy, Villejuif, France
Dr. Roberto Luksch, Cancer Research Institute Foundation, Milano
Prof. Franco Locatelli, Bambino Gesù Children's Hospital, Roma
Prof. Renata Pasqualini, MD Anderson Cancer Center, Houston, USA
Prof. Holger Lode, University of Greisswald, Germania
Dr. Angelo Corti, S. Raffaele Institute, Milano

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Study of microenvironment and therapeutic targeting in pediatric tumors
Objectives: 1) detailed analysis of pediatric tumor microenvironment, especially neuroblastoma and, to a lesser extent, lymphomas; 2) development of preclinical protocols of selective tumor targeting based on delivery of antitumoral or antiangiogenic drugs to tumor site through nanoparticles or on innovative immunotherapeutic modalities.
Description: Tumor microenvironment is characterized by the production of different families of immunosuppressive molecules that often "paralyse" immune response against tumor cells. In this project, we intend to analyse the contribution of some tumor-infiltrating cell populations to the production of immunosuppressive soluble factors, focusing on i) mesenchymal stromal cells (MSC), ii) myeloid suppressive cells (MDSC), and iii) natural killer cells (NK). Particular attention will be paid to the family of ectoenzymes (CD38, CD39, and CD73) expressed on the cell surface and able to generate adenosine, a potent immunosuppressive molecule. In vitro studies will be performed with purified cell populations from neuroblastoma or pediatric B-cell lymphomas and treated with different stimuli and/or inhibitors to identify, through biochemical assays, the mechanisms of production of immunosuppressive molecules.. Tumor targeting studies will be carried out using liposomes able to deliver selectively molecules capable of inhibiting tumor growth to the tumor or tumor microvessels. In particular, we will use siRNA that our previous studies

demonstrated to be effective in inhibiting in vivo growth of neuroblastoma in preclinical models. Animal models will be used to validate in vitro results.

Internal collaborations
Dr. Alberto Garaventa, Clinical and Experimental Oncology
Dr. Angela Sementa, Pathologic Anatomy
Dr. Andrea Petretto, Core Facilities
Prof. Cristina Bottino, Laboratory of Clinical and Experimental Immunology

External collaborations
Prof. Fabio Malavasi, University of Torino
Prof. Francesco Di Virgilio, University of Ferrara
Prof. Renata Pasqualini, Anderson Cancer Center, Houston, USA
Dr. Maurilio Ponzoni, S. Raffaele Institute, Milano

BEST PUBLICATIONS YEARS 2011-2013

1) Loi M, Di Paolo D, Soster M, Brignole C, Bartolini A, Emionite L, Sun J, Becherini P, Curnis F, Petretto A, Sani M, Gori A, Milanese M, Gambini C, Longhi R, Cilli M, Allen TM, Bussolino F, Arap W, Pasqualini R, Corti A, Ponzoni M, Marchiò S, Pastorino F. Novel phage display-derived neuroblastoma-targeting peptides potentiate the effect of drug nanocarriers in preclinical settings. J Control Release. 2013 Sep 10;170(2):233-41.
2) Di Paolo D, Pastorino F, Zuccari G, Caffa I, Loi M, Marimpietri D, Brignole C, Perri P, Cilli M, Nico B, Ribatti D, Pistoia V, Ponzoni M, Pagnan G. Enhanced anti-tumor and anti-angiogenic efficacy of a novel liposomal fenretinide on human neuroblastoma. J Control Release. 2013 Sep 28;170(3):445-51.
3) Calafiore L, Amoroso L, Della Casa Alberighi O, Luksch R, Zanazzo G, Castellano A, Podda M, Dominici C, Haupt R, Corrias MV, Garaventa A. Two-stage phase II study of imatinib mesylate in subjects with refractory or relapsing neuroblastoma. Ann Oncol. 2013 May;24(5):1406-13.
4) Di Carlo E, Bocca P, Emionite L, Cilli M, Cipollone G, Morandi F, Raffaghello L, Pistoia V, Prigione I. Mechanisms of the antitumor activity of human Vγ9Vδ2 T cells in combination with zoledronic acid in a preclinical model of neuroblastoma. Mol Ther. 2013 May;21(5):1034-43. doi: 10.1038/mt.2013.38
5) Expression of P2X7 receptor increases in vivo tumor growth. Adinolfi E, Raffaghello L, Giuliani AL, Cavazzini L, Capece M, Chiozzi P, Bianchi G, Kroemer G, Pistoia V, Di Virgilio F. Expression of P2X7 receptor increases in vivo tumor growth. Cancer Res. 2012 Jun 15;72(12):2957-69.
6) Cocco C, Di Carlo E, Zupo S, Canale S, Zorzoli A, Ribatti D, Morandi F, Ognio E, Airoldi I. Complementary IL-23 and IL-27 anti-tumor activities cause strong inhibition of human follicular and diffuse large B-cell lymphoma growth in vivo. Leukemia. 2012 Jun;26(6):1365-74.
7) Lee C, Raffaghello L, Brandhorst S, Safdie FM, Bianchi G, Martin-Montalvo A, Pistoia V, Wei M, Hwang S, Merlino A, Emionite L, de Cabo R, Longo VD. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. Sci Transl Med. 2012 Mar 7;4(124):124ra27.
8) Pezzolo A, Parodi F, Marimpietri D, Raffaghello L, Cocco C, Pistorio A, Mosconi M, Gambini C, Cilli M, Deaglio S, Malavasi F, Pistoia V. Oct-4+/Tenascin C+ neuroblastoma cells serve as progenitors of tumor-derived endothelial cells. Cell Res. 2011 Oct;21(10):1470-86.

9) Ferretti E, Montagna D, Di Carlo E, Cocco C, Ribatti D, Ognio E, Sorrentino C, Lisini D, Bertaina A, Locatelli F, Pistoia V, Airoldi I. Absence of IL-12Rβ2 in CD33(+)CD38(+) pediatric acute myeloid leukemia cells favours progression in NOD/SCID/IL2RγC-deficient mice. Leukemia. 2012 Feb;26(2):225-35.
10) Morandi F, Ferretti E, Castriconi R, Dondero A, Petretto A, Bottino C, Pistoia V.) Soluble HLA-G dampens CD94/NKG2A expression and function and differentially modulates chemotaxis and cytokine and chemokine secretion in CD56bright and CD56dim NK cells. Blood. 2011 Nov 24;118(22):5840-50

Laboratory of Molecular Biology

Director: Dr. Luigi Varesio

STAFF

Name	Position
Alessandra Eva	Biologist
Cristina Vanni	Researcher
Roberta Resaz	Researcher
Daniela Segalerba	Biologist

RESULTS YEAR 2013

We characterized a new murine model of glycogenosis 1a, that we recently generated, in which the glucose-6-phosphatase gene was inactivated only in the liver at birth. The characteristic of these mice is to survive even without glucose supplement, which makes it possible to focus on just one of the mostly affected organs, i.e. the liver, and to evaluate the long-term sequelae of the hepatic disease. We characterized this murine model evaluating animal liver parameters with histochemical techniques and G6Pase function tests on microsomes, we performed metabolic tests to assay cholesterol, triglycerides, fasting and non-fasting glycemia and histological analyses for liver damage evaluation. We demonstrated that these mice present all the pathologic liver characteristics of glycogenosis 1a, including hepatomegaly, glycogen storage disease, fasting hypoglycemia, steatosis, and inflammation. In addition, since 10 months of age, they develop liver adenomas and, from 18 months, liver carcinomas. This model will allow the selective study of liver tissue alterations, the possible treatment of liver dysfunction, and the effects of stem cell transplantation. To this end, we obtained in culture functioning hepatocytes from pluripotent stem cells derived from spermatogonial stem cells isolated from normal mice. In addition, we established the experimental conditions for infecting with recombinant lentivirus myelomonocytic cells isolated from the bone marrow of healthy mice. Mice will be inoculated with both cell types to evaluate their long-term therapeutic effect in the new murine model of glycogenosis 1a that we generated.

MAIN COLLABORATIONS YEAR 2013

Internal collaborations

1. Dr. Maja Di Rocco, Rare Disease section, Pediatrics Department: glycogenosis, diagnosis
2. Dr. Angela Rita Sementa, Pediatric Pathology Department: histopathological analyses

External collaborations

1. Prof. Fiorella Altruda, Dept. of Genetics, Biology and Medical Chemistry, University of Torino: stem cells
2. Dr. Luca Mastracci, Pathologic Anatomy unit, San Martino-IST Hospital, Genova: histopathological analyses
3. Dr. Federica Grillo, Pathologic Anatomy unit, San Martino-IST Hospital, Genova: histopathological analyses
4. Dr. Ottavia Barbieri, DIMES, San Martino-IST Hospital, Genova: animal facility
5. Dr. Janice Chou, NIH, NICHD HDB, Bethesda, USA: glycogenosis 1a, gene therapy

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: New strategies for the treatment and cure of glycogenosis 1a: from bench to bedside
Objective: Study of the use of stem cells for tissue regeneration and identification of new pharmacologic targets of altered metabolic pathways to improve and prolong life of patients with glycogenosis 1a.
Description: We will develop a therapeutic approach based on hematopoietic transplantation of stem cells dervied from the bone marrow and of spermatogonial stem cells derived from the testis, in order to obtain permanent expression of normal G6Pase gene in organs damaged by the disease. We will evaluate the optimal conditions for transplantation to guarantee a good localization and functioning of "therapeutic" cells in the liver using the animal model of GSD1a that we generated. In collaboration with Dr. M. Di Rocco, Rare Disease section, Pediatrics Department, treating GSD1a at Gaslini, we will collect plasma of patients undergoing follow-up visits. From these samples, we will purify miRNA, i.e. small RNA regulating gene expression and reflecting the degeneration of the tissue from which they originate, then we will evaluate the onset of long-term complications in affected patients.

BEST PUBLICATIONS YEARS 2011-2013

1. Bosco MC, Pierobon D., Blengio F., Raggi F., Vanni C., Gattorno M., Eva A., Novelli F., Cappello P., Giovarelli M., Varesio L. Hypoxia modulates the gene expression profile of immunoregulatory receptors in human mature dendritic cells: identification of TREM-1 as a novel hypoxic marker in vitro and in vivo. Blood. 2011 Mar 3;117(9):2625-39.
2. Ognibene M., Barbieri O., Vanni C., Mastracci L., Astigiano S., Emionite L., Salani B., Fedele M., Resaz R., Tenca C., Fais F., Sabatini F., De Santanna A., Altruda F., Varesio L., Hirsch E., Eva A. High frequency of development of B cell lymphoproliferation and diffuse large B cell lymphoma in Dbl knock-in mice. J Mol Med (Berl). 2011 May;89(5):493-504.
3. Ognibene M., Vanni C., Segalerba D., Mancini P., Merello E., Torrisi MR., Bosco MC., Varesio L., Eva A. The tumor suppressor hamartin enhances Dbl protein transforming activity through interaction with ezrin. J Biol Chem. 2011 Aug 26;286(34):29973-83. .
4. Cornero A., Acquaviva M., Fardin P., Versteeg R., Schramm A., Eva A., Bosco MC., Blengio F., Barzaghi S., Varesio L.. Design of a multi-signature ensemble classifier predicting neuroblastoma patients' outcome. BMC Bioinformatics. 2012 Mar 28;13 Suppl 4:S13.
5. Blengio F, Raggi F, Pierobon D, Cappello P, Eva A, Giovarelli M, Varesio L, Bosco MC.The hypoxic environment reprograms the cytokine/chemokine expression profile of human mature dendritic cells. Immunobiology. 2013 Jan;218(1):76-89.
6. Pierobon D., Bosco MC., Blengio F., Raggi F., Eva A., Filippi M., Musso T., Novelli F., Cappello P., Varesio L., Giovarelli M. Chronic hypoxia reprograms human immature dendritic cells by inducing a proinflammatory phenotype and TREM-1 expression. Eur J Immunol. 2013 Apr 43(4):949-66.
7. Sabatini F., Luppi F., Petecchia L., Stefano AD., Longo AM., Eva A., Vanni C., Hiemstra PS., Sterk PJ., Sorbello V., Fabbri LM., Rossi GA., Ricciardolo FL.. Bradykinin-induced asthmatic fibroblast/myofibroblast activities via bradykinin B2 receptor and different MAPK pathways. Eur J Pharmacol. 2013 Jun 15;710(1-3):100-9.
8. Cangelosi D., Blengio F., Versteeg R., Eggert A., Garaventa A., Gambini C., Conte M., Eva A., Muselli M., Varesio L. Logic Learning Machine creates explicit and stable rules stratifying neuroblastoma patients. BMC Bioinformatics. 2013;14 Suppl 7:S12.
9. Raggi F, Blengio F, Eva A, Pende D, Varesio L, Bosco MC. Identification of CD300a as a new hypoxia-inducible gene and a regulator of CCL20 and VEGF production by human monocytes and macrophages.Innate Immun. 2013 Oct 16.

Laboratory of postnatal stem cells and cell therapies

Director: Prof. Francesco Frassoni

STAFF

Name	Position
M. Podestà	Biologist
D. Di Martino	Biologist
F. Sabatini	Researcher
C. Cossu	Researcher
I.azzari	Laboratory technician
M. Dagnino	Laboratory technician

RESULTS YEAR 2013

Evaluation of the expression of genes involved in self-renewal before and after transplantation, reconstitution of hemopoietic progenitors in adult and pediatric subjects

The principle on which HSCT is based is stem cell ability to expand and maintain stable values of WBC, RBC, and platelets throughout the recipient's lifetime. However, different scientific data (serial transplantation in the murine model, long-term reconstitution in bone marrow transplantation) show that this forced expansion leads to a limited reconstitution of the stem cell reservoir. Since transplantation leads to an about 2 log expansion of stem cells for adult bone marrow (BM) and to 3 log expansion for cord blood (CB), it is clear that stem cells undergo changes in their gene expression supporting this phenomenon. Aim of the study is to identify involved genes, type and duration of changes, whether these changes are influenced by the transplanted tissue (i.e. CB or BM) and/or by the recipient's age, and whether hemopoietic stem cells grow old after transplantation.

Basal gene expression was evaluated on selected CD34+ cells from cord blood (CB) and bone marrow (BM) of healthy adult and pediatric subjects; IPS cells were used as positive control. Our samples included CD34 cells of patients (adults and children) transplanted with BM or CB at different time intervals from transplantation (+30,+ 90, +180, +360 days). The method used was low-density TaqMan-based CARDs on which 93 genes involved in cell cycle regulation, proliferation, differentiation, and self-renewal were selected. The analysis of the corresponding proteins was performed on CD34+ cells stained with corresponding fluoresceinated antibodies; they were quantified with confocal microscopy.

Ten "stem cell" genes, among which are Nanog, Oct4, and Sox2, with significantly different expression compared to hemopoietic stem cells before and after transplant, were identified. In particular, these genes result overexpressed in transplanted cord blood cells compared to their basal values, differently from the same genes that show significantly lower expression after transplantation in adult hemopoietic cells.

Surprisingly, these levels of expression are maintained over time, even when the hemopoietic system results completely reconstituted and functions according to standard maintenance levels.

MAIN COLLABORATIONS YEAR 2014

D Cilloni,Torino
F Bonifazi, Bologna
L Ramenghi, Gaslini
G Candiano, Gaslini

F Locatelli (BGH), Roma
E Lanino, Gaslini
F Fagioli, OIRM Torino
GQ Daley (Harvard), USA

PLANNED RESEARCH ACTIVITY YEARS 2014-2016

1) **Title**: Expression of genes involved in self-renewal of hematopoietic stem cells (HSC)
   Objective: Comparative evaluation of the expression of genes involved in self-renewal (stemness) in HSC from different sources before and after transplantation.
   Description: We started to evaluate whether genes that make and maintain hematopoietic stem cells (HSC) decline after allogenic transplantation.
   Preliminary data suggest that, after cord blood transplantation, HSC enhance stemness genes whereas, after bone marrow transplantation, these genes tend to decline. We will then carry out the following:
   a) Confirmation of data including also new genes important for self-renewal.
   b) Evaluation of whether telomere length is correlated with data obtained.
   c) Comparative evaluation with iPS cells obtained from different cells
   d) Evaluation of whether CD34+ cells from cord blood after transplantation can be induced to become iPS in vitro.

2) Evaluation of hematopoietic and mesenchymal progenitors in umbilical cord blood of full-term and pre-term newborns.
   Characterization of hematopoietic and endothelial progenitors. Phenotype and differentiation potential and microvesicles of mesenchymal stem cells.

3) EphA3 Receptor: a new marker of malignancy for leukemias and solid tumors.
   C1. Study in multiple myeloma and myeloma vasculogenesis
   C2. Study in acute leukemias of adult and child
   C3. Study in proliferative diseases.
   In vitro and in vivo quantitative studies (NOD/SCID model) of EphA3 Receptor expression.
   Potential therapeutic target: evaluation of therapeutic efficacy of a MoAb developed ad hoc.

Internal collaborations:

- L Ramenghi
- G Candiano
- E Lanino

External collaborations:

- D Cilloni, Torino
- F Bonifazi, Bologna
- F Locatelli (BGH), Roma
- F Fagioli OIRM, Torino
- GQ Daley (Harvard), USA

BEST PUBLICATIONS YEARS 2011-2013

1) Della Chiesa M, Falco M, Podestà M, Locatelli F, Moretta L, Frassoni F, Moretta A Phenotypic and functional heterogeneity of human NK cells developing after umbilical cord blood transplantation: a role for human cytomegalovirus ? Blood. 2012 Jan 12;119(2):399-410. Epub 2011 Nov 17.

2) Sambuceti G, Massollo M, Marini C, Podestà M, Cassanelli C, Morbelli S, Fiz F, Buschiazzo A, Capitanio S, Augeri C, Curti G, Piana M, Frassoni F. Trafficking and homing of systemically administered stem cells: the need for appropriate analysis tools of radionuclide images. Q J Nucl Med Mol Imaging. 2013 Jun;57(2):207-15.
3) Rocha V, Labopin M, Ruggeri A, Podestà M, Gallamini A, Bonifazi F, Sanchez-Guijo FM, Rovira M, Socie G, Baltadakis I, Michallet M, Deconinck E, Bacigalupo A, Mohty M, Gluckman E, Frassoni F. Unrelated cord blood transplantation: outcomes after single-unit intrabone injection compared with double-unit intravenous injection in patients with hematological malignancies. Transplantation. 2013 May 27;95(10):1284-91.
4) Forni GL, Podestà M, Musso M, Piaggio G, Musallam KM, Balocco M, Pozzi S, Rosa A, Frassoni F. Differential effects of the type of iron chelator on the absolute number of hematopoietic peripheral progenitors in patients with beta-thalassemia major. Haematologica. 2013 Apr;98(4):555-9.
5) Marini C, Podestà M, Massollo M, Capitanio S, Fiz F, Morbelli S, Brignone M, Bacigalupo A, Piana M, Frassoni F, Sambuceti G. Intrabone transplant of cord blood stem cells establishes a local engraftment store: a functional PET/FDG study. J Biomed Biotechnol. 2012;2012:767369. doi: 10.1155/2012/767369. Epub 2012 Oct 2.
6) Chiesa S, Morbelli S, Morando S, Massollo M, Marini C, Bertoni A, Frassoni F, Bartolomé ST, Sambuceti G, Traggiai E, Uccelli A. Mesenchymal stem cells impair in vivo T-cell priming by dendritic cells. Proc Natl Acad Sci U S A. 2011 Oct 18;108(42):17384-9.
7. Sambuceti G, Brignone M, Marini C, Massollo M, Fiz F, Morbelli S, Buschiazzo A, Campi C, Piva R, Massone AM, Piana M, Frassoni F. Estimating the whole bone-marrow asset in humans by a computational approach to integrated PET/CT imaging. Eur J Nucl Med Mol Imaging. 2012 Aug;39(8):1326-38.
8. Giebel S, Labopin M, Mohty M, Mufti GJ, Niederwieser D, Cornelissen JJ, Janssen JJ, Milpied N, Vindelov L, Petersen E, Arnold R, Bacigalupo A, Blaise D, Craddock C, Nagler A, Frassoni F, Sadus-Wojciechowska M, Rocha V. The impact of center experience on results of reduced intensity: allogeneic hematopoietic SCT for AML. An analysis from the Acute Leukemia Working Party of the EBMT. Bone Marrow Transplant. 2013 Feb;48(2):238-42.
9. Cilloni D, Carturan S, Bracco E, Campia V, Rosso V, Torti D, Calabrese C, Gaidano V, Niparuck P, Favole A, Signorino E, Iacobucci I, Morano A, De Luca L, Musto P, Frassoni F, Saglio G. Aberrant activation of ROS1 represents a new molecular defect in chronic myelomonocytic leukemia. Leuk Res. 2013 May;37(5):520-30. doi: 10.1016/j.leukres.2013.01.014.
10. Bracco E, Rosso V, Serra A, Carnuccio F, Gaidano V, Nicoli P, Musto P, Saglio G, Frassoni F, Cilloni D. Design and application of a novel PNA probe for the detection at single cell level of JAK2V617F mutation in Myeloproliferative Neoplasms. BMC Cancer. 2013 Jul 18;13:348.

Laboratory of Clinical Chemical Analysis

Director: Prof. Giovanni Melioli/Dr. Gino Tripodi

STAFF

Name	Position
Roberto Bandettini	Physician
Raffaella Cozzani	Physician
Fabio Facco	Physician
Salvatore Mangraviti	Physician
Angelo Claudio Molinari	Physician
Paolo Montaldo	Physician
Maura Acquila	Biologost
Roberto Biassoni	Chemist
Maria Patrizia Bicocchi	Biologist
Carmela Cirillo	Biologist
Eddi Di Marco	Biologist
Candida Palmero	Biologist
Paolo Perutelli	Biologist
Luisa Pescetto	Biologist
Anna Maria Rabagliati	Biologist
Luigia Ricagni	Biologist
Rosella Ricci	Biologist
Elisabetta Ugolotti	Biologist
Ofelia Iovovich	Biologist
Patrizia Morelli	Biologist
Sebastiano Barco	Chemist
Giuliana Cangemi	Biologist
Irene Vanni	Biologist
Emanuela Grisanti	Biologist
Raffaele Lobello	Biologist
Alessio Chiarugi	Biologist
Iulian Gennai	Physician
Giovanni Liggieri	Physician
Dora Mangraviti	Biologist
Rodolfo Pessina	Laboratory technician
Stefano Amato	Laboratory technician
Roberto Bagnasco	Laboratory technician
Gyada Bazurro	Laboratory technician
Massimo Benvenuti	Laboratory technician
Roberto Bologna	Laboratory technician
Paola Bonifazio	Laboratory technician
Angela Cacciani	Laboratory technician
Antonella Casalaro	Laboratory technician
Emilio Facco	Laboratory technician
Manuela Filippetti	Laboratory technician
Domenico Gaggero	Laboratory technician

Gianna Galeazzi	Laboratory technician
Calogero Afflitto Gallo	Laboratory technician
Marco Garaventa	Laboratory technician
Vanda Maffei	Laboratory technician
Fernando Marotta	Laboratory technician
Anselmo Orsi	Laboratory technician
Giorgio Parodi	Laboratory technician
Anna Pellettieri	Laboratory technician
Angela Enrica Scarfo'	Laboratory technician
Fosca Truzzi	Laboratory technician
Vittorio Valente	Laboratory technician
Gian Franco Bacchiddu	Laboratory technician
Laura Barbagallo	Laboratory technician
Federico Bottini	Laboratory technician
Daniela Bugnone	Laboratory technician
Giovanni Di Maira	Laboratory technician
Paolo Fazzini	Laboratory technician
Maria Laura Fenu	Laboratory technician
Antonella Formiga	Laboratory technician
Elisabetta Fraternale	Laboratory technician
Carla Cinzia Gatti	Laboratory technician
Fabrizio Guidi	Laboratory technician
Angelo Maffia	Laboratory technician
Laura Marcomini	Laboratory technician
Emilio Pasquarella	Laboratory technician
Erika Rela	Laboratory technician
Mauro Stella	Laboratory technician
Marina Talio	Laboratory technician
Daniele Vailati	Laboratory technician
Valter Ventrella	Laboratory technician
Chiara Bernardini	Administrative
Margarita Pastoriza	Administrative
Rosella Vagheggi	Administrative

RESULTS YEAR 2013

In 2013, research activity started in previous years was continued. Research fields mainly included molecular medicine, microbiological diagnostics, study of new biomarkers, and assay of therapeutic ranges of relevant medications in pediatrics, especially the treatment of infectious diseases.

Concerning molecular medicine, two new Next Generation Sequencing tools were implemented which, in the short term, will yield extremely significant results in the field of genetics and molecular microbiology. Concerning the analysis of immune response at molecular level, the laboratory reached international renown in the study of IgE profiles in allergic patients. Microbiological diagnostics improved thanks to new molecular tools able to reduce dramatically time to response, thus making it possible to face resolutely the problem of antibiotic resistance. Even in this field, closely related to clinical pharmacology and therapeutic drug monitoring, the laboratory has made extremely significant advances, to the

point that it is considered an example of efficiency at least at national level. Finally, in the field of new biomarkers, research was focused on the study of the impact of these molecules on children and on the definition of reference values for pediatric age. In this field, innovative standards were defined, based on age as a continuous variable for the prediction of the reference range of biomarkers, which made it possible to overcome the obsolete classification into age ranges.

MAIN COLLABORATIONS YEAR 2013

- Institute of Microbiology, University of Ferrara (Herpes virus)
- Institute of Hematology, University of Parma (Stem cells)
- Pediatric Hematology, University of Padova (Leukemias and Lymphomas)
- Respiratory Disease Clinic, University of Genova (Allergology)
- Laboratory of Genetics, Istituto G. Gaslini
- Laboratory of Clinical and Experimental Immunology, Istituto G. Gaslini
- Laboratory of Oncology, Istituto G. Gaslini
- Core Facilities, Istituto G. Gaslini
- Infectious Disease unit, Istituto G. Gaslini
- Oncology, Hematology and Bone Marrow Transplantation unit, Istituto G. Gaslini

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: TMD (Therapeutic Drug Monitoring): Development and validation of methods for assay of antibiotic serum levels by liquid chromatography/tandem mass spectrometry.
Objective: The possibility of monitoring plasma concentration of antimicrobial agents using reproducible, rapid, and low cost tests is essential to individualization of therapy with improved efficacy and reduction of risk of onset of drug-resistant strains. In this context, it is very important to develop systems of assay of multiple drugs on a single small sample suitable even for low- or very low-weight patients.
Description: The need to assay accurately and rapidly antibiotic concentration is certainly one of the most important problems related to infections at the Istituto Gaslini. We planned a procedure of assay of wide-range concentrations of the most frequently used drugs at Gaslini (initially piperacillin, Tazobactam, Meropenem, Ceftazidime, and Linezolid, with possible extension of the method to other drugs) on small plasma samples (50-100 μL) using liquid chromatography/tandem mass spectrometry after rapid protein precipitation. We plan to use biological samples from hospitalized pediatric patients receiving antibiotic therapy and measure specificity, precision, and accuracy of single session assay (simultaneous).
The method will be evaluated using validation protocols based on international guidelines in order to include it among the rapid application methods for diagnostics at Gaslini.

Internal collaborations:

- Laboratory of Genetics
- Laboratory of Clinical and Experimental Immunology
- Laboratory of Oncology
- Core Facilities
- Infectious Disease unit
- Oncology, Hematology, and BMT unit

External collaborations:

- Institute of Microbiology, University of Ferrara

BEST PUBLICATIONS YEARS 2011-2013

1. Passalacqua G, Melioli G, Bonifazi F, Bonini S, Maggi E, Senna G, Triggiani M, Nettis E, Rossi RE, Vacca A, Canonica GW; Italian ISAC Study Group. The additional values of microarray allergen assay in the management of polysensitized patients with respiratory allergy. Allergy. 2013 Aug;68(8):1029-33.
2. Cangemi G, Barco S, Reggiardo G, Viscardi E, Di Cataldo A, Garaventa A, Melioli G, Conte M. Interchangeability between 24-hour collection and single spot urines for vanillylmandelic and homovanillic acid levels in the diagnosis of neuroblastoma. Pediatr Blood Cancer. 2013 Dec;60(12):E170-2.
3. Ricci R, Palmero C, Bazurro G, Riccio AM, Garelli V, Di Marco E, Cirillo C, Braido F, Canonica GW, Melioli G. The administration of a polyvalent mechanical bacterial lysate in elderly patients with COPD results in serological signs of an efficient immune response associated with a reduced number of acute episodes. Pulm Pharmacol Ther. 2013 Jun 21, Epub ahead of print.
4. Facco F, Agazzi A, Manfredini L, Dallorso S, Melioli G; MoLab Group. Evaluation of a mobile clinical pathology laboratory developed for the home care of pediatric patients following transplantation of peripheral blood precursor cells. Clin Chem Lab Med. 2013 Aug;51(8):1637-42.
5. Cangemi G, Pistorio A, Miano M, Gattorno M, Acquila M, Bicocchi MP, Gastaldi R, Riccardi F, Gatti C, Fioredda F, Calvillo M, Melioli G, Martini A, Dufour C.Diagnostic potential of hepcidin testing in pediatrics. Eur J Haematol. 2013 Apr;90(4):323-30.
6. Cangemi G, Barco S, Verrina EE, Scurati S, Melioli G, Della Casa Alberighi O. Micromethod for quantification of cinacalcet in human plasma by liquid chromatography-tandem mass spectrometry using a stable isotope-labeled internal standard. Ther Drug Monit. 2013 Feb;35(1):112-7.
7. Cangemi G, Di Iorgi N, Barco S, Reggiardo G, Maghnie M, Melioli G. Plasma total adiponectin levels in pediatrics: reference intervals calculated as a continuous variable of age. Clin Biochem. 2012 Dec;45(18):1703-5.
8. Scapolla C, Cangemi G, Barco S, Barbagallo L, Bugnone D, Maffia A, Melioli G, Profumo A, Benatti U, Damonte G. Identification and structural characterization by LC-ESI-IONTRAP and LC-ESI-TOF of some metabolic conjugation products of homovanillic acid in urine of neuroblastoma patients. J Mass Spectrom. 2012 Jul;47(7):816-24.
9. Melioli G, Marcomini L, Agazzi A, Bazurro G, Tosca M, Rossi GA, Minale P, Rossi R, Reggiardo G, Canonica GW, Passalacqua G. The IgE repertoire in children and adolescents resolved at component level: a cross-sectional study. Pediatr Allergy Immunol. 2012 Aug;23(5):433-40.
10. Ugolotti E, Bandettini R, Marchese A, Gualco L, Vanni I, Borzi L, Di Marco E, Castagnola E, Melioli G, Biassoni R. Molecular characterization of hospital-acquired methicillin-resistant Staphylococcus aureus strains in pediatric outbreaks using variable tandem repeat analysis with spa and ClfB typing. Diagn Microbiol Infect Dis. 2011 Feb;69(2):213-7.

Immunohematology and Transfusion Medicine

Director: Dr. Gino Tripodi

STAFF

Name	Position
Marco Risso	Physician (Apheretic Procedures)
Marina Martinengo	Physician
Mariapina Montera	Physician
Francesca Cottalasso	Physician
Cinzia Lo Giudice	Biologist
Fulvia Sindaco	Biologist
Angelo Arleo	Nurse
Cecilia Brighenti	Nurse
Simonetta Bosio	Nurse
Silvia Cecchini	Nurse
Nadia Fornaro	Nurse
Pietrina Mangiavillano	Nurse
Lucia Noviello	Nurse
Cinzia Nuara	Nurse
Loredana Tenerini	Nurse
Olga Schenone	Nurse
Massimo Solari	Technician
Diego Fabio Ardenghi	Technician
Daniela Bisi	Laboratory technician
Laura Bocciardo	Laboratory technician
Claudio Cermelli	Laboratory technician
Fabio Gallino	Laboratory technician
Mario Iannachino	Laboratory technician
Cristina Malavasi	Laboratory technician
Piero Messana	Laboratory technician
Mario Marcello	Laboratory technician
Maurizio Meta	Laboratory technician
Giuseppe Molè	Laboratory technician
Paola Nardi	Laboratory technician
Paola Petrone	Laboratory technician
Paolo Pietrasanta	Laboratory technician
Simona Rastelli	Laboratory technician
Corrado Schiazza	Laboratory technician
Patrizia Toselli	Laboratory technician

RESULTS YEAR 2013

The presence of high sHLA-I concentrations in many products (immunoglobulins, conserved blood components, blood coming in contact with biocompatible plastic surfaces during apheretic procedures) seems to be involved in the induction of a series of modulating effects (transfusion-related immunomodulation - TRIM) when transfused/infused intravenously. There are significant differences in importance and type of TRIM documentable in patients after infusion of large quantities of sHLA-I. Solubile CD8 molecule (sCD8) is able to bind to

biological membranes and to sHLA-I molecules, and it is therefore likely to play a role in modulating sHLA-I-mediated TRIM.
Materials and methods: sCD8 plasma levels were compared in patients with the same underlying disease but regularly transfused with two different blood components (pre- and post-storage leucodepleted unwashed erythrocyte concentrates with respectively low and high sHLA-I concentration levels). In addition, sFasL and sHLA-I concentrations in autologous platelet concentrates (prepared for topical use with three different modalities) were studied to evaluate whether they were able to induce TRIM via sHLA-I.
Results: in the plasma of patients transfused with unwashed post-storage leucodepleted erythrocyte concentrates (containing significantly higher levels of sHLA-I), significantly higher levels of circulating sCD8 were measured.
In autologous platelet concentrations with three different preparation modalities, sFasL and sHLA-I levels resulted very low, much lower than those obtainable from all available blood derivatives.
Conclusions. Though with the limits of indirect evidence, our results describe the possibility of a new active role of sCD8 molecules in sHLA-I-mediated TRIM.
In addition, the study of sFasL and sHLA-I concentrations in autologous platelet concentrates for topical use seems to exclude that these blood components can induce TRIM.

Main collaborations year 2013:

- Hematology/Oncology unit
- SIT Galliera hospital, Genova
- Chair of Clinical Immunology, University of Genova

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Immunomodulation due to apheretic procedures and TRIM (Transfusion Related ImmunoModulation): study of the effects of blood contact with biocompatible plastic materials (plastic circuits for cell sorters).
Objective: Similarly to what has been demonstrated for many blood derivatives and some blood components, prolonged contact of human blood with the biocompatible plastic materials of disposable circuits of cell sorters for apheresis determines important increases in sFasL and sHLA-I. Objective of the study is to evaluate whether soluble CD (sCD8) is involved even in this model.
Description: The presence of high concentrations of sHLA-I in many products (immunoglobulins, conserved blood components, blood coming into contact with biocompatible plastic surfaces during apheretic procedures) seems to be involved in the induction of a series of modulating effects in case of intravenous transfusion/infusion. There are significant differences in importance and type of biological changes observed in patients with autoimmune and/or inflammatory diseases compared to healthy subjects such as plasma and platelet donors. In all cases, sHLA-I increase in blood after prolonged contact was observed. Similarly to what has been studied after transfusion of erythrocyte concentrates, in this study we evaluated the role of soluble CD8 (sCD8) through the assay of its concentration on single samples and the possible correlation with the known sHLA-I increments.

Collaborations:

- Hematology/Oncology unit, Istituto Gaslini
- SIT Galliera Hospital, Genova
- Chair of Clinical Immunology, University of Genova

BEST PUBLICATIONS YEARS 2011-2013

1. Ratto GB, Costa R, Maineri P, Alloisio A, Piras MT, Agostino A, Tripodi G, Rivabella L, Dozin B, Bruzzi P, Melioli G. Neo-adjuvant chemo/immunotheraphy in the treatment of stage III (N2) non-small cell lung cancer: a phase I/II pilot study. Int J Immunopathol Pharmacol. 2011 Oct;24(4):1005-1016.
2. Corrias MV, Haupt R, Carlini B, Cappelli E, Giardino S, Tripodi G, Tonini GP, Garaventa A, Pistoia V, Pistorio A. Multiple target molecular monitoring of bone marrow and peripheral blood samples from patients with localized neuroblastoma and healthy donors. Pediatr Blood Cancer. 2012 Jan;58(1):43-9. doi: 10.1002/pbc.22960. Epub 2011 Jan 19.
3. Pierelli L, Perseghin P, Marchetti M, Accorsi P, Fanin R, Messina C, Olivieri A, Risso M, Salvaneschi L, Bosi A; for Società Italiana Di Emaferesi and Manipolazione Cellulare (SIDEM) and Gruppo Italiano Trapianto Midollo Osseo (GITMO). Best practice for peripheral blood progenitor cell mobilization and collection in adults and children: results of a Società Italiana Di Emaferesi e Manipolazione Cellulare (SIDEM) and Gruppo italiano Trapianto Midollo Osseo (GITMO) consensus process. Transfusion. 2012 Apr;52(4):893-905.
4. Ghio M, Contini P, Ubezio G, Ansaldi F, Setti M, Tripodi G. Blood transfusions with high levels of contaminating soluble HLA-I correlate with levels of soluble CD8 in recipients' plasma; a new control factor in soluble HLA-I-mediated transfusion-modulated immunomodulation? Blood Transfus. 2012 Dec 21:1-4. doi: 10.2450/2012.0199-12.
5. Ghio M, Contini P, Ansaldi F, Ubezio G, Setti M, Risso M, Tripodi G. A possibile role of solubile HLA-I molecole in the immunomodulatory effects of therapeutic apheresis. Blood Transfus. 2013 Apr 18:1-3. doi: 10.2450/2013.0026-13.
6. Ubezio G, Ghio M, Contini P, Bertorello R, Marino G, Tomasini A, Tripodi G. Bio-modulators in platelet-rich plasma: a comparison of the amounts in products from healthy donors and patients produced with three diffenet techiques. Blood Transfus. 2013 Jan 23:1-8. doi: 10.2450/2012.0128-12.
7. Perseghin P, Marchetti M, Messina C, Mazzoni A, Carlier P, Perotti C, Salvaneschi L, Risso M, Fanin R, Olivieri A, Accorsi P, Locatelli F, Bacigalupo A, Pierelli L, Bosi A. Best practice recommendations in: (1) Peripheral blood stem cell mobilization and collection and (2) acute and chronic GvHD treatment using extracorporeal photopheresis. A joint effort from SIdEM (Società Italiana di Emaferesi e Manipolazione Cellulare) and GITMO (Gruppo Italiano Trapianto di Midollo Osseo). Transfus Apher Sci. 2013 Apr;48(2):195-6. doi: 10.1016/j.transci.2013.02.034.
8. Montaldo E, Vitale C, Cottalasso F, Conte R, Glatzer T, Ambrosini P, Moretta L, Mingari MC. Human NK cells at early stages of differentiation produce CXCL8 and express CD161 molecule that functions as an activating receptor. Blood. 2012 Apr 26;119(17):3987-96. doi: 10.1182/blood-2011-09-379693.

Medical genetics

Director: Prof. Roberto Ravazzolo

STAFF

Name	Position
Margherita Lerone	Physician
Isabella Ceccherini	Biologist
Angela E. Covone	Biologist
Luis V Galietta	Biologist
Nicoletta Pedemonte	Biologist
Renata Bocciardi	Biologist
Aldamaria Puliti	Biologist
Cristina Cuoco	Biologist
Patrizia Fiorio	Biologist
Simona Porta	Biologist
Patrizia Ronchetto	Biologist
Ivana Matera	Chief Laboratory Technician
Francesco Caroli	Laboratory technician
Giuseppe Santamaria	Laboratory technician
Marco Bertorello	Laboratory technician
Corrado Torello	Laboratory technician
Loredana Velo	Administrative
Massimo Acquaviva	Biologist (bioinformatics specialist)
Tiziana Bachetti	Biologist
Silvia Borghini	Biologist
Emanuela Caci	Biologist
Serena Cappato	Biologist
Valeria Capurro	Biotechnologist
Maria Teresa Divizia	Physician
Eleonora Di Zanni	Biotechnologist
Loretta Ferrera	Biologist
Denise Ferrera	Biologist
Francesca Giacopelli	Biologist
Ambra Gianotti	Biologist
Paola Griseri	Biologist
Alessandra Lo Sardo	Biologist
Monica Marini	Biologist
Ilaria Musante	Biologist
Emanuela Pesce	Biologist
Marta Rusmini	Biotechnologist
Paolo Scudieri	Biologist
Elvira Sondo	Biologist
Elisa Tassani	Biologist
Elisa Tavella	Biologist
Laura Tonachini	Biologist

Carlotta Vaccari	Physician
Olga Zegarra Moran	Physician/Biologist

RESULTS YEAR 2013

The Medical Genetics unit carried out studies on different rare genetic diseases, according to a research strategy based on the characterization of genes responsible for monogenic hereditary diseases. In particular, we studied in depth disease pathogenetic mechanisms, interrelations between disease genes and functional pathways with functional genomics methods, and effects of cytogenetic anomalies and genomic imbalances. These studies allowed the acquisition of new knowledge useful for the development of new diagnostic tools, also by Next Generation Sequencing, and of innovative therapeutic approaches for rare genetic diseases.

In particular, the following results were obtained:

- Genes and mechanisms associated with the pathogenesis of Hirschsprung disease reported and described also as results of investigations performed within the International Consortium for Hirschsprung disease
- Genes and mechanisms involved in autoinflammatory diseases with description of new forms and new responsible genes.
- Genes and mechanisms involved in Alexander disease and Congenital Central Hypoventilation Syndrome.
- Further characterizations of genes coding for proteins of TMEM16 family: TMEM16A, TMEM16B, and TMEM16E.
- Advances in drug therapy strategies for cystic fibrosis.
- Animal model for drug therapy of spinocerebellar ataxia type 1.
- Mechanisms of ACVR1 gene regulation applicable to the search of chemical compounds with potential therapeutic efficacy for Fibrodysplasia Ossificans Progressiva.
- Genes and mechanisms involved in EEC and ADULT syndromes and in skeletal malformations with overgrowth.
- Genomic rearrangements in different regions of chromosomes 3, 2,14,15, and 22 including genes that can be associated with neuro-psychiatric syndromes and congenital malformations.

Main collaborations year 2013:

- Prof. Ferdinando Nicoletti, IRCCS Neuromed, Pozzilli, Italy: animal models for the treatment of neurologic diseases.
- International Consortium on Hirschsprung Disease: established in 2004 among groups in Baltimora, Paris, Groningen, Hong Kong, Sevilla, and Genova (Medical Genetics, Gaslini)
- Fred Kaplan and Eileen Shore, The University of Pennsylvania, School of Medicine: Pathogenetic mechanisms of Fibrodysplasia Ossificans Progressiva.
- Pediatric Rheumatology, Istituto Gaslini: Genetic aspects and molecular diagnosis of autoinflammatory diseases.
- Dr. Franco Pagani, Human Molecular Genetics, International Centre for Genetic Engineering and Biotechnology, Trieste, Italy: alternative splicing and TMEM16A isoforms.

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Genes, mechanisms, and therapeutic approaches for rare genetic diseases.

Objective: The study of genes and biological processes involved in disease mechanisms is the basis of the following:

A) development of new diagnostic methods;

B) identification of biological targets for new drug therapies. The Laboratory intends to pursue the objective of the project by using new sequencing technologies (Next Generation Sequencing) and high throughput screening of chemical compounds.
Description: New sequencing technologies (Next Generation Sequencing) available at Gaslini will be used for the following: A) Study of case series to identify new genes responsible for genetic diseases for which no causative gene has been identified through exome analysis applied to the study of malformations of brain median line structures with endocrine defects, autoinflammatory/autoimmune syndromes, Poland syndrome. B) development of CFTR gene sequencing for diagnostics of cystic fibrosis. C) Validation of the diagnostic method for syndromes with recurrent fever by sequencing of a panel of 11 candidate genes.
High Throughput Screening of chemical compounds will be used for: A) cystic fibrosis with screening of a new library of 30,000 compounds. B) Fibrodysplasia Ossificans Progressiva with screening of 1,200 compounds already approved for therapeutic use and screening of new compounds. C) Neuroblastoma, with screening of compounds already approved for therapeutic use. In addition, screening methods will be developed with a new technology, recently acquired at Gaslini, of High Content Imaging, characterized by automated image analysis and implemented in cell cultures on multiwell plates.

Internal collaborations:

- Pediatric Rheumatology, Istituto Gaslini: Genetic aspects and molecular diagnosis of autoinflammatory diseases.
- Pediatric Clinic, Endocrinology unit: malformations of brain median line structures
- Pediatric Surgery: Poland syndrome and Hirschsprung disease

External collaborations:

- Fred Kaplan and Eileen Shore, The University of Pennsylvania, School of Medicine: Fibrodysplasia Ossificans Progressiva
- International Consortium on Hirschsprung Disease: Hirschsprung disease
- M. Pacifici, Division of Orthopedic Surgery, The Children's Hospital of Philadelphia, USA: mechanisms and therapeutic approaches for the control of ectopic ossification.

BEST PUBLICATIONS YEARS 2011-2013

1. Scudieri P, Sondo E, Caci E, Ravazzolo R, Galietta LJ. TMEM16A-TMEM16B chimaeras to investigate the structure-function relationship of calcium-activated chloride channels. Biochem J. 2013 Jun 15;452(3):443-55.
2. Bachetti T, Chiesa S, Castagnola P, Bani D, Di Zanni E, Omenetti A, D'Osualdo A, Fraldi A, Ballabio A, Ravazzolo R, Martini A, Gattorno M, Ceccherini I. Autophagy contributes to inflammation in patients with TNFR-associated periodic syndrome (TRAPS). Ann Rheum Dis. 2013 Jun;72(6):1044-52.
3. Sanna-Cherchi S, Sampogna RV, Papeta N, Burgess KE, Nees SN, Perry BJ, Choi M, Bodria M, Liu Y, et al., Ravazzolo R, Kiryluk K, Al-Awqati Q, D'Agati VD, Drummond IA, Tasic V, Lifton RP, Ghiggeri GM, Gharavi AG. Mutations in DSTYK and dominant urinary tract malformations. N Engl J Med. 2013 Aug 15;369(7):621-9.
4. Giacopelli F, Cappato S, Tonachini L, Mura M, Di Lascio S, Fornasari D, Ravazzolo R, Bocciardi R. Identification and characterization of regulatory elements in the promoter of ACVR1, the gene mutated in Fibrodysplasia Ossificans Progressiva. Orphanet J Rare Dis. 2013 Sep 18;8(1):145.
5. Buzio R, Repetto L, Giacopelli F, Ravazzolo R, Valbusa U. Label-free, atomic force microscopy-based mapping of DNA intrinsic curvature for the nanoscale comparative analysis of bent duplexes. Nucleic Acids Res. 2012 Jun;40(11):e84.

6. Scudieri P, Caci E, Bruno S, Ferrera L, Schiavon M, Sondo E, Tomati V, Gianotti A, Zegarra-Moran O, Pedemonte N, Rea F, Ravazzolo R, Galietta LJ. Association of TMEM16A chloride channel overexpression with airway goblet cell metaplasia. J Physiol. 2012 Dec 1;590(Pt 23):6141-55.
7. Di Zanni E, Bachetti T, Parodi S, Bocca P, Prigione I, Di Lascio S, Fornasari D, Ravazzolo R, Ceccherini I. In vitro drug treatments reduce the deleterious effects of aggregates containing polyAla expanded PHOX2B proteins. Neurobiol Dis. 2012 Jan;45(1):508-18.
8. Sondo E, Tomati V, Caci E, Esposito AI, Pfeffer U, Pedemonte N, Galietta LJ. Rescue of the mutant CFTR chloride channel by pharmacological correctors and low temperature analyzed by gene expression profiling. Am J Physiol Cell Physiol. 2011 Oct;301(4):C872-85.
9. Puliti A, Rossi PI, Caridi G, Corbelli A, Ikehata M, Armelloni S, Li M, Zennaro C, Conti V, Vaccari CM, Cassanello M, Calevo MG, Emionite L, Ravazzolo R, Rastaldi MP. Albuminuria and glomerular damage in mice lacking the metabotropic glutamate receptor 1. Am J Pathol. 2011 Mar;178(3):1257-69.
10. Jacquemont S, Reymond A, Zufferey F, et al. Gimelli G, et al. Ravazzolo R, et al. Stefansson K, Blakemore AI, Beckmann JS, Froguel P.: Mirror extreme BMI phenotypes associated with gene dosage at the chromosome 16p11.2 locus. Nature. 2011 Aug 31;478(7367):97-102.

Centre of genetic and biochemical diagnostics of metabolic diseases

Director: Dr. Mirella Filocamo

STAFF

Name	Position
Marina Stroppiano,	Biologist
Fabio Corsolini,	Laboratory technician
Raffaella Mazzotti,	Laboratory technician
Susanna Lualdi,	Biologist
Serena Grossi	Biologist
Barbara Tappino	Biologist
Federica Lanza	Biologist
Giorgia Stroppiana,	Laboratory technician
Sara Galotto	*Data manager* – laboratory
Lorena Casareto	*Data manager* – Genetic Biobanks Network
Maurici Catena	Orderly

RESULTS YEAR 2013

Research interests of the centre include the study of molecular mechanisms underlying lisosomal diseases (LD) and some white matter disorders. Parallel research activities are related to the genetic biobank (GB) at the centre and to regulation of biobanking. The latter activity is carried out in collaboration with national and international working groups.

Among LD, Gaucher disease (GD), due to glucocerebrosidase deficiency (GBA), was studied in different projects. In particular, in collaboration with the Department of Cell Research and Immunology of the University of Tel Aviv, two parallel studies were carried out: a) both in fibroblasts of GD patients and in Drosophila animal model, the activation of UPR (unfolded protein response) in the presence of GD mutant alleles was demonstrated. The same mechanism was also hypothesized as jointly responsible together with ERAD (ER-associated degradation) of Parkinson disease onset in GD; b) in vitro demonstration of the efficacy of Ambroxol, used as pharmacological chaperone, in increasing the levels of the missing enzyme in a panel of fibroblasts, previously characterized at molecular level.

As regards the second research line, with the services of the genetic biobank (storage and distribution), the centre supported research projects at Gaslini and at national and international institutions, and continued the activity of coordination of 10 Italian biobanks (Telethon project). In addition, the centre has constantly made available to national (ERIC-BBMRI; Certification requisites-SIGU) and international (Bioresource Research Impact Factor-GEN2PHEN) working groups specific skills acquired in the field of organizational, legal, and ethical aspects related to biobanking. In particular, as regards BBMRI-IT, the centre has actively participated in the development of a questionnaire for the survey of biobanks that will be part of the Italian network. Finally, it continued monitoring of specific indicators of biobank regulations and, in parallel, it coordinated a SIGU (Italian Society of Human Genetics) working group for preparing the final version of the "Management System for Quality of Genetic Biobanks". In order to facilitate the integration of systems for management of quality, environment, safety, laboratory activity, the standard was made compatible with ISO 9001, SO14001,OHSAS 18001, SA8000, ISO15189, ISO17025.

Main collaborations year 2013:

- Department of Cell Research and Immunology, Tel Aviv University, Levanon St, Ramat Aviv 69978, Israel
- Centre of Regional Coordination for Rare Diseases, "Santa Maria della Misericordia" hospital, Udine
- Department of biomedical sciences – University of Padova
- NEST, Nanosciences Institute-CNR, Pisa
- Institute of Medical Genetics, School of Medicine, Cardiff University, Cardiff, UK
- Institut National de la Santé et de la Recherche Medicale INSERM, Paris, France
- Bambino Gesù hospital, Roma
- Department of sciences for the health of women and children, University of Firenze

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Genetic biobank: Service for diagnosis and research.
Objective: The biobank, created in 1976, presently stores almost 10,000 samples (cell lines and nucleic acids) from more than 8,000 patients with genetic diseases, from rare to very rare. About 40% of these patients, however, are still awaiting a definitive diagnosis. Objective of the project is to use new sequencing technologies (Next Generation System) in cohorts of selected patients for a posteriori diagnosis.
Description: In particular, the study will include samples of patients referred to the centre for diagnosis and storage in the genetic biobank. In particular, the patients will be divided into two groups, one including patients with a phenotype suggesting lisosomal storage and in which known defects have been excluded, the other including patients with still unknown defects causing hypomyelinization. Samples will be selected according to specific protocols (based on clinical, paraclinical, and instrumental data).
In parallel, the activity related to regulation and certification of biobanks will be continued.

Internal collaborations:

- Child Neuropsychiatry unit
- Pediatric Neuroradiology service
- Rare Diseases unit
- Muscular Pathology unit

External collaborations:

- Telethon Institute of Genetics and Medicine (TIGEM), Napoli
- Department of Cell Research and Immunology, Tel Aviv University, Ramat Aviv 69978, Israel
- Centre of Regional Coordination for Rare Diseases, "Santa Maria della Misericordia" hospital, Udine
- Institute of Medical Genetics, School of Medicine, Cardiff University, Cardiff, UK
- Epidémiologie et analyses en santé publique, Faculté de médecine, UMR1027 INSERM-Université de Toulouse III, 37 allées Jules Guesde, Toulouse

BEST PUBLICATIONS YEARS 2011-2013

1 Bertola F, Filocamo M, Casati G, Mort M, Rosano C, Tylki-Szymanska A, n Tüysüz B, Gabrielli O, Grossi S, Scarpa M, Parenti G, Antuzzi D, Dalmau J, Di Rocco M, Dionisi Vici C, Okur I, Rosell J, Rovelli A, Furlan F, Rigoldi M, Biondi A, Cooper D, Parini R. IDUA Mutational Profiling of a Cohort of 102 European Patients with Mucopolysaccharidosis type I: Identification and Characterization of 35 Novel alpha-L-iduronidase (IDUA) Alleles. Hum Mutat, 2011;32:E2189-210.

2 the BRIF workshop group, Cambon-Thomsen A, Thorisson GA; Named collaborators, Andrieu S, Bertier G, Boeckhout M, Cambon-Thomsen A, Carpenter J, Dagher G, Dalgleish R, Deschênes M, di Donato JH, Filocamo M, Goldberg M, Hewitt R, Hofman P, Kauffmann F, Leitsalu L, Lomba I, Mabile L, Melegh B, Metspalu A, Miranda L, Napolitani F, Oestergaard MZ, Parodi B, Pasterk M, Reiche A, Rial-Sebbag E, Rivalle G, Rochaix P, Susbielle G, Tarasova L, Thomsen M, Thorisson GA, Zawati MH, Zins M, Mabile L. The role of a bioresource research impact factor as an incentive to share human bioresources. Nat Genet. 2011;43:503-504.

3 Grossi S, Regis S, Biancheri R, Mort M, Lualdi S, Bertini E, Uziel G,Boespflug-Tanguy O, Simonati A, Corsolini F, Demir E, Marchiani V, Percesepe A,Stanzial F, Rossi A, Vaurs-Barriere C, Cooper DN, Filocamo M. Molecular Genetic Analysis of the PLP1 Gene in 38 Families with PLP1-related disorders: Identification and Functional Characterization of 11 Novel PLP1 Mutations. Orphanet J Rare Dis. 2011;6:40.

4 Chiefari E, Tanyolaç S, Paonessa F, Pullinger CR, Capula C, Iiritano S, Mazza T, Forlin M, Fusco A, Durlach V, Durlach A, Malloy MJ, Kane JP, Heiner SW, Filocamo M, Foti DP, Goldfine ID, Brunetti A. Functional variants of the HMGA1 gene and type 2 diabetes mellitus. JAMA. 2011 2;305:903-12.

5 Aureli M, Bassi R, Loberto N, Regis S, Prinetti A, Chigorno V, Aerts JM, Rolf G. Boot RG, Filocamo M and Sandro Sonnino S Cell surface associated glycohydrolases in normal and Gaucher disease fibroblasts. J Inherit Metab Dis. 2012, 35:1081-1091.

6 Zampieri S, Cattarossi S, Oller Ramirez AM, Rosano C, Marques Lourenco M, Passon N, Moroni I, Uziel G, Pettinari A, Stanzial F, Dodelson de Kremer R, Azar NB, Filocamo M, BembiB, Dardis A. Sequence and copy number analyses of HEXB gene in patients affected by Sandhoff disease: functional characterization of 9 novel sequence variants. Plos one, 2012;7(7):e41516.

7 Biancheri R, Rosano C, Denegri L, Lamantea E, Pinto F, Lanza F, Severino M, Filocamo M. Expanded spectrum of Pelizaeus-Merzbacher-like disease: literature revision and description of a novel GJC2 mutation in an unusually severe form. EJHG 2013;21(1):34-9.

8 Gali M, Filocamo M, Horowitz M. Itch Regulates Degradation of Mutant Glucocerebrosidase: Implications to Gaucher Disease. Hum Mol Genet. 2013 Apr 1;22(7):1316-27.

9 Filocamo M, Baldo C, Goldwurm S, Renieri A, Angelini C, Moggio M, Mora M, Merla G, Politano L, Garavaglia B, Casareto L, Dagna Bricarelli F for Telethon Network of Genetic Biobanks Staff. Telethon Network of Genetic Biobanks: a Key Service for Diagnosis and Research on Rare Diseases. Orphanet J Rare Dis., 2013; 8:129.

10 Regis S, Corsolini F, Grossi S, Tappino B, Cooper DN and Filocamo M. Restoration of the normal splicing pattern of the PLP1 gene by means of an antisense oligonucleotide directed against an exonic mutation. PlosOne, 2013; 8:e73633.

Pathologic Anatomy

Director: Dr. Claudio Gambini/Dr. Angela Rita Sementa (pro-tempore)

STAFF

Name	Position
Cristina Coccia	Physician
Paolo Nozza	Physician
Cesarina Savioli	Physician
Federico Comanducci	Head laboratory technician
Marco Ciuferri	Laboratory technician
Daniela Campanella	Laboratory technician
Barbara De Giovanni	Laboratory technician
Davide Ircolo'	Laboratory technician
Fabiana Malaguti	Laboratory technician
Manuela Ferraro	Laboratory technician
Daniele Murgia	Laboratory technician
Andrea Rossi	Laboratory technician
Francesca Negri	Biologist
Katia Mazzocco	Biologist
Raffaella Defferrari	Biologist
Martina Verroca	Administrative
Paola Ceriolo	Physician

RESULTS YEAR 2013

Research activities planned for 2013 were either completed or are still ongoing. The following results were obtained:

- The molecular genetic study of neuroblastic tumors in adolescents belonging to the Italian case series from the NB registry - in collaboration with the Department of Pediatric Hematology-Oncology – resulted in the identification of biomolecular peculiarities of this tumor in adolescents (in press; presentation at national and international congresses). A similar study on an adult neuroblastoma case series of 21 adult patients (one of the most numerous ever reported in the literature) yielded a paper in press.
- The study of Gaslini's series of atypical Spitz tumors, with biomolecular characteristics and immunohistochemical aspects, merged with the analysis of the national case series from the registry of rare pediatric tumors. The paper illustrating the results of this important study is in press.
- The study of minimal residual disease in patients with neuroblastoma (at onset and in different disease phases) by immunocytochemistry with anti-GD2 antibody on samples of bone marrow aspirate, peripheral blood, and apheretic collections, provided the basis of an international cooperative study on minimal residual disease in neuroblastoma, of which the Italian case series represents the best quantitative and qualitative contribution Statistical analysis is ongoing.
- The histological correlation study between biopsies at onset and samples obtained at delayed surfery of peripheral neuroblastic tumors in patients of the Unresectable protocol (2001 - 2006) is still ongoing.

Main collaborations year 2013

SIOPEN-R-NET (European Society of Paediatric Oncology Neuroblastoma Research Network). Department of Pathology Rikshospitalet, Oslo, (Dr. Klaus Beiske). Service de Pathologie, Hopital Robert Debré, Université (Prof. Michel Peuchmaur). University of Padova (Pathologic Anatomy Institute). Istituto Ortopedico Pini of Milano (Dr. Parafioriti). King's College, University of London (Prof. Knisely). St. John's Hospital, Dept. Dermatopathology, (prof E.Calonje) London. National Cancer Institute of Milano (dr. Collini). Pathologic Anatomy, Dept. Experimental Medicine of Roma (Prof. F. Giangaspero). Istitut fur Neuropathologie of Bonn, Deutschland, (Prof. T. Pietsch). Childrens Hospital of Los Angeles, USA, Dept Pathology (Prof. Hiro Shimada, Coordinator of INPC -International Neuroblastoma Pathology Committee).

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Histological and biomolecular study of neuroblastomas from the Italian registry.
Objective: In-depth study of the prognostic significance of histological and biological characteristics of primary tumor and circulating disease at diagnosis and as response to therapy in all cases of peripheral neuroblastic tumor diagnosed in Italy from Italian centres of pediatric oncology (AIEOP). Final objective is to identify new immunohistochemical and biomolecular patterns as the basis of new therapeutic protocols.
Description: Neuroblastoma (NB) is the most frequent pediatric solid tumor (in Italy about 130-150 new cases/year), fatal in 40% of cases. Main prognostic factors include age, disease extension at diagnosis, histology, and presence of some genetic alterations (*MYCN* amplification, 1p and 11q deletion, 17q duplication). The prognostic factors identified to date are however insufficient to define with certainty prognosis and treatment of each single patient: a "signature" of each single case can represent the rationale of the use of more recent medications, whose target is indicated on the basis of gene alterations. The study of histological and biomolecular characteristics of peripheral neuroblastic tumors diagnosed in Italy is based on the centralization at Gaslini of cases from 50 AIEOP Pediatric Oncology centres that, for each diagnosed patient, send to Gaslini tumor and biological samples, both at onset and during treatment, for complete tumor characterization. This study is further boosted by the Tissue-Genomic Integrated Biobank (BIT) established at Gaslini in 2009, that classifies tumors and generates a molecular database linked to the registry collecting clinical data of over 3,400 patients with NB. This system is available for use to interested researchers.

Internal collaborations:

Dept. of Hematology-Oncology, Dept. of Pediatric Surgery, Radiology and Neuroradiology unit; Epidemiology and Biostatistics Service, Laboratory of Clinical Chemical Analysis, Laboratory of Oncology, Laboratory of Molecular Biology, Laboratory of Cytogenetics, Laboratory of Postnatal Stem Cells and Cell Therapies.

External collaborations:

Neuroblastoma Foundation Laboratory, Padova; Immunologic Therapy unit, S.Martino-IST hospital, Genova; Pathologic Anatomy unit and Pediatric Oncology units (AIEOP) of the main Italian hospitals; European laboratories of Molecular Biology of ENQUA group (European Neuroblastoma Quality Assessment Group) for quality control.

BEST PUBLICATIONS YEARS 2011-2013

1. Miele E, Buttarelli FR, Arcella A, Begalli F, Garg N, Silvano M, Po A, Baldi C, Carissimo G, Antonelli M, Spinelli GP, Capalbo C, Donofrio V, Morra I, Nozza P, Gulino A, Giangaspero F, Ferretti E. High-throughput microRNA profiling of pediatric high-grade gliomas. Neuro Oncol. 2013 Dec 4.
2. Morana G, Piccardo A, Garrè ML, Nozza P, Consales A, Rossi A. Multimodal magnetic resonance imaging and 18F-L-dihydroxyphenylalanine positron emission tomography in early characterization of pseudoresponse and nonenhancing tumor progression in a pediatric patient with malignant transformation of ganglioglioma treated with bevacizumab. J Clin Oncol. 2013 Jan 1;31(1).
3. Raso A, Mascelli S, Biassoni R, Nozza P, Kool M, Pistorio A, Ugolotti E, Milanaccio C, Pignatelli S, Ferraro M, Pavanello M, Ravegnani M, Cama A, Garrè ML, Capra V. High levels of PROM1 (CD133) transcript are a potential predictor of poor prognosis in medulloblastoma. Neuro Oncol. 2011 May;13(5):500-8.
4. Ginevri F, Nocera A, Comoli P, Innocente A, Cioni M, Parodi A, Fontana I, Magnasco A, Nocco A, Tagliamacco A, Sementa A, Ceriolo P, Ghio L, Zecca M, Cardillo M, garibotto G, Ghiggeri GM, Poli F. Posttransplant de novo donor-specific hla antibodies identify pediatric kidney recipients at risk for late antibody-mediated rejection. Am J Transplant. 2012 Dec; (12): 3355-62.
5. Cattelani S, Ferrari-Amorotti G, Galavotti S, Defferrari R, Tanno B, Cialfi S, Vergalli J, Fragliasso V, Guerzoni C, Manzotti G, Soliera AR, Menin C, Bertorelle R, McDowell HP, Inserra A, Belli ML, Varesio L, Tweddle D, Tonini GP, Altavista P, Dominici C, Raschellà G, Calabretta B. The p53 codon 72 Pro/Pro genotype identifies poor-prognosis neuroblastoma patients: correlation with reduced apoptosis and enhanced senescence by the p53-72P isoform. Neoplasia. 2012 Jul;14(7):634-43.
6. Schleiermacher G, Michon J, Ribeiro A, Pierron G, Mosseri V, Rubie H, Munzer C, Bénard J, Auger N, Combaret V, Janoueix-Lerosey I, Pearson A, Tweddle DA, Bown N, Gerrard M, Wheeler K, Noguera R, Villamon E, Cañete A, Castel V, Marques B, de Lacerda A, Tonini GP, Mazzocco K, Defferrari R, de Bernardi B, di Cataldo A, van Roy N, Brichard B, Ladenstein R, Ambros I, Ambros P, Beiske K, Delattre O, Couturier J. Segmental chromosomal alterations lead to a higher risk of relapse in infants with MYCN-non-amplified localised unresectable/disseminated neuroblastoma (a SIOPEN collaborative study). Br J Cancer. 2011 Dec 6;105(12):1940-8.
7. Ambros IM, Brunner B, Aigner G, Bedwell C, Beiske K, Bénard J, Bown N, Combaret V, Couturier J, Defferrari R, Gross N, Jeison M, Lunec J, Marques B, Martinsson T, Mazzocco K, Noguera R, Schleiermacher G, Speleman F, Stallings R, Tonini GP, Tweddle DA, Valent A, Vicha A, Roy NV, Villamon E, Ziegler A, Preuner S, Drobics M, Ladenstein R, Amann G, Schuit RJ, Pötschger U, Ambros PF. A multilocus technique for risk evaluation of patients with neuroblastoma. Clin Cancer Res. 2011 Feb 15;17(4):792-804.
8. Kohler JA, Rubie H, Castel V, Beiske K, Holmes K, Gambini C, Casale F, Munzer C, Erminio G, Parodi S, Navarro S, Marquez C, Peuchmaur M, Cullinane C, Brock P, Valteau-Couanet D, Garaventa A, Haupt R. Treatment of children over the age of one year with unresectable localised neuroblastoma without MYCN amplification: results of the SIOPEN study. Eur J Cancer. 2013 Nov; 49(17):3671-9.
9. Loi M, Di Paolo D, Soster M, Brignole C, Bartolini A, Emionite L, Sun J, Becherini P, Curnis F, Petretto A, Sani M, Gori A, Milanese M, Gambini C, Longhi R, Cilli M, Allen TM, Bussolino F, Arap W, Pasqualini R, Corti A, Ponzoni M, Marchiò S, Pastorino F. Novel phage display-derived neuroblastoma-targeting peptides potentiate the effect of drug nanocarriers in preclinical settings. J Control Release. 2013 Sep 10;170(2):233-41.

10. Pezzolo A, Parodi F, Marimpietri D, Raffaghello L, Cocco C, Pistorio A, Mosconi M, Gambini C, Cilli M, Deaglio S, Malavasi F, Pistoia V. Oct-4+/Tenascin C+ neuroblastoma cells serve as progenitors of tumor-derived endothelial cells. Cell Res. 2011 Oct;21(10):1470-86.

Radiology

Director: Dr. Gian Michele Magnano

STAFF

Name	Position
Maria Beatrice Damasio	Radiologist
Mirella Ghiorzi	Radiologist
Claudio Giuseppe Granata	Radiologist
Giorgio Lucigrai	Radiologist
Francesca Magnaguagno	Radiologist
Anna Marzoli	Radiologist
Francesca Nardi	Radiologist
Francesca Rizzo	Radiologist
Nicola Stagnaro	Radiologist
Maura Maria Valle	Radiologist
Elisabetta Vignale	Radiologist
Alessi Lucia	Medical radiology technician
Baghino Roberta	Medical radiology technician
Barbieri Gianluca	Medical radiology technician
Barbieri Luca	Medical radiology technician
Bozzini simona	Medical radiology technician
Chessa Gianluca	Medical radiology technician
Chiossone Paola	Medical radiology technician
Del Mirto Paolo	Medical radiology technician
Franceschi Stefano	Medical radiology technician
Gagliardi Luisa	Medical radiology technician
Imbergamo Marco	Medical radiology technician
Maiuri Francesca	Medical radiology technician
Marabello Maria Vittoria	Medical radiology technician
Morasso Stefano	Medical radiology technician
Musso Paola	Medical radiology technician
Passerini Marco	Medical radiology technician
Penzo Roberto	Medical radiology technician
Perotto Valerio	Medical radiology technician
Piroli Giovanna	Medical radiology technician
Rimassa Luana	Medical radiology technician
Scaranari Barbara	Medical radiology technician
Sorrentino Maria Chiara	Medical radiology technician
Tindiglia Chiara	Medical radiology technician
Trapanese Paola	Medical radiology technician
Vassallo Marco	Medical radiology technician
Vinelli Monica	Medical radiology technician
Zendrini Luca	Medical radiology technician
Razzetti Matteo	Medical radiology technician
Ciccone Marco Antonio	Head laboratory technician
Chessa Gian Piero	Head laboratory technician
Rollando Michela	Pediatric nurse

Massabò Patrizia	Pediatric nurse
Corallo Marina	Pediatric nurse
Drago Marina	Pediatric nurse
Roccia Marilena	Pediatric nurse
Talircio Raffaella	Pediatric nurse
Ricci Rlaudia	Pediatric nurse

RESULTS YEAR 2013

New imaging techniques for evaluation of children with chronic rheumatic disease
Concerning joint cartilages, further implementation of sequences for T2 mapping and T1 mapping (dGEMRIC) was performed, with in vivo quantitative analysis of collagen/proteoglycans, to demonstrate early macromolecular alterations (i.e. without corresponding morphology). We also demonstrated that synovial CE in JIA can be quantified with both semiquantitative evaluation (synovitis scoring system) and with calculation of synovial volume and that it can be used for disease monitoring. Concerning whole body MR in rheumatic disease: definitive validation of its use in CRMO (diagnosis and disease monitoring) and in JDM (good correlation between disease activity and alteration/distribution of muscular signal).

Uro-MRI with even functional evaluation of kidneys in nephrourologic disease
In 2013, about 100 uro-MRI examinations with functional evaluation were acquired. All examinations were discussed in occasion of meetings of the uro-nephrologic multidisciplinary group (URANO). In collaboration with the University of Rouen, we are carrying out a comparative evaluation to validate fMRU versus sequential renal scintigraphy. In collaboration with the University of Genova (DISI), specific software is being implemented for automatic segmentation of renal volume and calculation of renal volume, and for more refined analysis of variation curves of the contrast medium. MR with DWI seq in UTI: patient enrolment is ongoing.

Main collaborations year 2013:

- Prof A. Dacher, Department of Diagnostic Imaging Rouen University de France for MR Urography with functional evaluation
- ESPR Uroradiology Force (Coordinator Prof Michael Riccabona)
- European Excellence Network on Pediatric Radiology Research of ESPR
- Euronet PHL-C1 add on study on WholeBody Magnetic Resonance Imaging in Hodgkin Lymphoma (Coordinator Rutger J. Nievelstein, Utrecht, NL)
- SIOPEN commission (International Society of Paediatric Oncology European Neuroblastoma) deticated to Neuroblastoma Diagnostic Imaging Guidelines
- ESPR (European Society of Pediatric Radiology) oncologic task force
- Prof. Andrew Taylor Cardiac-MRI unit of GOSH , London
- AIFM (Italian Association Health Physics) and University of Palermo (Chair of Radiology) for the definition of new national reference dosimetric levels for CT use in children.

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: new nephrourologic, rheumatologic, cardiovascular, and pediatric oncologic imaging with containment of/alternative to radiation exposure.
Objective: Low radiation dose quantitative and functional diagnostic imaging
Description: For this project, the following activities will be carried out:

1. Whole body MRI with STIR/DWIBS seq. and functional imaging in diagnosis and follow up of oncologic diseases;

2. MD Paedigree: European multicentre study to build computerized models of pediatric diseases, in particular JIA, as predictors of outcome
3. Functional uro-MR as an alternative to sequential scintigraphy, as diagnostics "all in one" without radiant energy in nephrourologic disease
4. MR with DWI seq. In UTI to select a population at higher risk of relapse and/or complications to prevent IR
5. Cardiovascular MR as an alternative to CT, in particular in pectus excavatum: definition of new pathologic indexes for surgical decision-making
6. Optimization of radiation dose in children (in particular CT) at Gaslini as SIRM pilot centre

Internal collaborations:

- Nephrology (Dr. Ghiggeri)
- Rheumatology (Prof Martini)
- Surgery (Dr. Buffa)
- Miniinvasive surgery (Prof Mattioli)
- URANO Group

External collaborations:

- Prof A. Dacher, Diagnostic Imaging, Rouen University de France per la fRM
- ESPR Uroradiology Force (Prof Michael Riccabona) for fRM and DWI IVU study
- European Excellence Network on Pediatric Radiology Research of ESPR
- Euronet PHL-C1 add on study on WholeBody Magnetic Resonance Imaging in Hodgkin Lymphoma (Coordinator Rutger J. Nievelstein, Utrecht, NL)
- Prof. Andrew Taylor Cardiac-MRI unit of (GOSH) , London for CV MR

BEST PUBLICATIONS YEARS 2011-2013

1. Lambot K, Boavida P, Damasio MB, Tanturri de Horatio L, Desgranges M, Malattia C, Barbuti D, Bracaglia C, Müller LS, Elie C, Bader-Meunier B, Quartier P, Rosendahl K, Brunelle F. MRI assessment of tenosynovitis in children with juvenile idiopathic arthritis: inter- and intra-observer variability. Pediatr Radiol. 2013 Jul;43(7):796-802. doi: 10.1007/s00247-012-2613-x. Epub 2013 Feb 5. PubMed PMID: 23381299.
2. Damasio MB, Darge K, Riccabona M. Multi-detector CT in the paediatric urinary tract. Eur J Radiol. 2013 Jul;82(7):1118-25. doi: 10.1016/j.ejrad.2011.12.005. Epub 2012 Jul 2. PubMed PMID: 22762970.
3. Damasio MB, Costanzo S, Podestà E, Ghiggeri G, Piaggio G, Faranda F,Degl'innocenti ML, Jasonni V, Magnano GM, Buffa P, Montobbio G, Mattioli G.Magnetic resonance urography and laparoscopy in paediatric urology: a case series. Pediatr Radiol. 2013 Nov;43(11):1516-27. doi: 10.1007/s00247-013-2724-z. Epub 2013 Jul 31. PubMed PMID: 23900764.
4. Damasio MB, de Horatio LT, Boavida P, Lambot-Juhan K, Rosendahl K, Tomà P,Muller LO. Imaging in juvenile idiopathic arthritis (JIA): an update withparticular emphasis on MRI. Acta Radiol. 2013 Nov 1;54(9):1015-23. doi: 10.1177/0284185113493777. Epub 2013 Jul 19. PubMed PMID: 23873885.
5. Malattia C, Damasio MB, Madeo A, Pistorio A, Providenti A, Pederzoli S, Viola S, Buoncompagni A, Mattiuz C, Beltramo A, Consolaro A, Ravelli A, Ruperto N, Picco P, Magnano GM, Martini A. Whole-body MRI in the assessment of disease activity in juvenile dermatomyositis. Ann Rheum Dis. 2013 May 1. [Epub ahead of print].

6. Granata C, Magnano G. Computerized tomography in pediatric oncology. Eur J Radiol. 2013 Jul;82(7):1098-107. doi: 10.1016/j.ejrad.2011.12.008. Epub 2011 Dec 29.
7. Dalmonte P, Granata C, Fulcheri E, Vercellino N, Gregorio S, Magnano G. Intra-articular venous malformations of the knee. J Pediatr Orthop. 2012 Jun;32(4):394-8. doi: 10.1097/BPO.0b013e31824b29ef. PMID:22584841 [PubMed - indexed for MEDLINE].
8. Riccabona M, Avni FE, Damasio MB, Ording-Müller LS, Blickman JG, Darge K, Lobo ML, Papadopoulou F, Vivier PH, Willi U. ESPR Uroradiology Task Force and ESUR Paediatric Working Group--Imaging recommendations in paediatric uroradiology, part V: childhood cystic kidney disease, childhood renal transplantation and contrast-enhanced ultrasonography in children. Pediatr Radiol. 2012 Oct;42(10):1275-83. doi: 10.1007/s00247-012-2436-9. Epub 2012 Sep 22. PMID: 23001574 [PubMed - indexed for MEDLINE]
9. Damasio MB, Malattia C, Tanturri de Horatio L, Mattiuz C, Pistorio A, Bracaglia C, Barbuti D, Boavida P, Juhan KL, Ording LS, Rosendahl K, Martini A, Magnano G, Tomà P. MRI of the wrist in juvenile idiopathic arthritis: proposal of a paediatric synovitis score by a consensus of an international working group. Results of a multicentre reliability study. Pediatr Radiol. 2012 Sep;42(9):1047-55. doi: 10.1007/s00247-012-2392-4. Epub 2012 Jul 26. Erratum in: Pediatr Radiol. 2013 Jan;43(1):124.
10. Malattia C, Damasio MB, Basso C, Santoro M, Verri A, Pederzoli S, Mattiuz C, Viola S, Buoncompagni A, Madeo A, Mazzoni M, Rosendahl K, Lambot-Juhan K, Tanturri de Horatio L, Magnano GM, Ravelli A, Martini A. Novel automated system for magnetic resonance imaging quantification of the inflamed synovial membrane volume in patients with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2012 Nov;64(11):1657-64. doi: 10.1002/acr.21739.

Neuroradiology

Director: Dr. Andrea Rossi

STAFF

Name	Position
Carlo Gandolfo	Physician
Giovanni Morana	Physician
Mariasavina Severino	Physician
Piero Sorrentino	Head laboratory technician
Claudia Ricci	Head nurse

RESULTS YEAR 2013

The project was aimed at combining data of integrated diagnostics with 18F-DOPA PET and MR to evaluate their synergic diagnostic role and clinical impact in pediatric patients with brain tumors. Specific research fields concerned the evaluation pre- and post-treatment of diffusely infiltrating low grade and other grade gliomas.
Thirty pediatric patients were studied to date, and the analysis of functional MR data is being evaluated. As first step, comparison and merging of DOPA PET data with conventional MR data for diagnostic, therapeutic, and prognostic purposes were completed and results were published in the Journal of Nuclear Medicine (IF: 5.77). A book chapter is being pusblished on the role of DOPA PET in pediatric brain tumors. Finally, the results of our research were presented as oral communication in occasion of the XXXVII Congress of the European Society of Neuroradiology.

MAIN COLLABORATIONS YEAR 2013

- Nuclear Medicine, Galliera Hospital, Genova (Dr. A. Piccardo): execution of brain DOPA-PET, PET-MR fusion.
- DINOGMI University of Genova (Dr. Bonzano, Dr. Roccatagliata): bioengineering reworking of fMRI and DTI.
- Starting Grant project, funded by European Research Council: "Understanding the basis of cerebellar and brainstem congenital defects: from clinical and molecular characterization to the development of a novel neuroembryonic in vitro model" (Prof. E.M. Valente, Istituto Mendel, Roma).
- Children's Hospital of Philadelphia Department of Neuroradiology (Prof. R.A. Zimmerman): training in advanced neuroradiology .

PLANNED RESEARCH ACTIVITY YEAR 2014

Titolo: Advanced MRI in childhood brain tumors
Objective:

- To evaluate childhood brain tumors through the acquisition of an integrated system of morphofunctional data, obtained with non-invasive advanced MR methods (diffusion, tractography, perfusion, spectroscopy, fMRI).
- To translate data in neurosurgical and neurooncologic management, with evaluation of overall diagnostic impact and influence on therapeutic decision-making

Description: All pediatric patients followed at the Istituto Giannina Gaslini with brain tumor and receiving surgery and/or chemo-radiotherapeutic protocols will be eligible for inclusion in the study. The patients will undergo MR, including advanced diffusion sequences, diffusion tensor imaging (DTI), perfusion, and spectroscopy; on the basis of clinical indication, collaborating patients will undergo fMRI for cortical activation.

Data will be evaluated on the basis of histopathological and surgical results to determine their contribution to presurgical diagnostic definition, surgical planning, and monitoring during adjuvant therapy.

Internal collaborations:

Neurosurgery unit, Neurooncology unit, Pathologic Anatomy unit: multidisciplinary evaluation of patients with CNS tumors
Radiology unit: sharing of diagnostic equipment and technicians/nurses.

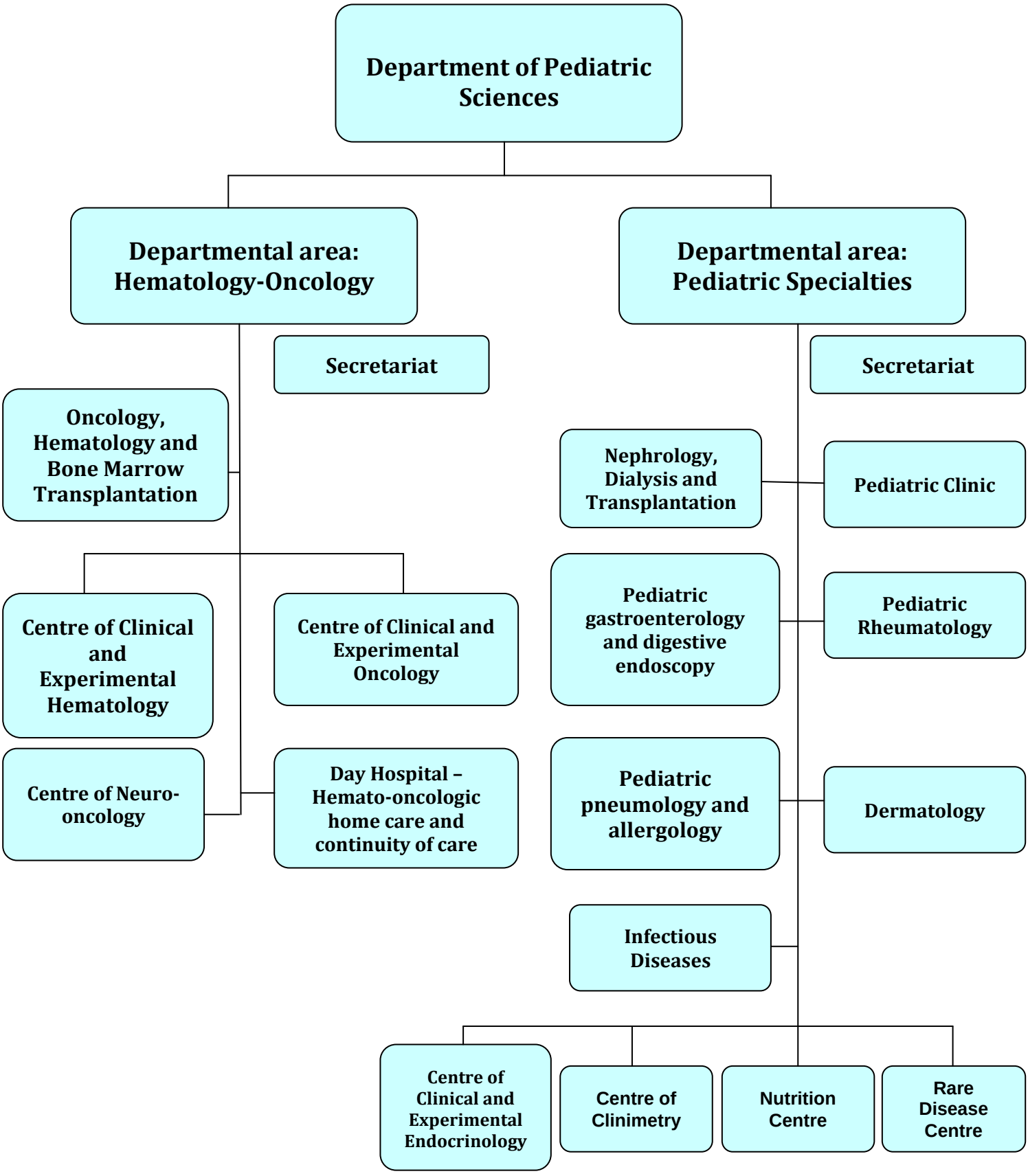
External collaborations:

- Nuclear Medicine unit, Ospedali Galliera, Genova (Dr. A. Piccardo): execution of brain DOPA-PET tests, PET-MR fusion.
- DINOGMI University of Genova (Dr. Bonzano, Dr. Roccatagliata): bioengineering reworking of fMRI and DTI.
- Starting Grant project, funded by the European Research Council, "Understanding the basis of cerebellar and brainstem congenital defects: from clinical and molecular characterization to the development of a novel neuroembryonic in vitro model" (Prof. E.M. Valente, Istituto Mendel, Roma).
- Children's Hospital of Philadelphia Department of Neuroradiology (Prof. R.A. Zimmerman): training in advanced neuroradiology.

BEST PUBLICATIONS YEARS 2011-2013

1. Morana G et al, Value of 18F-DOPA PET/MRI fusion in pediatric supratentorial infiltrative astrocytomas. A prospective pilot study J Nucl Med 2014, in press.
2. Morana G, Piccardo A, Garrè ML, Nozza P, Consales A, Rossi A. Multimodal Magnetic Resonance Imaging and 18F-L-Dihydroxyphenylalanine Positron Emission Tomography in Early Characterization of Pseudoresponse and Nonenhancing Tumor Progression in a Pediatric Patient With Malignant Transformation of Ganglioglioma Treated With Bevacizumab. J Clin Oncol. 2013 Jan 1;31(1):e1-5.
3. De Marco P, Merello E, Rossi A, Piatelli G, Cama A, Kibar Z, Capra V. FZD6 is a novel gene for human Neural Tube Defects. Hum Mutat. 2012 Feb;33(2):384-90.
4. Fruehwald-Pallamar J, Puchner SB, Rossi A, Garre ML, Cama A, Koelblinger C, Osborn AG, Thurnher MM. Magnetic resonance imaging spectrum of medulloblastoma. Neuroradiology. 2011 Jun;53(6):387-96.
5. Rossi DP, Doria Lamba L, Pistorio A, Pedemonte M, Veneselli E, Rossi A. Chronic inflammatory demyelinating polyneuropathy of childhood: clinical and neuroradiological findings. Neuroradiology. 2013 Oct;55(10):1233-9.
6. Rossi A, Biancheri R. Magnetic resonance spectroscopy in metabolic disorders. Neuroimaging Clin N Am. 2013 Aug;23(3):425-48.
7. Biancheri R, Zara F, Rossi A, Mathot M, Nassogne MC, Yalcinkaya C, Erturk O, Tuysuz B, Di Rocco M, Gazzerro E, Bugiani M, van Spaendonk R, Sistermans EA, Minetti C, van der Knaap MS, Wolf NI. Hypomyelination and congenital cataract: broadening the clinical phenotype. Arch Neurol. 2011 Sep;68(9):1191-4.
8. Feraco P, Mirabelli-Badenier M, Severino M, Alpigiani MG, Di Rocco M, Biancheri R, Rossi A. The shrunken, bright cerebellum: a characteristic MRI finding in congenital disorders of glycosylation type 1a. AJNR Am J Neuroradiol. 2012 Dec;33(11):2062-7.
9. De Marco P, Merello E, Rossi A, Piatelli G, Cama A, Kibar Z, Capra V. FZD6 is a novel gene for human Neural Tube Defects. Hum Mutat. 2012 Feb;33(2):384-90.

10. Biancheri R, Zara F, Rossi A, Mathot M, Nassogne MC, Yalcinkaya C, Erturk O, Tuysuz B, Di Rocco M, Gazzerro E, Bugiani M, van Spaendonk R, Sistermans EA, Minetti C, van der Knaap MS, Wolf NI. Hypomyelination and congenital cataract: broadening the clinical phenotype. Arch Neurol. 2011 Sep;68(9):1191-4.


Department of Pediatric Sciences
Departmental area: Hematology-Oncology
Secretariat
Oncology, Hematology and Bone Marrow Transplantation
Centre of Clinical and Experimental Hematology
Centre of Clinical and Experimental Oncology
Centre of Neuro-oncology
Day Hospital – Hemato-oncologic home care and continuity of care
Departmental area: Pediatric Specialties
Secretariat
Nephrology, Dialysis and Transplantation
Pediatric Clinic
Pediatric gastroenterology and digestive endoscopy
Pediatric Rheumatology
Pediatric pneumology and allergology
Dermatology
Infectious Diseases
Centre of Clinical and Experimental Endocrinology
Centre of Clinimetry
Nutrition Centre
Rare Disease Centre

Oncology, Hematology and Bone Marrow Transplantation

Director: Dr. Giorgio Dini/Dr. Francesco Frassoni

STAFF

Name	Position
Francesco Frassoni	Director (pro-tempore)
Edoardo Lanino	Physician
Maura Faraci	Physician
Giuseppe Morreale	Physician
Stefano Giardino	Physician
Paola Terranova	Biologist

RESULTS YEAR 2013

- We continued the recruitment of candidate patients undergoing allogenic HSCT from voluntary donor (total n=260) and of patients with solid tumors (neuroblastoma n=404; brain tumors n=195). We also continued the recruitment in the BMT programme of patents with non neoplastic diseases (Fanconi's anemia n=27, severe bone marrow aplasia n=42, congenital errors and thalassemia n= 84). Patients with acute Graft versus Host Disease not responding to first line treatment were treated according to prospective therapeutic protocols with use of monoclonal antibodies (anti-rTNFα; 20 enrolled patients), lymphophotoaferesis.
- In some patients eligible for haploidentical HSCT, we are carrying out a project using the platform with post-HSCT cyclophosphamide (without cell manipulation) (patients n=5)
- In 2013, we obtained the confirmation of JACIE accreditation obtained in 2011 for our transplant programme.
- We completed the European study for the prophylaxis of venocclusive disease in pediatric patients at higher risk for this complication.
- In collaboration with the Infectious Disease unit, we completed some studies on infectious complications in subjects undergoing HSCT.
- We promoted and participated in Italian and European clinical studies on some acute and late complications in patients undergoing HSCT and we contributed to the development of guidelines for the preservation of fertility.
- We promoted and managed internal training programmes on the main critical aspects in the hematological/oncological patients undergoing HSCT.

Main collaborations year 2013

- Hematology/Oncology unit and Neuro-oncology unit, Istituto Gaslini.
- Italian Association of Pediatric Hematology and Oncology (AIEOP).
- European Group Bone Marrow Transplantation (EBMT) with participation in the pediatric working party on late complications and quality of life.
- Cooperative project with Pediatric Oncology/Hematology, HU Marrakech
- Radiotherapy unit, San Martino-IST Hospital, Genova.
- Flow Cytometry Unit, Tettamanti Research Center - Pediatric Clinic University of Milano Bicocca Technical Director/Qualified Person – Laboratory of Cell Therapy Stefano Verri San Gerardo hospital.
- Nuclear Medicine unit, Galliera hospital, Genova.
- IBMDR and Tissue Typing Laboratory – Galliera hospital, Genova.
- Livio Sciutto Foundation for Biomedical Research in Orthopedics, Pietra Ligure.

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Implementation of new platforms for HSCT, with focus on alternative donor.
Objective: improvement of outcome in patients undergoing allogenic HSCT and reduction of the main HSCT-related complications (GvHD, viral infections) through the development of drug and/or cell strategies for the treatment of the main post-HSCT complications.
Description: Use of cell therapy strategies (pathogen-specific CTL) for the treatment of viral reactivations (CMV, EBV, Adenovirus, BK virus). Use of stromal mesenchymal stem cells in the treatment of acute GVHD resistant to first line therapy. Use of new drugs for the treatment of acute and chronic GVHD.

Internal collaborations:

Laboratory of cell therapies, Transfusion Centre, Laboratory of molecular biology.

External collaborations:

- Pediatric Hematology-Oncology, San Gerardo hospital, Monza.
- Flow Cytometry Unit Tettamanti Research Center - Pediatric Clinic University of Milano Bicocca Technical Director/Qualified Person – Laboratory of Cell Therapy Stefano Verri San Gerardo hospital.
- Pediatric Hematology-Oncology, Padova.
- Pediatric Hematology-Oncology, San Matteo hospital, Pavia.
- Bambino Gesù hospital, Roma.

BEST PUBLICATIONS YEARS 2011-2013

1. Faraci M, Bagnasco F, Giardino S, Conte M, Micalizzi C, Castagnola E,Lampugnani E, Moscatelli A, Franceschi A, Carcillo JA, Haupt R. Intensive Care Unit Admission in Children With Malignant or Nonmalignant Disease: Incidence,Outcome, and Prognostic Factors: A Single-Center Experience. J Pediatr Hematol Oncol. 2013 Oct 31.
2. Faraci M, Zecca M, Pillon M, Rovelli A, Menconi MC, Ripaldi M, Fagioli F, Rabusin M, Ziino O, Lanino E, Locatelli F, Daikeler T, Prete A; Italian Association of Paediatric Haematology and Oncology. Autoimmune Hematological Diseases after Allogeneic Hematopoietic Stem Cell Transplantation in Children: An Italian Multicenter Experience. Biol Blood Marrow Transplant.2013 Nov 23.
3. Styczynski J, Gil L, Tridello G, Ljungman P, Donnelly JP, van der Velden W, Omar H, Martino R, Halkes C, Faraci M, Theunissen K, Kalwak K, Hubacek P, Sica S,Nozzoli C, Fagioli F, Matthes S, Diaz MA, Migliavacca M, Balduzzi A, Tomaszewska A, Camara Rde L, van Biezen A, Hoek J, Iacobelli S, Einsele H, Cesaro S; Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Response to rituximab-based therapy and risk factor analysis in epstein barr virus-related lymphoproliferative disorder after hematopoietic stem cell transplant in children and adults: a study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Clin Infect Dis. 2013 Sep;57(6):794-802.
4. Daikeler T, Labopin M, Ruggeri A, Crotta A, Abinun M, Hussein AA, Carlson K,Cornillon J, Diez-Martin JL, Gandemer V, Faraci M, Lindemans C, O'Meara A, Mialou V, Renard M, Sedlacek P, Sirvent A, Socié G, Sora F, Varotto S, Sanz J, Voswinkel J, Vora A, Yesilipek MA, Herr AL, Gluckman E, Farge D, Rocha V. New autoimmune diseases after cord blood transplantation: a retrospective study of EUROCORD and the Autoimmune Disease Working Party of the European Group for Blood and Marrow Transplantation. Blood. 2013 Feb 7;121(6):1059-64.

5. Faraci M, Caviglia I, Biral E, Morreale G, Giardino S, Garbarino L, Castagnola E,Dini G, Lanino E. Acute graft-versus-host disease in pediatric allogeneic hematopoietic stem cell transplantation. Single-center experience during 10 yr. Pediatr Transplant. 2012 Dec;16(8):887-93.
6. Corbacioglu S, Cesaro S, Faraci M, Valteau-Couanet D, Gruhn B, Rovelli A, Boelens JJ, Hewitt A, Schrum J, Schulz AS, Müller I, Stein J, Wynn R, Greil J, Sykora KW,Matthes-Martin S, Führer M, O'Meara A, Toporski J, Sedlacek P, Schlegel PG,Ehlert K, Fasth A, Winiarski J, Arvidson J, Mauz-Körholz C, Ozsahin H, Schrauder A, Bader P, Massaro J, D'Agostino R, Hoyle M, Iacobelli M, Debatin KM, Peters C, Dini G. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomized controlled trial. Lancet. 2012 Apr 7;379(9823):1301-9.
7. Rego I, Severino M, Micalizzi C, Faraci M, Pende D, Dufour C, Aricò M, Rossi A. Neuroradiologic findings and follow-up with magnetic resonance imaging of the genetic forms of haemophagocytic lymphohistiocytosis with CNS involvement. Pediatr Blood Cancer. 2012 May;58(5):810-4.
8. Faraci M, Morana G, Bagnasco F, Barra S, Polo P, Hanau G, Fioredda F, Caruso S,Rossi A, Spaziante R, Haupt R. Magnetic resonance imaging in childhood leukemia survivors treated with cranial radiotherapy: a cross sectional, single center study. Pediatr Blood Cancer. 2011 Aug;57(2):240-6.
9. Fagioli F, Quarello P, Zecca M, Lanino E, Rognoni C, Balduzzi A, Messina C, Favre C, Foà R, Ripaldi M, Rutella S, Basso G, Prete A, Locatelli F. Hematopoietic stem cell transplantation for children with high-risk acute lymphoblastic leukemia in first complete remission: a report from the AIEOP registry. Haematologica. 2013 Aug;98(8):1273-81.
10. Fagioli F, Zecca M, Rognoni C, Lanino E, Balduzzi A, Berger M, Messina C, Favre C, Rabusin M, Lo Nigro L, Masetti R, Prete A, Locatelli F; AIEOP-HSCT Group. Allogeneic hematopoietic stem cell transplantation for Philadelphia-positive acute lymphoblastic leukemia in children and adolescents: a retrospective multicenter study of the Italian Association of Pediatric Hematology and Oncology (AIEOP). Biol Blood Marrow Transplant. 2012 Jun;18(6):852-60.

Clinical and experimental hematology

Director: Dr. Carlo Dufour

STAFF

Name	Position
Cetti Micalizzi	Physician
Francesca Fiorredda	Physician
Maurizio MIano	Physician
Joahnna Svahn	Physician
Micahela Calvillo	Physician
Marina Lanciotti	Biologist
Enrico Cappelli	Biologist
Tiziana Lanza	Biologist

RESULTS YEAR 2013

Study of p38MAPK inhibitors in bone marrow injury in patients with Fanconi's anemia (continued).
Study on the effects of antioxidants on Fanconi's cells (continued).
Genetic study of Italian patients with Fanconi's anemia (completed).
Study on viral inclusion in the genome of patients with Fanconi's anemia (completed).
Italian registry of neutropenias (sited at Gaslini) (implemented).
Study on the outcome of Italian patients with genetic neutropenia (completed).
Study on the outcome of 537 adolescent patients with acquired bone marrow aplasia in collaboration with EBMT (completed).
Enrolment of patients with resistant acute leukemia in experimental clinical protocols (Midostaurin, Clofarabin) (implemented).

Main collaborations year 2013:

- Oregon Health and Science University (OHSU). Portland, Oregon, USA.
- Children's Hospital Cincinnati OH, USA.
- Sick Children Hospital, Toronto,ON, CANADA.
- Harvard Medical School, Boston, MA, USA.
- Indiana University, Indianapolis, Indianapolis, IN, USA.
- University of Minnesota,Minneapolis, MN, USA.
- La Jolla University, Dan Diego, CA, USA.
- Lund University Medical School (LUMC) Leiden, The Netherlands.
- Hopital St Louis, Paris, France.
- French Registry of Neutropenas.
- Severe Congenital Neutropnia International Registry (SCNIR).
- Fanconi Anemia Gene Therapy International Working Group.
- University of Dusseldorf.
- University of Achen.
- European Group for Bone Marrow Transplantation (EBMT).
- European Hematology Association(EHA).

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Bone marrow failure and high-risk leukemias
Objective: To implement the disease registries presently coordinated by our unit, to improve the organizational clinical care model for bone marrow failure, to continue the study of

mediators of bone marrow damage in bone marrow failure, to implement experimental clinical studies on new therapeutic agents in resistant acute leukemias.
Description: Neutropenia and Fanconi's anemia registries will be updated.
A permanent staff physician will stay for 9 months at the Children's Hospital of Cincinnati (OH) to improve the clinical and research model of bone marrow failure.
New activatory and inhibiting molecules of p38 MAPK pathway in Fanconi's anemia will be tested.
New eligible patients for experimental clinical studies on resistant leukemias will be recruited.

Internal collaborations:

- Hematopoietic Stem Cell Transplantation unit
- Laboratory of Stem Cells
- Genetics unit
- Epidemiology unit

External collaborations:

- Children's Hospital Cincinnati OH, USA
- Children's Hospital Cincinnati OH, USA
- La Jolla University, Dan Diego, CA, USA.
- Indiana University, Indianapolis, IN, USA
- EHA
- EBMT
- Aieop centres

BEST PUBLICATIONS YEARS 2011-2013

1. Peffault de Latour R, Porcher R, Dalle JH, Aljurf M, Korthof ET, Svahn J, Willemze R, Barrenetxea C, Mialou V, Soulier J, Ayas M, Oneto R, Bacigalupo A, Marsh JC, Peters C, Socie G, Dufour C; FA Committee of the Severe Aplastic Anemia Working Party and the Pediatric Working Party of the European Group for Blood and Marrow Transplantation. Allogeneic hematopoietic stem cell transplantation in Fanconi anemia: the European Group for Blood and Marrow Transplantation experience. Blood. 2013 Dec 19;122(26):4279-86. doi: 10.1182/blood-2013-01-479733. Epub 2013 Oct 21.
2. Cappelli E, Ravera S, Vaccaro D, Cuccarolo P, Bartolucci M, Panfoli I, Dufour C, Degan P. Mitochondrial respiratory complex I defects in Fanconi anemia. Trends Mol Med. 2013 Sep;19(9):513-4.
3. Manara E, Bisio V, Masetti R, Beqiri V, Rondelli R, Menna G, Micalizzi C, Santoro N, Locatelli F, Basso G, Pigazzi M. Core-binding factor acute myeloid leukemia in pediatric patients enrolled in the AIEOP AML 2002/01 trial: screening and prognostic impact of c-KIT mutations. Leukemia. 2013 Nov 14.
4. Pession A, Masetti R, Rizzari C, Putti MC, Casale F, Fagioli F, Luciani M, Lo Nigro L, Menna G, Micalizzi C, Santoro N, Testi AM, Zecca M, Biondi A, Pigazzi M, Rutella S, Rondelli R, Basso G, Locatelli F; AIEOP AML Study Group. Results of the AIEOP AML 2002/01 multicenter prospective trial for the treatment of children with acute myeloid leukemia. Blood. 2013 Jul 11;122(2):170-8

5. Galbiati M, Lettieri A, Micalizzi C, Songia S, Morerio C, Biondi A, Dufour C, Cazzaniga G. Natural history of acute lymphoblastic leukemia in neurofibromatosis type 1 monozygotic twins. Leukemia. 2013 Aug;27(8):1778-81
6. Lo Nigro L, Mirabile E, Tumino M, Caserta C, Cazzaniga G, Rizzari C, Silvestri D, Buldini B, Barisone E, Casale F, Luciani M, Locatelli F, Messina C, Micalizzi C, Pession A, Parasole R, Santoro N, Masera G, Basso G, Aricò M, Valsecchi M, Biondi A, Conter V. Validation of flow cytometric phospho-STAT5 as a diagnostic tool for juvenile myelomonocytic Detection of PICALM-MLLT10 (CALM-AF10) and outcome in children with T-lineage acute lymphoblastic leukemia. Leukemia. 2013 Dec;27(12):2419-21
7. Marsh JC, Bacigalupo A, Schrezenmeier H, Tichelli A, Risitano AM, Passweg JR, Killick SB, Warren AJ, Foukaneli T, Aljurf M, Al-Zahrani HA, Höchsmann B, Schafhausen P, Roth A, Franzke A, Brummendorf TH, Dufour C, Oneto R, Sedgwick P, Barrois A, Kordasti S, Elebute MO, Mufti GJ, Socie G; European Blood and Marrow Transplant Group Severe Aplastic Anaemia Working Party. Prospective study of rabbit antithymocyte globulin and cyclosporine for aplastic anemia from the EBMT Severe Aplastic Anaemia Working Party. Blood. 2012 Jun 7;119(23):5391-6.
8. Anur P, Yates J, Garbati MR, Vanderwerf S, Keeble W, Rathbun K, Hays LE, Tyner JW, Svahn J, Cappelli E, Dufour C, Bagby GC. p38 MAPK inhibition suppresses the TLR-hypersensitive phenotype in FANCC- and FANCA-deficient mononuclear phagocytes. Blood. 2012 Mar 1;119(9):1992-2002. doi: 10.1182/blood-2011-06-354647. Epub 2012 Jan 10.
9. Puga I, Cols M, Barra CM, He B, Cassis L, Gentile M, Comerma L, Chorny A, Shan M, Xu W, Magri G, Knowles DM, Tam W, Chiu A, Bussel JB, Serrano S, Lorente JA, Bellosillo B, Lloreta J, Juanpere N, Alameda F, Baró T, de Heredia CD, Torán N, Català A, Torrebadell M, Fortuny C, Cusí V, Carreras C, Diaz GA, Blander JM, Farber CM, Silvestri G, Cunningham-Rundles C, Calvillo M, Dufour C, Notarangelo LD, Lougaris V, Plebani A, Casanova JL, Ganal SC, Diefenbach A, Aróstegui JI, Juan M, Yagüe J, Mahlaoui N, Donadieu J, Chen K, Cerutti A. B cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. Nat Immunol. 2011 Dec 25;13(2):170-80. doi: 10.1038/ni.2194.
10. European Blood and Marrow Transplant Group, Severe Aplastic Anaemia Working Party.Lancet. Rabbit ATG for aplastic anaemia treatment: a backward step? 2011 Nov 26;378(9806):1831-3. doi: 10.1016/S0140-6736(11)60817-9. Epub 2011 Jul 5.

Clinical Oncology

Director: Alberto Garaventa

STAFF

Name	Position
Massimo Conte	Physician
Loredana Amoroso	Physician
Carla Manzitti	Physician
Marilina Nantron	Physician

Research activity year 2013

The following studies were completed: European study for the treatment of inoperable neuroblastoma; study of Italian neuroblastoma adult case series and of spinal compression case series; study on single micturition urine markers for the diagnosis of neuroblastoma.
We participated in the DOPO project on long survivors after tumor treatment in pediatric age. It is a project for monitoring and management of medium- and long-term sequelae of treatment; it is still ongoing and is carried out in collaboration with other hematology/oncology departmental units.
We are carrying out some projects on neuroblastoma aimed at identifying new prognostic factors and innovative therapeutic modalities, and we are conducting phase I and II studies on new antiblastic drugs in pediatric oncology.

Planned research activity year 2014

The studies illustrated above will be continued and the following will be started:

1. Implementation of guidelines for the prevention and early diagnosis of late effects in patients treated for tumor in pediatric age, with focus on preservation of fertility
2. Evaluation of the prognostic value of gene signatures and circulating disease in neuroblastoma in collaboration with the Pathologic Anatomy unit, the Laboratory of Molecular Biology, and the Laboratory of Experimental Oncology of Gaslini, and with Italian pediatric oncology centres.
3. In collaboration with Italian and European centres, continuation of of phase I-II and phase III studies to evaluate toxicity and activity of different immunotherapy schemes in neuroblastoma.
4. In collaboration with the ITCC consortium, continuation of phase I-II studies with antiblastic drugs in different tumors in pediatric age.

Main national collaborations:

- Italian Association of Pediatric Hematology and Oncology (AIEOP)
- Department of Pediatric Hematology and Oncology, Pausilipon Hospital, Napoli.
- Dept. of Orthopedic Surgery, Careggi hospital, Firenze.
- Laboratory Neuroblastoma Foundation, Padova.
- Thyroid Surgery, Galliera hospital, Genova.
- Nuclear Medicine, Galliera hospital, Genova.
- Pediatric Radiotherapy, USMI, Genova.

Main international collaborations:

- European Commission, Contract QLRT-2001-01768, SIOPEN-R-NET.
- European Neuroblastoma Cooperative Group(E.S.I.O.P.- NB).
- ITCC Consortium (Innovative therapy in children with cancer).

Best publications (years 2009-2013)

1. Vermeulen J, De Preter K, Naranjo A, Vercruysse L, Van Roy N, Hellemans J, Swerts K, Bravo S, Scaruffi P, Tonini GP, De Bernardi B, Noguera R, Piqueras M, Cañete A, Castel V, Janoueix-Lerosey I, Delattre O, Schleiermacher G, Michon J, Combaret V, Fischer M, Oberthuer A, Ambros PF, Beiske K, Bénard J, Marques B, Rubie H, Kohler J, Pötschger U, Ladenstein R, Hogarty MD, McGrady P, London WB, Laureys G, Speleman F, Vandesompele J. Predicting outcomes for children with neuroblastoma using a multigene-expression signature: a retrospective SIOPEN/COG/GPOH study. Lancet Oncol. 2009 Jul;10(7):663-71. doi: 10.1016/S1470-2045(09)70154-8. Epub 2009 Jun 8.
2. Mussolin L, Pillon M, d'Amore ES, Conter V, Piglione M, Lo Nigro L, Garaventa A, Buffardi S, Aricò M, Rosolen A. Minimal disseminated disease in high-risk Burkitt's lymphoma identifies patients with different prognosis. J Clin Oncol. 2011 May 1;29(13):1779-84. doi: 10.1200/JCO.2010.32.8161. Epub 2011 Mar 21.
3. Rubie H, De Bernardi B, Gerrard M, Canete A, Ladenstein R, Couturier J, Ambros P, Munzer C, Pearson AD, Garaventa A, Brock P, Castel V, Valteau-Couanet D, Holmes K, Di Cataldo A, Brichard B, Mosseri V, Marquez C, Plantaz D, Boni L, Michon J. Excellent outcome with reduced treatment in infants with nonmetastatic and unresectable neuroblastoma without MYCN amplification: results of the prospective INES 99.1. J Clin Oncol. 2011 Feb 1;29(4):449-55. doi: 10.1200/JCO.2010.29.5196. Epub 2010 Dec 20.
4. Ladenstein R, Pötschger U, Siabalis D, Garaventa A, Bergeron C, Lewis IJ, Stein J, Kohler J, Shaw PJ, Holter W, Pistoia V, Michon J. Dose finding study for the use of subcutaneous recombinant interleukin-2 to augment natural killer cell numbers in an outpatient setting for stage 4 neuroblastoma after megatherapy and autologous stem-cell reinfusion. J Clin Oncol. 2011 Feb 1;29(4):441-8. doi: 10.1200/JCO.2009.23.5465. Epub 2010 Dec 13.
5. Schleiermacher G, Michon J, Ribeiro A, Pierron G, Mosseri V, Rubie H, Munzer C, Bénard J, Auger N, Combaret V, Janoueix-Lerosey I, Pearson A, Tweddle DA, Bown N, Gerrard M, Wheeler K, Noguera R, Villamon E, Cañete A, Castel V, Marques B, de Lacerda A, Tonini GP, Mazzocco K, Defferrari R, de Bernardi B, di Cataldo A, van Roy N, Brichard B, Ladenstein R, Ambros I, Ambros P, Beiske K, Delattre O, Couturier J. Segmental chromosomal alterations lead to a higher risk of relapse in infants with MYCN-non-amplified localised unresectable/disseminated neuroblastoma (a SIOPEN collaborative study). Br J Cancer. 2011 Dec 6;105(12):1940-8. doi: 10.1038/bjc.2011.472. Epub 2011 Nov 10.
6. Taggart DR, London WB, Schmidt ML, DuBois SG, Monclair TF, Nakagawara A, De Bernardi B, Ambros PF, Pearson AD, Cohn SL, Matthay KK. Prognostic value of the stage 4S metastatic pattern and tumor biology in patients with metastatic neuroblastoma diagnosed between birth and 18 months of age. J Clin Oncol. 2011 Nov 20;29(33):4358-64. doi: 10.1200/JCO.2011.35.9570. Epub 2011 Oct 3.
7. Lopci E, Piccardo A, Nanni C, Altrinetti V, Garaventa A, Pession A, Cistaro A, Chiti A, Villavecchia G, Fanti S. 18F-DOPA PET/CT in neuroblastoma: comparison of conventional imaging with CT/MR. Clin Nucl Med. 2012 Apr;37(4):e73-8. doi: 10.1097/RLU.0b013e3182485172.
8. Bisogno G, Compostella A, Ferrari A, Pastore G, Cecchetto G, Garaventa A, Indolfi P, De Sio L, Carli M. Rhabdomyosarcoma in adolescents: a report from the AIEOP Soft Tissue Sarcoma Committee. Cancer. 2012 Feb 1;118(3):821-7. doi: 10.1002/cncr.26355. Epub 2011 Jul 12.
9. Kohler JA, Rubie H, Castel V, Beiske K, Holmes K, Gambini C, Casale F, Munzer C, Erminio G, Parodi S, Navarro S, Marquez C, Peuchmaur M, Cullinane C, Brock P, Valteau-Couanet D, Garaventa A, Haupt R. Treatment of children over the age of one year with unresectable localised neuroblastoma without MYCN amplification: results of the SIOPEN study. Eur J Cancer. 2013 Nov;49(17):3671-9. doi: 10.1016/j.ejca.2013.07.002. Epub 2013 Jul 29.

10. Calafiore L, Amoroso L, Della Casa Alberighi O, Luksch R, Zanazzo G, Castellano A, Podda M, Dominici C, Haupt R, Corrias MV, Garaventa A. Two-stage phase II study of imatinib mesylate in subjects with refractory or relapsing neuroblastoma. Ann Oncol. 2013 May;24(5):1406-13. doi: 10.1093/annonc/mds648. Epub 2013 Feb 7.

Nephrology, dialysis and transplantation
Laboratory of physiopathology of uremia

Director: Dr. Gian Marco Ghiggeri

STAFF

Name	Position
Giovanni Candiano	Biologist
Armando Di Donato	Biologist
Alba Maria Carrea	Biologist
Roberta Bertelli	Biologist
Marco Di Duca	Biomedical Laboratory technician
Gianluca Caridi	Biomedical Laboratory technician
Monica Dagnino	Researcher - biologist
Michela Cioni	Researcher – biologist
Maurizio Bruschi	Researcher – biologist
Laura Santucci	Researcher - biologist
Francesca Lugani	Researcher – physician
Alice Bonanni	Researcher - physician

RESULTS YEAR 2013

The research activity of the Laboratory of Physiopathology of Uremia includes three main areas:

Genetics area including congenital renal diseases:

In 2013, we obtained the following results:

a) Identification of a new gene for nephronophthisis associated with bronchiectasis in a familial case followed in our unit
b) Identification of new mutations in genes associated with steroid-resistant nephrotic syndrome thanks to genetic screening of patients within a dedicated European network
c) Genotype-phenotype correlations in patients with Alport syndrome and validation of diagnostic tests based on Next Generation Sequencing.
d) Identification of the genetic defect responsible for the spontaneous murine model of renal malformation and caudal regression (*Danforth's* short tail).
e) Identification and characterization of new mutations of *ALB* gene associaed with congenital analbuminemia.
f) Identification of the first gene associated with renal hypoplasia and urinary tract malformation

Proteomics area:

a) Technological development related to the analysis of proteins/peptides with low expression in biological fluids through capture systems for marbles and resins.

Biochemistry area:

a) Developments related to structure and function of albumin in biological fluids

Main collaborations year 2013

Mass spectrometry and peptide analysis

Andrea Petretto, Proteomic Core Facilities, Istituto G. Gaslini, Genova.

Genetics of renal malformations

Ali Gharavi & Simone Sanna-Cherchi. Dep. Nephrology. Columbia University NY USA.

Hyperuricemic nephropathies and tubulointerstitial fibrosis.
Luca Rampoldi, Dulbecco Telethon Institute, San Raffaele hospital, Milano
Francesco Scolari. Chair of Nephrology. University of Brescia.
Antonio Amoroso. Chair of Genetics. University of Torino
Genetics of congenital analbuminemias
Lorenzo Minchiotti – Dept. Biochemistry, Univerisity of Pavia.

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Genetic, immunological, and environmental factors as elements predisposing and causing human and experimental glomerulonephritis.

Objective:

1. Molecular screening through Next Generation Sequencing in renal glomerular and tubulointerstitial diseases.
2. Analysis of biohumoral markers of immunological activity associated with the development of glomerulonephritis in humans.
3. Characterization of mechanisms related to innate and adaptive immunity in animal models of glomerulosclerosis.

Description:

1. Use of IonTorrent platform for the systematic analysis of 30 genes associated with steroid-resistant nephrotic syndrome and development of a new system for tubulointerstitial fibrosis.
2. Development of tests allowing the identification of immunological biomarkers in patients with autoimmune glomerulonephritis and focal glomerulosclerosis. This approach will be conducted in parallel with point 3.
3. Analysis of the mechanisms involved in animal models of the diseases mentioned above. In particular, evaluation of the mechanisms causative for experimental nephropathies induced by LPS.

Internal collaborations:

Laboratory of Molecular Genetics.
Department of Translational Medicine and Core Facilities

External collaborations:

Ali Gharavi & Simone Sanna-Cherchi. Dep. Nephrology. Columbia University NY USA.
Luca Rampoldi, Dulbecco Telethon Institute, San Raffaele hospital, Milano.
Francesco Scolari. Chair of Nephrology. University of Brescia.
Antonio Amoroso. Chair of Genetics. University of Torino.
Lorenzo Minchiotti – Dept. Biochemistry, Univerisity of Pavia.

BEST PUBLICATIONS YEARS 2011-2013

1. Hurd TW, Otto EA, Mishima E, Gee HY, Inoue H, Inazu M, Yamada H, Halbritter J, Seki G, Konishi M, Zhou W, Yamane T, Murakami S, Caridi G, Ghiggeri G, Abe T, Hildebrandt F. Mutation of the Mg2+ transporter SLC41A1 results in a nephronophthisis-like phenotype. J Am Soc Nephrol. 2013 May;24(6):967-77.
2. Lipska BS, Iatropoulos P, Maranta R, Caridi G, Ozaltin F, Anarat A, Balat A, Gellermann J, Trautmann A, Erdogan O, Saeed B, Emre S, Bogdanovic R, Azocar M, Balasz-Chmielewska I, Benetti E, Caliskan S, Mir S, Melk A, Ertan P, Baskin E, Jardim H, Davitaia T, Wasilewska A, Drozdz D, Szczepanska M, Jankauskiene A, Higuita LM, Ardissino G, Ozkaya O, Kuzma-Mroczkowska E, Soylemezoglu O, Ranchin B, Medynska A, Tkaczyk M, Peco-Antic A, Akil I, Jarmolinski T, Firszt-Adamczyk A, Dusek J, Simonetti GD, Gok F, Gheissari A, Emma F, Krmar RT, Fischbach M, Printza N, Simkova E, Mele C, Ghiggeri

GM, Schaefer F; PodoNet Consortium. Genetic screening in adolescents with steroid-resistant nephrotic syndrome. Kidney Int. 2013 Jul;84(1):206-13.
3. Fallerini C, Dosa L, Tita R, Del Prete D, Feriozzi S, Gai G, Clementi M, La Manna A, Miglietti N, Mancini R, Mandrile G, Ghiggeri G, Piaggio G, Brancati F, Diano L, Frate E, Pinciaroli A, Giani M, Castorina P, Bresin E, Giachino D, De Marchi M, Mari F, Bruttini M, Renieri A, Ariani F. Unbiased next generation sequencing analysis confirms the existence of autosomal dominant Alport syndrome in a relevant fraction of cases. Clin Genet. 2013 Sep 4. doi: 10.1111/cge.12258.
4. Sanna-Cherchi S, Sampogna RV, Papeta N, Burgess KE, Nees SN, Perry BJ, Choi M, Bodria M, Liu Y, Weng PL, Lozanovski VJ, Verbitsky M, Lugani F, Sterken R, Paragas N, Caridi G, Carrea A, Dagnino M, Materna-Kiryluk A, Santamaria G, Murtas C, Ristoska-Bojkovska N, Izzi C, Kacak N, Bianco B, Giberti S, Gigante M, Piaggio G, Gesualdo L, Kosuljandic Vukic D, Vukojevic K, Saraga-Babic M, Saraga M, Gucev Z, Allegri L, Latos-Bielenska A, Casu D, State M, Scolari F, Ravazzolo R, Kiryluk K, Al-Awqati Q, D'Agati VD, Drummond IA, Tasic V, Lifton RP, Ghiggeri GM, Gharavi AG. Mutations in DSTYK and dominant urinary tract malformations. N Engl J Med. 2013 Aug 15;369(7):621-9.
5. Lugani F, Arora R, Papeta N, Patel A, Zheng Z, Sterken R, Singer RA, Caridi G, Mendelsohn C, Sussel L, Papaioannou VE, Gharavi AG. A retrotransposon insertion in the 5' regulatory domain of Ptf1a results in ectopic gene expression and multiple congenital defects in Danforth's short tail mouse. PLoS Genet. 2013;9(2):e1003206.
6. Murtas C, Bruschi M, Candiano G, Moroni G, Magistroni R, Magnano A, Bruno F, Radice A, Furci L, Argentiero L, Carnevali ML, Messa P, Scolari F, Sinico RA, Gesualdo L, Fervenza FC, Allegri L, Ravani P, Ghiggeri GM. Coexistence of different circulating anti-podocyte antibodies in membranous nephropathy. Clin J Am Soc Nephrol. 2012 Sep;7(9):1394-400.
7. Santucci L, Candiano G, Bruschi M, D'Ambrosio C, Petretto A, Scaloni A, Urbani A, Righetti PG, Ghiggeri GM.Combinatorial peptide ligand libraries for the analysis of low-expression proteins: Validation for normal urine and definition of a first protein MAP. Proteomics. 2012 Feb;12(4-5):509-15.
8. Schaeffer C, Cattaneo A, Trudu M, Santambrogio S, Bernascone I, Giachino D, Caridi G, Campo A, Murtas C, Benoni S, Izzi C, De Marchi M, Amoroso A, Ghiggeri GM, Scolari F, Bachi A, Rampoldi L. Urinary secretion and extracellular aggregation of mutant uromodulin isoforms. Kidney Int. 2012 Apr;81(8):769-78.
9. Sanna-Cherchi S, Kiryluk K, Burgess KE, Bodria M, Sampson MG, Hadley D, Nees SN, Verbitsky M, Perry BJ, Sterken R, Lozanovski VJ, Materna-Kiryluk A, Barlassina C, Kini A, Corbani V, Carrea A, Somenzi D, Murtas C, Ristoska-Bojkovska N, Izzi C, Bianco B, Zaniew M, Flogelova H, Weng PL, Kacak N, Giberti S, Gigante M, Arapovic A, Drnasin K, Caridi G, Curioni S, Allegri F, Ammenti A, Ferretti S, Goj V, Bernardo L, Jobanputra V, Chung WK, Lifton RP, Sanders S, State M, Clark LN, Saraga M, Padmanabhan S, Dominiczak AF, Foroud T, Gesualdo L, Gucev Z, Allegri L, Latos-Bielenska A, Cusi D, Scolari F, Tasic V, Hakonarson H, Ghiggeri GM, Gharavi AG. Copy-number disorders are a common cause of congenital kidney malformations. Am J Hum Genet. 2012 Dec 7;91(6):987-97.
10. Gigante M, Caridi G, Montemurno E, Soccio M, d'Apolito M, Cerullo G, Aucella F, Schirinzi A, Emma F, Massella L, Messina G, De Palo T, Ranieri E, Ghiggeri GM, Gesualdo L. TRPC6 mutations in children with steroid-resistant nephrotic syndrome and atypical phenotype. Clin J Am Soc Nephrol. 2011 Jul;6(7):1626-34.

Pediatric clinic

Director: Prof. Renata Lorini

STAFF

Name	Position
Giuseppe d'Annunzio	Physician
Sara Bolloli	Physician
Sara Gialetti	Psychologist
Antonia Gigante	Project Manager
Nicola Minuto	Physician
Alessandro Salina	Biologist
Concetta Aloi	Biologist
Francesca Lugani	Physician

RESULTS YEAR 2013

Differential diagnosis of forms of non autoimmune diabetes mellitus

In 2013, in the laboratory of diabetology of the Pediatric Clinic, the activity of molecular diagnosis of non-autoimmune diabetes mellitus was increased, as well as the study of genes involved in other diseases of glucide metabolism.

In particular, molecular analysis was performed by direct sequencing of genomic DNA of 80 subjects who, after evaluation of anamnestic, clinical, and glycometabolic data, were diagnosed clinically with hyperglycemia/diabetes mellitus/non-autoimmune gestational diabetes (documented absence of immunological markers of diabetes mellitus type 1). We evaluated patients with clinical diagnosis of MODY (Maturity Onset Diabetes of the Young) for *GCK/MODY2, HNF1a/MODY3, HNF1b/MODY5, HNF4a/MODY1* genes, Wolfram syndrome 1 and 2 for *WFS1 and ZCD2* genes, neonatal diabetes for *GCK/MODY2*, *KCNJ11, KIR6.2 ABCC8* genes. We also analyzed patients with gestational diabetes (*GCK/MODY2* gene), children with familial renal glycosuria (*SLC5A2* gene), newborns with congenital hyperinsulinism (*INS; KCNJ11, ABCC8, HNF4a* genes). Of the 80 analyzed patients, 32 were followed in the regional centre of diabetology of the Pediatric Clinic and 48 were followed in other centres. In all cases, informed consent was obtained.

GCK gene sequencing was performed in 26 cases, 14 resulting mutated. *HNF1a* gene sequencing was performed in 4 subjects and *HNF1b* gene sequencing in 2: no patients resulted mutated. *KCNJ11* gene sequencing was performed in 6 cases, 1 resulted mutated. *SLC5A2* gene sequencing was performed in 2 cases, both mutated. *WFS1* gene sequencing was performed in 22 cases: 2 carried a mutation in compound homozygosis/heterozygosis and 13 relatives resulted carriers of mutations in heterozygosis. *ZCD2* gene sequencing was performed in 4 cases; 1 presented a deletion in homozygosis, the remaining 3 resulted carriers. *ABCC8* gene sequencing was performed in 11 cases, 5 resulting mutated. *HNF4a* gene sequencing was performed in 2 cases, none resulting mutated. *INS* gene sequencing was performed in 1 case, not resulting mutated.

Main collaborations year 2013

- Ospedale Maggiore, Novara.
- HCS, Regione Sardegna.
- HCS, Regione Campania.
- Federico II University hospital, Napoli.
- Carlo Poma hospital, Mantova.

- Regional Health Service, Piemonte.
- HCS, Regione Lombardia.
- HCS, regione Puglia.
- Integrated University Hospital, Verona.
- Regional health service, Emilia Romagna.

Multicenter prospective randomized open with a blinded end point (PROBE) parallel-group study on treatment with biphasic insulin BIAsp70/30 and short-acting insulin or rapid-acting analogue plus glargine in comparison with short-acting insulin or rapid-acting analogue plus glargine to evaluate the metabolic control and quality of life in children and adolescents with type 1 diabetes mellitus over 12 months (AIFA FARM8MR2J7 study).

The necessary bureaucratic steps have been taken to allow the participating centres to continue patient enrolment, which to date has been carried out at the coordinating centre, where 7 children and adolescents with diabetes mellitus type 1 have been enrolled and the clinical characteristics reported in the feasibility survey. A document on IMP has been produced, aimed at standardizing the management of the experimental drug in the different centres/clusters and at having a continuous traceability of each SOP. Concerning cultural adaptation and validation in Italian language of the questionnaires on the quality of life, specific for diabetes (PedsQoL TM 3.0- Diabetes Module), psychometric evaluation and statistical analysis of the questionnaires have been performed, including both the modules for children and adolescents and for parents. A report has been produced including the statistical analyses on a population of 169 children (age range 5-18 years) and 100 parents, from the 6 centres participating in the study (Catania, Firenze, Genova, Napoli, Roma, Torino). A paper has been submitted to a scientific journal with IF. The results of the validation study were presented in occasion of national (SIEDP) and international (ESPE) meetings as posters and oral communication, respectively.

Main collaborations year 2013:

- Centre of Diabetology, Pediatric Clinic, Regina Margherita hospital, Torino.
- Pediatric Clinic, Piemonte Orientale University, Novara.
- Diabetology unit, Meyer hospital, Firenze.
- Pediatric Diabetology unit, Salesi hospital, Ancona.
- Endocrinology and Diabetology, Bambino Gesù hospital, Roma.
- Pediatric Diabetology centre, Federico II University, Napoli.
- Pediatric Diabetology centre, II University, Napoli.
- Pediatrics unit, Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo (Fg).
- Pediatric Clinic, Pediatric Diabetology centre, University of Catania.

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Genetic causes of diabetes mellitus and anomalies of glucide metabolism
Objective: The study is aimed at defining the genetic diagnosis of forms of diabetes mellitus and other anomalies of glucide metabolism in newborns, nurslings, children, adolescents, young adults, and pregnant women with hyperglycemia/diabetes mellitus/gestational diabetes, with hypoglycemia due to hyperinsulinism or renal glycosuria without documented alterations of glucide metabolism.
Description: Patients previously undergoing collection of patient and family history data, metabolic screening of glucide metabolism and of immunological markers of diabetes mellitus type 1 were evaluated for possible diagnosis of non autoimmune diabetes mellitus.

For pregnant patients, the diagnosis of gestational diabetes according to recent guidelines will be essential. On the basis of the results of clinical data collection, genetic analysis will be performed by direct sequencing for genes associated with non autoimmune diabetes mellitus. In particular, mutations of genes for MODY (*GCK/MODY2, HNF1a/MODY3, HNF1b/MODY5, HNF4a/MODY1*), Wolfram syndrome 1 and 2 (*WFS1 and ZCD2*), neonatal diabetes (*GCK/MODY2*, *KCNJ11, KIR6.2 ABCC8*) will be searched. In patients with gestational diabetes and family history of hyperglycemia, mutations of *GCK/MODY2* gene will be searched. Mutations of *SLC5A2* gene will be searched in children with familial renal glycosuria, and mutations of *INS; KCNJ11, ABCC8, HNF4a* genes will be searched in newborns with congenital hyperinsulinism. Genetic analysis will allow a correct diagnosis, appropriate treatment, the definition of the natural history of each single disease, and disclosure of diagnosis to relatives with psychological support and genetic counseling.

Internal collaborations:

- Nephrology, Dialysis and Transplantation, Laboratory of Physiopathology of Uremia.
- Neonatology and Neonatal Disease.
- PICU.
- Obstetrics and Gynecology.
- Neuroradiology, Ophthalmology, Radiology.

External collaborations:

- Obstetrics and Gynecology, San Marino hospital, Genova.
- Liguria pediatric diabetology network
- National centres of pediatric and adult diabetology referring patients or sending biological material for genetic diagnosis.

BEST PUBLICATIONS YEARS 2011-2013

1. Scaramuzza A, Cherubini V, Tumini S, Bonfanti R, Buono P, Cardella F, d'Annunzio G, Frongia AP, Lombardo F, Monciotti AC, Rabbone I, Schiaffini R, Toni S, Zucchini S, Frontino G, Iafusco D; Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetology. Recommendations for self-monitoring in pediatric diabetes: a consensus statement by the ISPED. Acta Diabetol. 2013 Oct 27. [Epub ahead of print]
2. Piccinno E, Ortolani F, Vendemiale M, Tummolo A, Masciopinto M, Natale M, De Luca A, Agolini E, Aloi C, Salina A, D'Annunzio G, Fischetto R, Papadia F. Novel homozygous mutation in exon 5 of WFS1 gene in an Apulian family with mild phenotypic expression of Wolfram syndrome. Clin Genet. 2013 Oct 3. doi: 10.1111/cge.12260.
3. Bason C, Lorini R, Lunardi C, Dolcino M, Giannattasio A, d'Annunzio G, Rigo A, Pedemonte N, Corrocher R, Puccetti A. In type 1 diabetes a subset of anti-coxsackievirus B4 antibodies recognize autoantigens and induce apoptosis of pancreatic beta cells.PLoS One. 2013;8(2):e57729 d'Annunzio G, Marchi M, Aloi C, Salina A, Lugani F, Lorini R. Hyperglycaemia and β-cell antibodies: is it always pre-type 1 diabetes? Diabetes Res Clin Pract. 2013;100:e20-2.
4. Marigliano M, Morandi A, Maschio M, Costantini S, Contreas G, D'Annunzio G, Calcaterra V, Maffeis C. Diabetic ketoacidosis at diagnosis: role of family history and class II HLA genotypes. Eur J Endocrinol. 2012;10;168(1):107-11
5. Tosca MA, Silvestri M, Olcese R, D'Annunzio G, Pistorio A, Lorini R, Ciprandi G, Rossi GA. Allergic sensitization and symptoms, body mass index, and respiratory function in children with type 1 diabetes mellitus. Ann Allergy Asthma Immunol. 2012;108:128-9.

6. Aloi C, Salina A, Pasquali L, Lugani F, Perri K, Russo C, Tallone R, Ghiggeri GM, Lorini R, d'Annunzio G. Wolfram syndrome: new mutations, different phenotype. PLoS One. 2012;7(1):e29150.
7. Salina A, Aloi C, Pasquali L, Mascagni A, Cassanello M, Tallone R, Lugani F, Lorini R, d'Annunzio G. Comment on: Clinical application of best practice guidelines for genetic diagnosis of MODY2. Diabetes Res Clin Pract. 2012;95:e29-30.
8. Russo C, Salina A, Aloi C, Iafusco D, Lorini R, d'Annunzio G. Mother and daughter carrying the same KCNJ11 mutation but with a different response to switching from insulin to sulfonylurea. Diabetes Res Clin Pract. 2011;94:e50-2.
9. Tosca MA, Ciprandi G, Silvestri M, D'Annunzio G, Lorini R, Rossi GA. T1 diabetes and allergic diseases in children: correspondence to the paper of Thomsen et al., Allergy 2011; 66: 645-647. Allergy. 2011;66:1612-3.

Clinical and Experimental Endocrinology

Director: Professor Mohamad Maghnie

STAFF

Name	Position
Roberto Gastaldi	Physician
Natascia Di Iorgi	Researcher
Flavia Napoli	Physician
Anna Elsa Allegri	Physician
Annalisa Calcagno	Physician

RESULTS YEAR 2013

Research activity was focused on some aspects of endocrine diseases in pediatric age, in particular:
The study of prognostic factors associated with hyperthyroidism showed that the absence of goiter, a low level of anti-TSH receptor antibodies (TRAb) at diagnosis, their normalization and normalization velocity during medical therapy were associated with favourable outcome.
Another important aspect concerns etiological diagnosis of central diabetes insipidus. In particular, research led to differential diagnosis in 96% of cases and the identification of markers of long-term outcome.

Main collaborations year 2013:

- Italian multicentre collaboration (Bambino Gesù, Roma, Microcitemico, Cagliari, Federico II, Napoli) : Project for diagnosis of GH deficiency in transitional age
- Luca Persani, Istituto Auxologico, Milano. Genetic study on hypogonadotropic hypogonadism
- Mehul Dattani, Great Ormond Street, Londra (OTX2 gene in pituitary development)

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Next generation sequencing in congenital hypopituitarism and median line anomalies
Description: We will enroll patients with diagnosis of combined or multiple pituitary defects with median line anomalies including structural malformations of hypothalamus-pituitary gland region with or without extrahypophyseal brain anomalies.
Exome analysis will be performed in familial cases and in cases with de novo disease in “Trios" /Father, mother, and proband.
The first analysis will exclude known disease genes and, in negative cases, exome study will be started. Available Gaslini equipment (ion proton) will be used.
Objectives: Identification of new genes involved in the early development of median brain structures and in hypophyseal organogenesis in order to guarantee a genetic diagnosis of hereditary diseases using Next Generation sequencing.
Definition of a rapid diagnosis of mutations of known genes (HESX1, LHX3, LHX4, PROP-1, POUIF-1, SOX2, SOX3, OTX2, GLI2, GLI3, SHH, FGF8, FGFR1, CDH7, PROKR2).
Availability of genetic counselling for future pregnancies.

Internal collaborations:

- Roberto Ravazzolo, Angela Covone, Molecular Genetics and Cytogenetics
- **Mirella Filocamo** Coordinator, Telethon Network of Genetic Biobanks http://www.biobanknetwork.com/

External collaborations:

- Bambino Gesù hospital, Roma
- Regina Margherita hospital. Torino
- San Raffaele Institute, Milano
- S Orsola Hospital, Bologna

BEST PUBLICATIONS YEARS 2011-2013

1. Libri DV, Kleinau G, Vezzoli V, Busnelli M, Guizzardi F, Sinisi AA, Pincelli AI, Mancini A, Russo G, Beck-Peccoz P, Loche S, Crivellaro C, Maghnie M, Krausz C, Persani L, Bonomi M; on behalf of the Italian study group on Idiopathic Central Hypogonadism (ICH). Germline prokineticin receptor 2 (prokr2) variants associated with central hypogonadism cause differental modulation of distinct intracellular pathways. J Clin Endocrinol Metab. 2013 Nov 25. [Epub ahead of print]
2. Di Iorgi N, Maria Allegri AE, Napoli F, Calcagno A, Calandra E, Fratangeli N, Vannati M, Rossi A, Bagnasco F, Haupt R, Maghnie M. Central Diabetes Insipidus in Children and Young Adults: Etiological Diagnosis and Long - Term Outcome of Idiopathic Cases. J Clin Endocrinol Metab. 2013 Nov 25. [Epub ahead of print]
3. Street ME, Smerieri A, Montanini L, Predieri B, Iughetti L, Valenzise M, De Luca F, Vigone M, Weber G, Maghnie M, Bernasconi S. Interactions among pro-inflammatory cytokines, IGF system and thyroid function in pre-pubertal obese subjects. J Biol Regul Homeost Agents. 2013 Jan-Mar;27(1):259-66.
4. Maghnie M, Lindberg A, Koltowska-Häggström M, Ranke MB. Magnetic resonance imaging of CNS in 15,043 children with GH deficiency in KIGS (Pfizer International Growth Database). Eur J Endocrinol. 2013 Jan 17;168(2):211-7. doi: 10.1530/EJE-12-0801. Print 2013 Feb.
5. Cangemi G, Di Iorgi N, Barco S, Reggiardo G, Maghnie M, Melioli G. Plasma total adiponectin levels in pediatrics: reference intervals calculated as a continuous variable of age. Clin Biochem. 2012 Dec;45(18):1703-5. doi: 10.1016/j.clinbiochem.2012.08.001. Epub 2012 Aug 10.
6. Bedogni G, Giannone G, Maghnie M, Giacomozzi C, Di Iorgi N, Pedicelli S, Peschiaroli E, Melioli G, Muraca M, Cappa M, Cianfarani S. Serum insulin-like growth factor-I (IGF-I) reference ranges for chemiluminescence assay in childhood and adolescence. Data from a population of in- and out-patients. Growth Horm IGF Res. 2012 Jun-Aug;22(3-4):134-8. doi: 10.1016/j.ghir.2012.04.005. Epub 2012 May 14.
7. Gana S, Veggiotti P, Sciacca G, Fedeli C, Bersano A, Micieli G, Maghnie M, Ciccone R, Rossi E, Plunkett K, Bi W, Sutton VR, Zuffardi O. 19q13.11 cryptic deletion: description of two new cases and indication for a role of WTIP haploinsufficiency in hypospadias. Eur J Hum Genet. 2012 Aug;20(8):852-6. doi: 10.1038/ejhg.2012.19. Epub 2012 Feb 29.
8. Rygg M, Pistorio A, Ravelli A, Maghnie M, Di Iorgi N, Bader-Meunier B, Da Silva C, Roldan-Molina R, Barash J, Dracou C, Laloum SG, Jarosova K, Deslandre CJ, Koné-Paut I, Garofalo F, Press J, Sengler C, Tauber T, Martini A, Ruperto N; Paediatric Rheumatology International Trials Organisation (PRINTO). A longitudinal PRINTO study on growth and puberty in juvenile systemic lupus erythematosus. Ann Rheum Dis. 2012 Apr;71(4):511-7. doi: 10.1136/annrheumdis-2011-200106. Epub 2011 Oct 13.
9. Di Iorgi N, Allegri AE, Napoli F, Bertelli E, Olivieri I, Rossi A, Maghnie M. The use of neuroimaging for assessing disorders of pituitary development. Clin Endocrinol (Oxf). 2012 Feb;76(2):161-76. doi: 10.1111/j.1365-2265.2011.04238.x. Review. Erratum in: Clin Endocrinol (Oxf). 2012 Apr;76(4):607. Iorgi, Natascia D [corrected to Di Iorgi, Natascia].

10. Secco A, Allegri AE, di Iorgi N, Napoli F, Calcagno A, Bertelli E, Olivieri I, Pala G, Parodi S, Gastaldi R, Rossi A, Maghnie M. Posterior pituitary (PP) evaluation in patients with anterior pituitary defect associated with ectopic PP and septo-optic dysplasia. Eur J Endocrinol. 2011 Sep;165(3):411-20. doi: 10.1530/EJE-11-0437. Epub 2011 Jul 12.

Pediatric Gastroenterology with digestive endoscopy

Director: Dr. Arrigo Barabino

STAFF

Name	Position
Paolo Gandullia	Physician
Angela Calvi	Physician
Silvia Vignola	Physician
Lia Giovannini	Physician
Serena Arrigo	Physician
Monica Franzi	Head Nurse
Cristina Pacetti	Nurse
Monica Mantero	Nurse
Annamaria Salvi	Nurse
Silvia Dapelo	Nurse
Annamaria Giammona	Nurse
Amalia Cirillo	Nurse
Alessandra Conte	Nurse
Miriam Bevegni	Nurse
Tamara Pedemonte	Nurse
Tiziana Spagnoli	Nurse
Stefaniia Muneghina	Nurse
Piera Anfosso	Nurse
Barbara Longo	Nurse
Daniela Torre	Nurse
Rosaria Grammegna	Orderly
Sonia Rabissoni	Orderly
Antonietta Lama	Orderly
Andrea Bruno	Administrative

RESULTS YEAR 2013

Italian multicentre study on treatment of esophageal varices in pediatrics: medical and endoscopic therapy (ligature vs sclerosis: complications, relapses) (in press), showing better outcome with ligature. Use of glucose breath test for diagnosis and treatament of CIBO in cystic fibrosis (in collaboration with Gaslini's Pediatric Clinic): diagnosis possible in 70% of cases; with targeted treatment, gastrointestinal and respiratory improvement can be obtained. Diagnosis, treatment and outcome of portal cavernoma (Italian multicentre study): data are being processed. Dietetic treatment of short bowel with different semi-elemental and elemental mixtures (in collaboration with Bambino Gesù Hospital): no difference among the various tested mixtures in the impact on patient's outcome.

Italian multicentre study (coordinator: our unit) on the evolution of esophageal stenosis according to treatment (balloon dilatations vs savary: complications, relapses): the two methods proved to be similar. Multicentre observational study of children with Crohn's disease, mainly concerning the possible intake of anti-TNFα: no data are available yet since the study is very long-term (20 years).

Multicentre study on the appropriateness of colonoscopy (coordinator: Dr. Lombardi, Pescara): data are undergoing statistical analysis. Multicentre study on "early IBD" with onset below 5 years of life, with data from the new online registry (coordinator: La Sapienza University, in press): this type of IBD has a RCU-like phenotype, is clinically more severe, and can require early colectomy. Statistical analysis of safety and efficacy of CyA in severe attack refractory to cortisone (our study with additional data from Mayer hospital of Firenze): CyA avoids urgency colectomy in about 65% of cases and maintains the colon in the long term (3 years) in a third of cases. Study on the expression of eotaxin-2 in intraepithelial lymphocytes and on perineural degranulation of mast cells in order to differentiate allergic colitis from classical forms of IBD. Allergic colitis share spatially eotaxin and IL5 with nerve endings affecting their motility and therefore maybe causing clinical problems as diarrhoea, stipsis, or abdominal pain.

Main collaborations year 2013:

Burlo Garofolo hospital, Trieste, Bambino Gesù hospital, Roma, La Sapienza University, Roma Pediatric Gastroenterology unit

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Maintenance of remission in ulcerative rectocolitis in pediatric age: new therapeutic strategies (funded by AIFA).
Objective: double-blind study to evaluate whether the early introduction of azathioprine can change disease natural history.
Description: prospective, multicentre, double-blind, placebo-controlled study in 130 pediatric patients with new diagnosis of moderate to severe URC defined by the presence of a clinical disease index (PUCAI) ≥ 35 requiring steroid therapy to induce disease remission. Half patients will receive randomly azathioprine plus mesalazine, and the other half placebo plus melasazine. The size of the study will be calculated on the basis of the percentage of patients reaching primary outcome at 18 months (mucosal remission, as defined by endoscopy).

Internal collaborations:
- Laboratory of Clinical Chemical Analysis for routine analysis.
- Laboratory of Molecular Genetics for molecular determination of TPMT gene involved in thiopurine metabolism.

External collaborations:
- Anna Maria Staiano (coordinator), Pediatric Dept., Federico II University, Napoli.
- Prof. S. Cucchiara, Gastroenterology and Hepatology, La Sapienza University, Roma.
- Dr R. Francavillla, Pediatrics Dept., University of Bari.

BEST PUBLICATIONS YEARS 2011-2013

1. Lazzerini M, Martelossi S, Magazzù G, Pellegrino S, Lucanto MC, Barabino A, Calvi A, Arrigo S, Lionetti P, Lorusso M, Mangiantini F, Fontana M, Zuin G, Palla G, Maggiore G, Bramuzzo M, Pellegrin MC, Maschio M, Villanacci V, Manenti S, Decorti G, De Iudicibus S, Paparazzo R, Montico M, Ventura A. Effect of thalidomide on clinical remission in children and adolescents with refractory Crohn disease: a randomized clinical trial. JAMA. 2013 Nov 27;310(20):2164-73. doi: 10.1001/jama.2013.280777. PMID: 24281461.
2. Barabino A, Nardi F, Arrigo S, Gandullia P, Vignola S, Muraca M, Montobbio G, Pini-Prato A. Tubular Esophageal Duplication In A Boy: Further Evidence of A Possible Endoscopic Treatment. J Pediatr Gastroenterol Nutr. 2012 Aug 7. [Epub ahead of print] No abstract available. PMID: 22874428.

3. Cangemi G, Barabino A, Barco S, Parodi A, Arrigo S, Melioli G. A validated HPLC method for the monitoring of thiopurine metabolites in whole blood in paediatric patients with inflammatory bowel disease. Int J Immunopathol Pharmacol. 2012 Apr-Jun;25(2):435-44. PMID: 22697075.
4. Romeo E, Jasonni V, Caldaro T, Barabino A, Mattioli G, Vignola S, di Abriola GF, De Angelis P, Pane A, Torroni F, Rea F, Dall'Oglio L. Strictureplasty and intestinal resection: different options in complicated pediatric-onset Crohn disease. J Pediatr Surg. 2012 May;47(5):944-8. doi: 10.1016/j.jpedsurg.2012.01.054. PMID: 22595578.
5. Barabino A, Arrigo S, Gandullia P, Vignola S. Duodenal web: complications and failure of endoscopic treatment. Gastrointest Endosc. 2012 May;75(5):1123-4. doi: 10.1016/j.gie.2011.12.036. No abstract available. PMID: 22520887.
6. Mattioli G, Guida E, Pini-Prato A, Avanzini S, Rossi V, Barabino A, Coran AG, Jasonni V. Technical considerations in children undergoing laparoscopic ileal-J-pouch anorectal anastomosis for ulcerative colitis. Pediatr Surg Int. 2012 Apr;28(4):351-6. doi: 10.1007/s00383-011-3030-1. Epub 2011 Nov 30. PMID: 22127486.
7. Barabino AV, Gandullia P, Calvi A, Vignola S, Arrigo S, Marco RD. Sudden blindness in a child with Crohn's disease. World J Gastroenterol. 2011 Oct 14;17(38):4344-6. doi: 10.3748/wjg.v17.i38.4344. PMID: 22090792.
8. Pini Prato A, Rossi V, Fiore M, Avanzini S, Mattioli G, Sanfilippo F, Michelazzi A, Borghini S, Disma N, Montobbio G, Barabino A, Nozza P, Ceccherini I, Gimelli S, Jasonni V. Megacystis, megacolon, and malrotation: a new syndromic association? Am J Med Genet A. 2011 Aug;155A(8):1798-802. doi: 10.1002/ajmg.a.34119. Epub 2011 Jul 7. PMID: 21739599.
9. Mattioli G, Pini-Prato A, Barabino A, Gandullia P, Avanzini S, Guida E, Rossi V, Pio L, Disma N, Mameli L, Mirta DR, Montobbio G, Jasonni V. Laparoscopic approach for children with inflammatory bowel diseases. Pediatr Surg Int. 2011 Aug;27(8):839-46. doi: 10.1007/s00383-011-2885-5. Epub 2011 Mar 27. PMID: 21442425.
10. Barabino A, Gandullia P, Arrigo S, Vignola S, Mattioli G, Grattarola C. Successful endoscopic treatment of a double duodenal web in an infant. Gastrointest Endosc. 2011 Feb;73(2):401-3. doi: 10.1016/j.gie.2010.06.052. Epub 2010 Sep 24. No abstract available. PMID: 20869053.

Pediatric Rheumatology

Director: Prof. Alberto Martini

STAFF

Name	Position
Antonella Buoncompagni	Physician
Maja Di Rocco	Physician
Marco Gattorno	Physician
Angelo Ravelli	Physician
Paolo Picco	Physician
Nicolino Ruperto	Physician
Stefania Viola	Physician
Clara Malattia	Physician
Simona Angioloni	Administrative
Alessandra Rebolino	Administrative
Luca Villa	Administrative
Alessandro Consolaro	Researcher
Federica Penco	Researcher
Francesca Schena	Biologist
Arinna Bertoni	Biologist
Claudia Pastorino	Biologist
Chiesa Sabrina	Biologist
Francesca Bovis	Administrative
Laura Carenini	Administrative
Elisa Patrone	Administrative
Giuseppe Silvestri	Administrative
Mariangela Rinaldi	Administrative
Chiara Pallotti	Administrative
Irene Gregorini	Administrative
Eugenia Mosci	Administrative
Marco Garrone	Administrative
Silvia Scala	Administrative
Stefano Lanni	Researcher
Slvia Pederzoli	Researcher

Specializzandi in pediatria dal primo al quinto anno in rotazione presso la nostra U.O.

RESULTS YEAR 2013

Thanks to the collaboration with pediatric rheumatology centres of the Paediatric Rheumatology International Trials Organisation (PRINTO) network (www.printo.it), in 2013 the unit carried out different research projects, both institutional and funded by external sponsors (pharmaceutical industry or government agencies). In particular, PRINTO was involved in the implementation and management of a EU-funded pharmacovigilance project (Pharmachild) for drugs used in the treatment of juvenile idiopathic arthritis (JIA) enrolling over 3000 patients, as well as in the management of different phase III studies on biological drugs (tocilizumab, canakinumab, golimumab) in collaboration with pharmaceutical industries, and in the updating of a website for families containing information on rheumatic disease in over 50 languages.

In 2013, our unit was also involved in the development and validation of new parameters of quantitative evaluation of disease activity, functional ability, clinical damage, pain, and quality of life of children with rheumatic disease, with over 9000 collected subjects.
The unit was also involved in the standardization of methods of quantitative assessment of conventional radiology, magnetic resonance, and US examination in rheumatic diseases.
In the field of immunology, research was focused on the analysis of the role of adaptive immunity in the pathogenesis of rheumatic diseases. In particular, research projects were started on the influence of innate immunity in the development of TH17 cells, on the characterization of the immunological and functional phenotype of the different populations of B cells, and on the role of TLRs and purinergic receptors in the process of B cell development.
As national reference centre for the diagnosis and treatment of autoinflammatory diseases, our unit has been promoting since 2009 an EU project (Eurofever) aimed at creating a registry of autoinflammatory diseases. From March 2009, samples and clinical data of about 3000 patients with autoinflammatory diseases were collected. In 2013, laboratory activities were focused on the pathogenesis of diseases related to CIAS1 and to TNF receptor-related periodic syndromes (TRAPS).

Main collaborations year 2013:

- Collaboration with centres of the Pediatric Rheumatology International Trials Organisation (PRINTO) whose coordinating centre is located at Gaslini. PRINTO is a nonprofit research network of about 60 countries all over the world with over 400 pediatric rheumatology centres.
- Collaboration with Histiocyte Society, Childhood Arthritis & ***Rheumatology*** Research Alliance (CARRA), and Pediatric Rheumatology Collaborative Study Group (PRCSG) for the development of new diagnostic criteria for the macrophage activation syndrome.
- Collaboration with Childhood Arthritis & ***Rheumatology*** Research Alliance (CARRA) for the study of future clinical applications of the Juvenile Arthritis Disease Activity Score (JADAS)
- Collaborations with the Department of Informatics, Bioengineering, Robotics and System Engineering (DIBRIS) of the University of Genova.
- Collaboration with ESAOTE S.p.A. and CAMELOT Biomedical Systems S.rl. (CAMELOT) within the 7th European framework programme named EUTRAIN (*EUropean TRanslational training for Autoimmunity and Immune manipulation Network*) – Grant Agreement Number 289903
- Collaboration with the Department of Mechanical Engineering of the University of Sheffield and with the Departement of Cognitive Computing & Medical Imaging of Fraunhofer within the European project FP7-ICT-2011-9, MD-PAEDEGREE (*Model-Driven European Paediatric Digital Repository*) , Grant agreement no: 600932.
- OMERACT (Outcome Measure Rheumatoid Arthritis Clinical Trials) Juvenile Idiopathic Arthritis-MRI Special Interest Group.
- EULAR-PRES Task Force for the development of recommendations for the use of imaging techniques for the diagnosis and treatment of patients with juvenile idiopathic arthritis.

PLANNED RESEARCH ACTIVITY YEAR 2014

Main research projects:
- Multinational study on epidemiology, treatment, and long-term evolution of JIA.
- Development of new diagnostic criteria of macrophage activation syndrome in systemic JIA.

- Comparative therapeutic study on the efficacy of intraarticular steroid injection with or without methotrexate in JIA (funded by AIFA).
- Development of new clinical measures for the evaluation of disease state in children with juvenile dermatomyositis.
- Evaluation of clinical evolution in children with JIA treated with etanercept (funded by Pfizer).
- Iridocyclitis in JIA: identification of risk factors and definition of optimal screening programme
- Preliminary definition of cutoffs of Juvenile Arthritis Disease Activity Score (JADAS) for high disease activity in JIA
- Pharmacovigilance in juvenile idiopathic arthritis patients (Pharmachild) treated with biologic agents and/or methotrexate (EU FP7, project 260353)
- Anti-Biopharmaceutical Immunization: Prediction and analysis of clinical relevance to minimize the risk (ABIRISK). (funded by EU - Innovative Medicine Initiative)
- Single HUB and Access Point for Paediatric Rheumatology in Europe (SHARE) (funded by EU, project **201112 02**)
- Development and validation of software for automatic reading of erosive damage progression by MR in patients with JIA
- MR in JIA: relationship between bone intraspongious edema and progression of structural damage
- MR evaluation of early damage of joint cartilage in patients with JIA.
- Standardization and quantification of disease activity and of progression of structural damage by joint US examination in patients with JIA
- Analysis and development of software for the quantification of disease activity and progression of structural damage by joint US examination in patients with JIA
- Study of the impact of biomechanical alterations at joint level on progrssion of structural damage in JIA
- Study of genotype-phenotype relationship and pathogenetic mechanisms of PAPA syndrome
- Clinical impact of Q703K mutation of NLRP3 gene
- Evaluation of CAPS patients (in collaboration with Eurofever registry) and development of new diagnostic criteria for autoinflammatory diseases

BEST PUBLICATIONS YEARS 2011-2013

1. Picco P, Naselli A, Pala G, Marsciani A, Buoncompagni A, Martini A. Recurrent pericarditis in Myhre syndrome. Am J Med Genet A. 2013 May;161A(5):1164-6.
2. Gattorno M, Martini A. Beyond the NLRP3 inflammasome: autoinflammatory diseases reach adolescence. Arthritis Rheum. 2013 May;65(5):1137-47.
3. Consolaro A, Ravelli A. It is worth including assessment of disease activity state in juvenile arthritis clinical trials. Arthritis Care Res (Hoboken). 2013Aug;65(8):1207-10.
4. Consolaro A, Ravelli A. Paediatric rheumatology: Juvenile idiopathic arthritis-are biologic agents effective for pain? Nat Rev Rheumatol. 2013 Aug;9(8):447-8.
5. Lanni S, Wood M, Ravelli A, Magni Manzoni S, Emery P, Wakefield RJ. Towards a role of ultrasound in children with juvenile idiopathic arthritis. Rheumatology, (Oxford). 2013 Mar;52(3):413-20.
6. Schena F, Volpi S, Faliti CE, Penco F, Santi S, Proietti M, Schenk U, Damonte, G, Salis A, Bellotti M, Fais F, Tenca C, Gattorno M, Eibel H, Rizzi M, Warnatz K, Idzko M, Ayata CK, Rakhmanov M, Galli T, Martini A, Canossa M, Grassi F, Traggiai E. , Dependence of

immunoglobulin class switch recombination in B cells on vesicular release of ATP and CD73 ectonucleotidase activity. Cell Rep. 2013 Jun 27;3(6):1824-31.
7. Di Rocco A, Loggini A, Di Rocco M, Di Rocco P, Rossi RP, Gimelli G, Bazil C. Paradoxical worsening of seizure activity with pregabalin in an adult with isodicentric 15 (IDIC-15) syndrome involving duplications of the GABRB3, GABRA5 and GABRG3 genes. BMC Neurol. 2013 May 10;13:43.
8. Erba PA, Minichilli F, Giona F, Linari S, Dambrosia J, Pierini A, Filocamo M, Di Rocco M, Buffoni F, Brady RO, Mariani G. 99mTc-Sestamibi Scintigraphy to Monitor the Long-Term Efficacy of Enzyme Replacement Therapy on Bone Marrow Infiltration in Patients with Gaucher Disease. J Nucl Med. 2013, Oct;54(10):1717-24.
9. Caorsi R, Lepore L, Zulian F, Alessio M, Stabile A, Insalaco A, Finetti M, Battagliese A, Martini G, Bibalo C, Martini A, Gattorno M. The schedule of administration of canakinumab in cryopyrin associated periodic syndrome is driven by the phenotype severity rather than the age. Arthritis Res Ther. 2013 Feb 26;15(1).
10. Schena F, Volpi S, Faliti CE, Penco F, Santi S, Proietti M, Schenk U, Damonte G, Salis A, Bellotti M, Fais F, Tenca C, Gattorno M, Eibel H, Rizzi M, Warnatz K, Idzko M, Ayata CK, Rakhmanov M, Galli T, Martini A, Canossa M, Grassi F, Traggiai E. Dependence of immunoglobulin class switch recombination in B cells on vesicular release of ATP and CD73 ectonucleotidase activity. Cell Rep. 2013 Jun 27;3(6):1824-31.
11. Kaplan P, Baris H, De Meirleir L, Di Rocco M, El-Beshlawy A, Huemer M, Martins AM, Nascu I, Rohrbach M, Steinbach L, Cohen IJ. Revised recommendations for the management of Gaucher disease in children. Eur J Pediatr. 2013 Apr;172(4):447-58.
12. Consolaro A, Ravelli A. Paediatric rheumatology: Juvenile idiopathic arthritis--are biologic agents effective for pain? Nat Rev Rheumatol. 2013 Aug;9(8):447-8.
13. Malattia C, Martini A. Paediatric-onset systemic lupus erythematosus. Best Pract Res Clin Rheumatol. 2013;27(3):351-62.
14. Malattia C, Damasio MB, Madeo A, Pistorio A, Providenti A, Pederzoli S, Viola S, Buoncompagni A, Mattiuz C, Beltramo A, Consolaro A, Ravelli A, Ruperto N, Picco P, Magnano GM, Martini A. Whole-body MRI in the assessment of disease activity in juvenile dermatomyositis. Ann Rheum Dis. 2013 May 1.
15. Solari N, Palmisani E, Consolaro A, Pistorio A, Viola S, Buoncompagni A, Gattorno M, Picco P, Ruperto N, Malattia C, Martini A, Ravelli A. Factors associated with achievement of inactive disease in children with juvenile idiopathic arthritis treated with etanercept. J Rheumatol. 2013;40(2):192-200.
16. Damasio MB, Malattia C, Tanturri de Horatio L, Mattiuz C, Pistorio A, Bracaglia C, Barbuti D, Boavida P, Juhan KL, Ording LS, Rosendahl K, Martini A, Magnano G, Tomà P. MRI of the wrist in juvenile idiopathic arthritis: proposal of a paediatric synovitis score by a consensus of an international working group. Results of a multicentre reliability study. Pediatr Radiol. 2012 Sep;42(9):1047-55. Erratum in: Pediatr Radiol. 2013;43(1):124.
17. Malattia C, Consolaro A, Pederzoli S, Madeo A, Pistorio A, Mazzoni M, Mattiuz C, Magnano GM, Viola S, Buoncompagni A, Palmisani E, Hasija R, Ruperto N, Ravelli A, Martini A. MRI versus conventional measures of disease activity and structural damage in evaluating treatment efficacy in juvenile idiopathic arthritis. Ann Rheum Dis. 2013;72(3):363-8.
18. Lazarevic D, Pistorio A, Palmisani E, Miettunen P, Ravelli A, Pilkington C, Wulffraat NM, Malattia C, Garay SM, Hofer M, Quartier P, Dolezalova P, Penades IC, Ferriani VP, Ganser G, Kasapcopur O, Melo-Gomes JA, Reed AM, Wierzbowska M, Rider LG, Martini A, Ruperto N; for the Paediatric Rheumatology International Trials Organisation (PRINTO). The PRINTO criteria for clinically inactive disease in juvenile dermatomyositis. Ann Rheum Dis. 2013;72(5):686-93.

Pediatric Pneumology and Allergology

Director: Professor Giovanni A. Rossi

STAFF

Name	Position
Oliviero Sacco	Physician
Donata Girosi	Physician
Maria Angela Tosca	Physician
Roberta Olcese	Physician
Serena Panigada	Physician
Nicoletta Solari	Physician
Michela Silvestri	Clinical Research Associate
Annalisa Firenze	Administrative
Lorella Santato	Head nurse
Cristina De Barbieri	Nurse
Rita Cennicola	Nurse
Cristina Baschieri	Nurse
Maria Grazia Ferrario	Nurse
Stefania Riccardi	Nurse
Cristina Sburlino	Nurse
Enrica Canepa	Nurse
Edvige Turrato	Nurse
Giovanna Ranzoni	Nurse
Annunziata Langella	Nurse
Alessandra Ugoletti	Nurse
Silvia Craviotto	Nurse
Anna Vitali	Nurse
Enrica Cassano	Nurse
Concetta Scala	Nurse
Silvia Leveratto	Nurse
Stefania Springhetti	Nurse
Puppo Antonella	Nurse
Suor Ester	Nurse
Pietrina Giannarelli	Nurse
Piera Sale	Nurse
Anna Sabatino	Nurse

RESULTS YEAR 2013

In 2013, research projects were mainly focused on the following topics:

Vitamin D and respiratory infections in pediatric age

It is still not known what are the serum levels of 25-hydroxy vitamin D (vitD) during acute respiratory infection and whether they tend to increase spontaneously after resolution. We therefore evaluated prospectively the trend of vitD serum levels in children on admission for lower airway acute respiratory infections (IR) and after 30 days from discharge (follow-up=FU). During infection, 62% of patients presented vitD levels <20 ng/ml (vitamin deficiency) and VitD levels, that did not correlated with RI severity, increased at FU in % of patients, irrespective of the levels observed during infection. At discharge, in no cases vitD or dietary changes were prescribed.

Children showing increased VitD during FU had more frequently fever >38°C on admission, had been treated more frequently with i.v. antiobiotics on admission, were more frequently allergic, showed more frequently positive pharyngeal swab and/or blood culture for pathogens. For this reason, VitD levels increase spontaneously in some patients after an acute RI episode. Irrespective of basal values, subjects with a natural increase in vitD levels had more severe diseases. Therefore: a) vitD levels on admission do not correlate with infection severity; b) the spontaneous increase in FU values in children with more severe disease seems to suggest vitD consumption in acute disease phase.

Mycoplasma pneumoniae resistance to macrolides

In order to evaluate the prevalence and clinical impact of Mycoplasma pneumoniae resistance to macrolides, we recruited 54 children aged 17 months to 17 years, 27 males and 27 females, affected by lower respiratory tract infections, ascertained on the basis of clinical and radiological evidence. Compared to the sample estimated in the statistical analysis, 19% of estimated cases was reached (54 patients of estimated 288). The reason for this limited numerosity is the lack of infection epidemics recorded to date. The prevalence of mycoplasma infection was 15%. At present, 2 cases of resistance to macrolides were recorded, with mutations already described in the literature: the sequence of DNA coding for V domain of rRNS 23S revealed A2064G punctiform mutation. The study will be continued in 2014.

Main collaborations year 2013

- Fabio LM. Ricciardolo, Respiratory Tract Disease Clinic, University of Torino.
- Andrew A. Colin. Division of Pediatric Pulmonology, University of Miami, FL, USA.
- Giorgio Ciprandi. Dept. of Internal Medicine, University of Genova.
- Andrew Bush.Department of Paediatric Respirology,Royal Brompton Hospital,London, UK.
- Franca Rusconi, Epidemiology unit, Meyer Children's Hospita, Firenze.
- Angelo Barbato. Department of Pediatrics, University of Padova .
- Massimo Pifferi, Pediatric Clinic, University of Pisa.
- Anna Marchese, Microbiology, University of Genova
- Nicola Principi, Pediatric Clinic, University of Milano.

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Anaphylaxis: diagnostic and therapeutic process.

Objective: Improvement of management of anaphylaxis: regarding therapy, through early detection of cases and appropriate and rapid treatment (appropriateness of adrenalin use); regarding diagnosis, through the identification of the triggering cause with 2nd and 3rd level allergologic diagnosis.

Description: We will evaluate longitudinally all the patients admitted to the Pediatric Pneumology/Allergology unit already treated in the Emergency unit or referred by the attending physician for suspected anaphylaxis and/or severe food allergy and/or suspected anaphylaxis due to hymenopters.

We will analyse the criteria for the definition of anaphylaxis and the appropriateness of treatment, and we will define the levels of serum IgE for each single allergen (ImmunoCAP) as well as the molecular profile of single sensitizations (ISAC test). The objective is the management of anaphylaxis. In addition, we will evaluate whether molecular diagnostics can improve allergologic diagnosis and prognosis, by establishing clinical severity criteria and characterizing the phenotype of the patient at risk of anaphylaxis and severe allergic reactions, with an impact on therapeutic, dietetic, and preventive decisions. We will monitor over time the possible evolution towards spontaneous tolerance, in case of food allergies or

after specific immunotherapy, in case of allergy to hymenopter venom also through the identification of biomarkers predictive of food intolerance (IgG4-IgA).

Internal collaborations:

- Statistics and Epidemiology unit
- Emergency unit
- Laboratory of Clinical and Chemical Analysis

External collaborations:

- G. Ciprandi, DIMI, San Martino Hospital, Genova

BEST PUBLICATIONS YEARS 2011-2013

1. Ghezzi M, Silvestri M, Guida E, Pistorio A, Sacco O, Mattioli G, Jasonni V,Rossi GA. Acid and weakly acid gastroesophageal refluxes and type of respiratory symptoms in children. Respir Med. 2011;105(7):972-978.
2. Ciprandi, Signori, Tosca M.A., Cirillo I. Bronchodilation test in patients with allergic rhinitis. Allergy. 2011; 66:694–698.
3. Esposito S, Marchese A, Tozzi AE, Rossi GA, Da Dalt L, Bona G, Pelucchi C, Schito GC, Principi N; Italian Pneumococcal CAP Group. Bacteremic pneumococcal community-acquired pneumonia in children less than 5 years of age in Italy. Pediatr Infect Dis J. 2012; 31: 705-710.
4. Quizon A, Colin AA, Pelosi U, Rossi GA. Treatment of disorders characterized by reversible airway obstruction in childhood: are anti-cholinergic agents the answer? Curr Pharm Des. 2012; 18: 3061-3085.
5. Ricciardolo FL, Di Stefano A, Silvestri M, Van Schadewijk AM, Malerba M, Hiemstra PS, Sterk PJ. Exhaled nitric oxide is related to bronchial eosinophilia and airway hyperresponsiveness to bradykinin in allergen-induced asthma exacerbation. Int J Immunopathol Pharmacol. 2012; 25(1):175-182.
6. Petecchia L, Sabatini F, Usai C, Caci E, Varesio L, Rossi GA. Cytokines induce tight junction disassembly in airway cells via an EGFR-dependent MAPK/ERK1/2-pathway. Lab Invest. 2012; 1140-1148.
7. Michele Ghezzi, Edoardo Guida, Nicola Ullmann, Oliviero Sacco, Girolamo Mattioli, Vincenzo Jasonni, Giovanni A. Rossi and Michela Silvestri. Weakly Acidic Gastroesophageal Refluxes Are Frequently Triggers in Young Children With Chronic Cough. Pediatric Pulmonology. 2013; 48:295–302.
8. Silvestri M, Crimi E, Oliva S, Senarega D, Tosca MA, Rossi GA, Brusasco V. Pulmonary function and airway responsiveness in young competitive swimmers. Pediatr Pulmonol. 2013 Jan;48(1):74-80.
9. Ullmann N, Bossley CJ, Fleming L, Silvestri M, Bush A, Saglani S. Blood eosinophil counts rarely reflect airway eosinophilia in children with severe asthma. Allergy. 2013; 68(3):402-406.
10. Ricciardolo FL, Sorbello V, Silvestri M, Giacomelli M, Debenedetti VM, Malerba M, Ciprandi G, Rossi GA, Rossi A, Bontempelli M. TNF-alpha, IL-4R-alpha and IL-4 polymorphisms in mild to severe asthma from Italian Caucasians. Int J Immunopathol Pharmacol. 2013;26(1):75-84.

Dermatology

Director: Dr. Corrado Occella

STAFF

Name	Position
Corrado Occella	Director
Dario Bleidl	Physician
Gianmaria Viglizzo	Physician
Valentina Fausti	Physician

RESULTS YEAR 2013

STUDY OF ICOS GENE AND OF CYTOKERATIN 17 IN PATIENTS WITH ALOPECIA AREATA.
Recent studies showed the involvement of Treg lymphocytes in the development of alopecia areata. In particular, a lower suppressory functional activity of these lymphocytes present in affected patients compared to Treg in healthy subjects was found. In this context, polymorphisms in the UTR 3' region of genes coding for molecules closely involved in Treg function could alter gene expression, with an impact on Treg activity.
The results of the study showed that: a) rs4404254 (C) and rs4675379 (C) allelic variants of ICOS gene are more frequent in patients with alopecia areata than in healthy controls; b) rs4404254 (C) and rs4675379 (C) allelic variants are associated with a reduced ICOS gene expression; c) miR303 is more highly expressed in PBMC of patients, while miR27b and miR101 are more highly expressed in PBMC of healthy controls. These data suggest that a reduced expression of ICOS in patients with alopecia areata could induce a functional deficit in Treg, favouring the onset of an autoimmune reaction against some autoantigens expressed in the hair bulb and important for hair growth cycle.
This data could contribute to the therapeutic approaches developed over the last few years, based on gene therapy directed towards hair follicle cells. Different oligonucleotides, such as antisense oligonucleotides, and small interfering RNAs mimicking or interfering with microRNA function were proposed as drug for the treatment of diseases related to hair bulb growth deficiency.

MAIN COLLABORATIONS YEAR 2013

Laboratory of Immunology of CEBR (University of Genova, San Martino hospital, Genova).

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Study of ICOS gene and of cytokeratin 17 in patients with alopecia areata
Objective: recruitment of new patients for confirmation of obtained results and definition of the role of cytokeratin 17 alterations in the pathogenesis of alopecia areata
Description: continuation of the study

External collaborations:

Laboratory of Immunology of CEBR (University of Genova, San Martino hospital, Genova).

BEST PUBLICATIONS YEARS 2011-2013

1. Vercellino N, Romanini MV, Pelegrini M, Rimini A, Occella C, Dalmonte P. The use of propranolol for complicated infantile hemangiomas. Int J Dermatol. 2013 Sep;52(9):1140-6. doi: 10.1111/j.1365-4632.2012.05795.x. Epub 2013 Jul 8.
2. Occella C, Bleidl D, Nozza P, Mascelli S, Raso A, Gimelli G, Gimelli S, Tassano E..Identification of an interstitial 18p11.32-p11.31 duplication including the EMILIN2 gene in a family with porokeratosis of Mibelli. PLoS One. 2013 Apr 10;8(4):e61311. doi: 10.1371/journal.pone.0061311. Print 2013.

3. Striano P, Consales A, Severino M, Prato G, Occella C, Rossi A, Cama A, Nozza P, Baglietto MG. A 3-year-old boy with drug-resistant complex partial seizures. Brain Pathol. 2012 Sep;22(5):725-8.
4. Alpigiani MG, Salvati P, Schiaffino MC, Occella C, Castiglia D, Covaciu C, Lorini R. A new SPINK5 mutation in a patient with Netherton syndrome: a case report. Pediatr Dermatol. 2012 Jul-Aug;29(4):521-2.

Infectious diseases

Director (pro-tempore): Dr. Elio Castagnola

STAFF

Name	Position
Elisabetta Bondi	Physician
Emilio Cristina	Physician
Giuseppe Losurdo	Physician
Anna Loy	Physician
Cristina Moroni,	Physician
Angela Tacchella	Physician
Manuela Rescali	Administrative
Ilaria Caviglia	Biologist

RESULTS YEAR 2013

We completed and analysed the epidemiologic study on bacteremias and invasive fungal infections in children undergoing allogenic bone marrow transplantation, which showed that acute graft-versus-host disease (aGvHD, equivalent to organ rejection) is a crucial factor for the development of invasive fungal infection. In fact, the more severe was this complication, the higher was the incidence of fungal infections. This data was confirmed also by a cooperative prospective study of the Italian Bone Marrow Transplantation Group (GITMO), in which Gaslini has participated (Infectious Disease unit, Hematology/Oncology unit, BMT section). Concerning bacteremias, Gaslini's data showed that, in BMT, lower donor-recipient compatilibity is associated with a higher incidence of bacteremias, while aGvHD would not have a relevant role in the development of this complication. These data have an important impact on the choice of prophylactic, diagnostic, and/or therapeutic strategies in BMT patients.

We continued the epidemiologic studies on sensitivity to antibodies of bacterial strains isolated from blood culture in pediatric patients at risk. The analysis of sensitivity to different drugs of methycillin-resistant staphylococci isolated from blood of hemato-oncological, surgical, PICU or NICU or Infectious Disease unit patients showed a tendency towards an increase in strains with reduced sensitivity to vancomycin. The analysis of the efficacy of other alternative drugs demonstrated that a considerable percentage of these strains presents reduced sensitivity also to alternative drugs as daptomycin and linezolid. This data is important for the definition of therapeutic strategies.

Finally, we continued the collection of data regarding sensitivity to antibiotics of Gram-negative bacteria isolated in urine culture and etiology and localization of yeast infections in patients hospitalized at Gaslini. In addition, we continued the observational studies on invasive fungal infections in collaboration with the Italian association of pediatric hematology and oncology (AIEOP) and with the international study group on fungal infections (Pediatric Fungal Network, PFN). After the collection of an appropriate number of subjects, the analysis of these series is likely to lead to important results for the clinical management of patients.

Main collaborations year 2013

1) Pediatric Fungal Network (PFN): international collection of data on invasive fungal infection in pediatric age;
2) European Conference on Infectons in Leukemia (ECIL): preparation of guidelines/recommendations;

3) European Society for Clinical Microbiology and Infectious Diseases (ESCMID), Invasive Fungal Infections Group (IFIG): preparation of guidelines/recommendations;
4) Italian Bone Marrow Transplantation Group (GITMO): collection of data on bacterial infections due to resistant Gram-negatives, preparation of guidelines/recommendations on fungal infections.

PLANNED ACTIVITY YEAR 2014

Title: Epidemiology and therapy of bacteremias and invasive fungal infections in critical pediatric patients
Objective: Description of the etiology of bacteremias and invasive fungal infections in pediatric age, also in terms of sensitivity to medications, and evaluation of the clinical-microbiological response to therapies according to pharmacokinetics and pharmacodynamics parameters.
Description: We will continue collection of data on etiology and sensitivity to antibiotics of strains causing bacteremias in hematological/oncological patients and on invasive fungal infections in all Gaslini's patients. In parallel, we will start collecting data on monitoring of blood levels of anti-infectious drugs to evaluate kinetics parameters in pediatric age and possible correlations with clinical efficacy.

Internal collaborations:

- Clinical units (in order of priority Hematology-Oncology unit, PICU, and Neonatology unit);
- Laboratory of Clinical Chemical Analysis (Microbiology and Clinical Chemistry);
- Epidemiology and Biostatistics service.

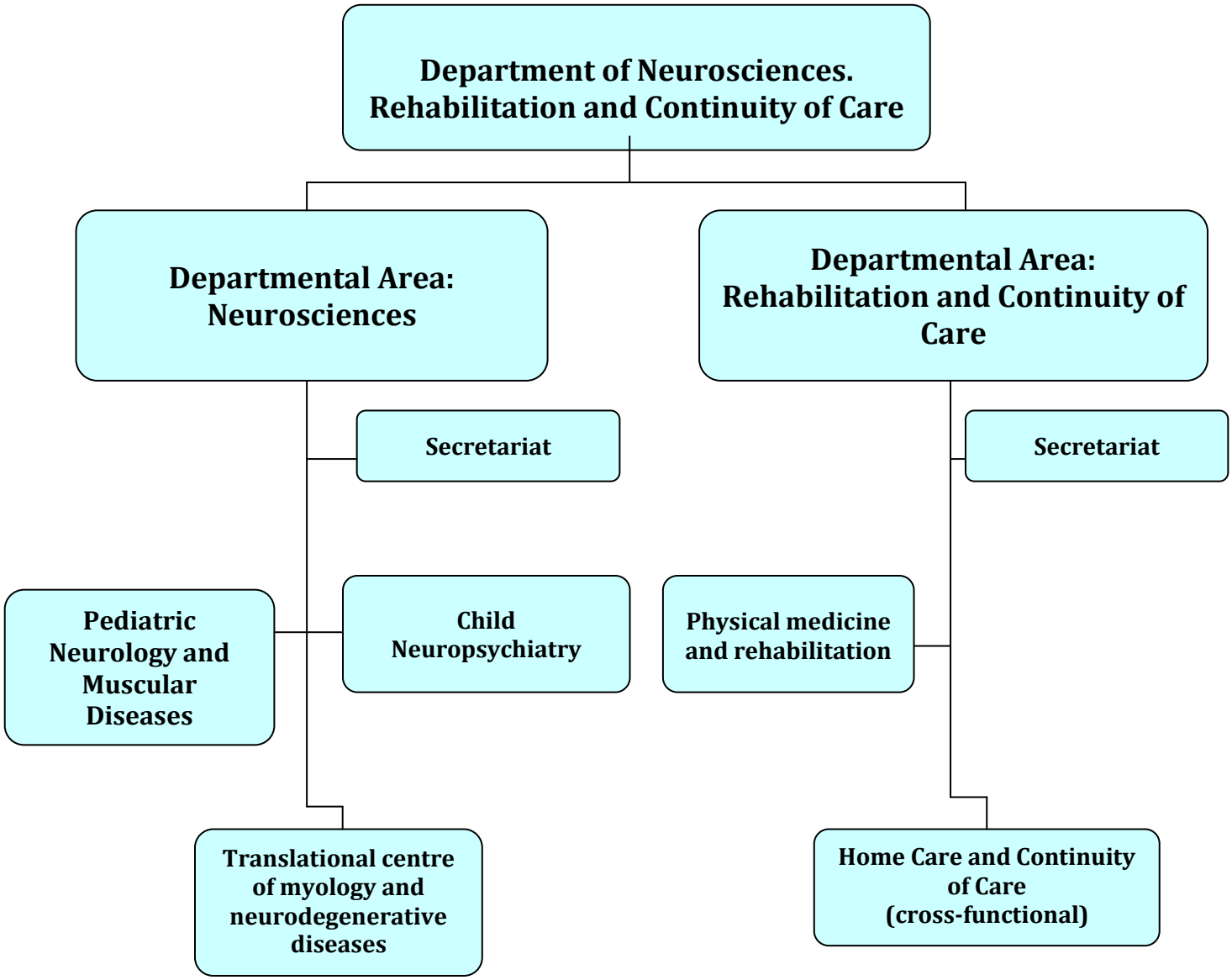
External collaborations:

- Institute of Pharamacology, University of Genova;
- Centres of the Italian Association of Pediatric Hematology and Oncology (AIEOP);
- Pediatric Fungal Network;
- Italian Bone Marrow Transplantation Group;
- Infectious Disease Clinic, University of Genova.

BEST PUBLICATIONS YEARS 2011-2013

1. Garazzino S, Krzysztofiak A, Esposito S, Castagnola E, Plebani A, Galli L, Cellini M, Lipreri R, Scolfaro C, Bertaina C, Calitri C, Bozzola E, Lancella L, Quondamcarlo A, Bosis S, Pugni L, Losurdo G, Soresina A, De Gaudio M, Mariotti I, Mancini L, Gabiano C, Tovo PA. Use of linezolid in infants and children: a retrospective multicentre study of the Italian Society for Paediatric Infectious Diseases. J Antimicrob Chemother. 2011 Oct;66(10):2393-7.
2. Lamoth F, Cruciani M, Mengoli C, Castagnola E, Lortholary O, Richardson M, Marchetti O; Third European Conference on Infections in Leukemia (ECIL-3). β-Glucan antigenemia assay for the diagnosis of invasive fungal infections in patients with hematological malignancies: a systematic review and meta-analysis of cohort studies from the Third European Conference on Infections in Leukemia (ECIL-3). Clin Infect Dis. 2012 Mar 1;54(5):633-43.
3. Phillips RS, Sutton AJ, Riley RD, Chisholm JC, Picton SV, Stewart LA; PICNICC Collaboration. Predicting infectious complications in neutropenic children and young people with cancer (IPD protocol). Syst Rev. 2012 Feb 9;1:8.

4. Steinbach WJ, Roilides E, Berman D, Hoffman JA, Groll AH, Bin-Hussain I, Palazzi DL, Castagnola E, Halasa N, Velegraki A, Dvorak CC, Charkabarti A, Sung L, Danziger-Isakov L, Lachenauer C, Arrieta A, Knapp K, Abzug MJ, Ziebold C, Lehrnbecher T, Klingspor L, Warris A, Leckerman K, Martling T, Walsh TJ, Benjamin DK Jr, Zaoutis TE; International Pediatric Fungal Network. Results from a prospective, international, epidemiologic study of invasive candidiasis in children and neonates. Pediatr Infect Dis J. 2012 Dec;31(12):1252-7.
5. Lehrnbecher T, Phillips R, Alexander S, Alvaro F, Carlesse F, Fisher B, Hakim H, Santolaya M, Castagnola E, Davis BL, Dupuis LL, Gibson F, Groll AH, Gaur A, Gupta A, Kebudi R, Petrilli S, Steinbach WJ, Villarroel M, Zaoutis T, Sung L; International Pediatric Fever and Neutropenia Guideline Panel. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. J Clin Oncol. 2012 Dec 10;30(35):4427-38.
6. Fioredda F, Calvillo M, Burlando O, Riccardi F, Caviglia I, Tucci F, Bonanomi S, Ghilardi R, Martire B, Farruggia P, Mastrodicasa E, Barone A, Castagnola E, Dufour C. Infectious complications in children with severe congenital, autoimmune or idiopathic neutropenia: a retrospective study from the Italian Neutropenia Registry. Pediatr Infect Dis J. 2013 Apr;32(4):410-2.
7. Hope WW, Castagnola E, Groll AH, Roilides E, Akova M, Arendrup MC, Arikan-Akdagli S, Bassetti M, Bille J, Cornely OA, Cuenca-Estrella M, Donnelly JP, Garbino J, Herbrecht R, Jensen HE, Kullberg BJ, Lass-Flörl C, Lortholary O, Meersseman W, Petrikkos G, Richardson MD, Verweij PE, Viscoli C, Ullmann AJ; ESCMID Fungal Infection Study Group. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: prevention and management of invasive infections in neonates and children caused by Candida spp. Clin Microbiol Infect. 2012 Dec;18 Suppl 7:38-52.
8. Castagnola E, Ginocchio F. Rescue therapy of difficult-to-treat indwelling central venous catheter-related bacteremias in cancer patients: a review for practical purposes. Expert Rev Anti Infect Ther. 2013 Feb;11(2):179-86.
9. Phillips B, Ranasinghe N, Stewart LA; PICNICC Collaboration. Ethical and regulatory considerations in the use of individual participant data for studies of disease prediction. Arch Dis Child. 2013 Jul;98(7):567-8.
10. Castagnola E, Mikulska M, Barabino P, Lorenzi I, Haupt R, Viscoli C. Current research in empirical therapy for febrile neutropenia in cancer patients: what should be necessary and what is going on. Expert Opin Emerg Drugs. 2013 Sep;18(3):263-78.


Department of Neurosciences. Rehabilitation and Continuity of Care
Departmental Area: Neurosciences
Departmental Area: Rehabilitation and Continuity of Care
Secretariat
Secretariat
Pediatric Neurology and Muscular Diseases
Child Neuropsychiatry
Physical medicine and rehabilitation
Translational centre of myology and neurodegenerative diseases
Home Care and Continuity of Care (cross-functional)

Pediatric neurology and muscular diseases

Director: Professor Carlo Minetti

STAFF

Name	Position
Claudio Bruno	Physician
Marina Pedemonte	Physician
Daniela Massocco	Physician
Pasquale Striano	Physician
Eugenio Bonioli	Associate Professor
Chiara Fiorillo	Physician
Marianna Pezzella	Physician
Guido Morcaldi	Physician
Maria Stella Vari	Physician
Giovanna Giudizioso	Neurophysiology technician
Federico Zara	Biologist
Francesca Madia	Biologist
Paolo Broda	Laboratory technician
Fabrizio Giusquiami	Laboratory technician
Giuseppe Minniti	Laboratory technician
Angela Robbiano	Biotechnologist
Elisabetta Gazzerro	Physician
Floriana Fruscione	Biologist
Stefania Assereto	Biologist
Monica Traverso	Biologist

RESULTS YEAR 2013

Study of functional molecular mechanisms in the pathogenesis of neuromuscular and neurogenetic diseases: perspectives on new therapeutic trends

General objective is the improvement of knowledge in the field of neurosciences in developmental age, in particular neuromuscular and neurodegenerative diseases of genetic origin (mainly idiopathic epilepsies), through a multidisciplinary approach including clinical-laboratory, neuropsychological, neuroradiological, neurosurgical, and rehabilitative aspects linked to applied research aspects, also based on cellular and in vivo experimental models.

This research line includes highly specialized etiopathogenetic research applied to the clinical practice and aimed at diagnostic and therapeutic outcomes, also through the identification and functional characterization of genes for rare neurodevelopmental diseases using new generation sequencing techniques.

To this end, we selected 21 families with undiagnosed or unclassified recessive diseases and we typed them with AXION 587k slide. We also analyzed a murine model of deletion of the hyccin gene, the protein identified in our laboratory and involved in hypomyelinization and congenital cataract disorder.

The ultimate objective of the research project is to improve the quality of life of patients and their families through an effective sociomedical care and the rationalization and reduction of direct and indirect sociomedical costs, as well as costs related to cultural, social, school, and work problems of pediatric patients.

Research groups are therefore actively involved in the achievement of the following objectives:

- Integrate the different diagnostic activities (electrophysiology, neuroradiology, genetics) to improve the diagnostic ability of the unit.
- Raising of qualitative standards of the service for the management of highly complex patients in order to guarantee to Ligurian patients high health care levels and to attract patients from other regions.
- Development of guidelines on the use of pharmacologic and non pharmacologic therapies, also aimed at rationalization of costs.

Main collaborations year 2013:

Participation in European and International Consortiums

- FUNCTIONAL GENOMICS AND NEUROBIOLOGY OF EPILEPSY: A BASIS FOR NEW THERAPEUTIC STRATEGIES (EPICURE study) in the European Consortium supported by the Sixth Framework Programme
- EUROEPINOMICS consortium ('Studying genetic epilepsies through Next Generation sequencing techniques'') in collaboration with Max-Delbrück-Center for Molecular Medicine, Berlin, Germany, and University of Helsinki, Finland
- CoGIE project (Complex genetics of idiopathic epilepsies) in collaboration with the University of Ulm, Germany (Prof. H. Lerche)
- EpiPGX study ("Epilepsy Pharmacogenomics: delivering biomarkers for clinical use "), funded by European Community, 7th Framework programme, coordinated by University College London, UK
- ILAE Consortium on Complex Epilepsies, (coordinato da S. Berkovic, University of Melbourne, Australia)
- EUROMAC European Registry of patients with McArdle Disease and very rare muscle glycogenolytic disorders (MGD) with exercise intolerance as the major symptom (PR-MDMGM), 7th Framework programme, coordinated by Hospital Vall d'Hebron, Barcelona, Spain

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Identification of genes for neuropediatric diseases by new generation sequencing techniques
Objective: Identification of the genetic bases of neurologic diseases of the child and definition of genotype-phenotype correlations by new sequencing techniques (NGS).
Description:
The project includes different phases:

1) Selection of cases and collection of clinical data.

Cases will be subdivided into the following categories:

- Familial cases with Mendelian inheritance (AR or AD)
- Sporadic cases

2) Collection of biological material. From each subject and 1st degree relative, blood will be collected for DNA extraction
3) NGS sequencing

Exome sequencing will be performed with the Illumina platform.

4) Analysis of NGS data

NGS data will be analysed by GATK pipeline for the identification of rare variants not reported in the population database.

5) Genotype-phenotype correlations

The identified variants will be analysed to identify common genes in cohorts of patients with similar diseases and/or for cosegregation in families.

Internal collaborations:

- Dr. Roberta Biancheri, Neuropsychiatry unit
- Dr. Mirella Filocamo, Metabolic Diseases unit
- Prof. Roberto Ravazzolo, Medical Genetics unit

External collaborations:

- Dr. E. Bertini, Bambino Gesù hospital, Roma
- Prof. G. Casari, San Raffaele hospital and Vita e Salute University, Milano
- Dr. M. Elia, Istituto Oasi Maria SS, Troina (EN)
- Prof. R. Guerrini, Meyer Hospital, Firenze
- Prof. E. Mercuri, Cattolica University, A. Gemelli hospital, Roma
- Dr. F.M. Santorelli, Stella Maris Foundation, Pisa
- Dr. E. Zito, Mario Negri Institute, Milano
- Prof. Berkovic, University of Melbourne (AUS)
- Prof. S. DiMauro, Columbia University, New York (USA)
- Dr. F. Grassi, IRB, Bellinzona (SUI)
- Dr. AE Lehesjoki, University of Helsinki (FIN)
- Prof. B. Minassian, The Hospital for Sick Children, Toronto (CAN)
- Dr. T. Sander, Max-Delbrück-Center for Molecular Medicine, Berlin (GER)

BEST PUBLICATIONS YEARS 2011-2013

1. Striano P, Paravidino R, Sicca F, Chiurazzi P, Gimelli S, Coppola A, Robbiano A, Traverso M, Pintaudi M, Giovannini S, Operto F, Vigliano P, Granata T, Coppola G, Romeo A, Specchio N, Giordano L, Osborne LR, Gimelli G, Minetti C, Zara F. West syndrome associated with 14q12 duplications harboring FOXG1. Neurology. 2011; 76:1600-1602.
2. Striano P, Weber YG, Toliat MR, Schubert J, Leu C, Chaimana R, Baulac S, Guerrero R, LeGuern E, Lehesjoki AE, Polvi A, Robbiano A, Serratosa JM, Guerrini R, Nürnberg P, Sander T, Zara F, Lerche H, Marini C; EPICURE Consortium. GLUT1 mutations are a rare cause of familial idiopathic generalized epilepsy. Neurology. 2012 Feb 21;78(8):557-62.
3. EPICURE Consortium; EMINet Consortium, Steffens M, Leu C, Ruppert AK, Zara F, Striano P, Robbiano A, Capovilla G, Tinuper P, Gambardella A, Bianchi A, La Neve A, Crichiutti G, de Kovel CG, Kasteleijn-Nolst Trenité D, de Haan GJ, Lindhout D, Gaus V, Schmitz B, Janz D, Weber YG, Becker F, Lerche H, Steinhoff BJ, Kleefuß-Lie AA, Kunz WS, Surges R, Elger CE, Muhle H, von Spiczak S, Ostertag P, Helbig I, Stephani U, Møller RS, Hjalgrim H, Dibbens LM, Bellows S, Oliver K, Mullen S, Scheffer IE, Berkovic SF, Everett KV, Gardiner MR, Marini C, Guerrini R, Lehesjoki AE, Siren A, Guipponi M, Malafosse A, Thomas P, Nabbout R, Baulac S, Leguern E, Guerrero R, Serratosa JM, Reif PS, Rosenow F, Mörzinger M, Feucht M, Zimprich F, Kapser C, Schankin CJ, Suls A,

Smets K, De Jonghe P, Jordanova A, Caglayan H, Yapici Z, Yalcin DA, Baykan B, Bebek N, Ozbek U, Gieger C, Wichmann HE, Balschun T, Ellinghaus D, Franke A, Meesters C, Becker T, Wienker TF, Hempelmann A, Schulz H, Rüschendorf F, Leber M, Pauck SM, Trucks H, Toliat MR, Nürnberg P, Avanzini G, Koeleman BP, Sander T. Genome-wide association analysis of genetic generalized epilepsies implicates susceptibility loci at 1q43, 2p16.1, 2q22.3 and 17q21.32. Hum Mol Genet. 2012; 21:5359-2372.

4. Bello L, Piva L, Barp A, Taglia A, Picillo E, Vasco G, Pane M, Previtali SC, Torrente Y, Gazzerro E, Motta MC, Grieco GS, Napolitano S, Magri F, D'Amico A, Astrea G, Messina S, Sframeli M, Vita GL, Boffi P, Mongini T, Ferlini A, Gualandi F, Soraru' G, Ermani M, Vita G, Battini R, Bertini E, Comi GP, Berardinelli A, Minetti C, Bruno C, Mercuri E, Politano L, Angelini C, Hoffman EP, Pegoraro E. Importance of SPP1 genotype as a covariate in clinical trials in Duchenne muscular dystrophy. Neurology. 2012; 79: 159-162.
5. Conti V, Carabalona A, Pallesi-Pocachard E, Parrini E, Leventer RJ, Buhler E, McGillivray G, Michel FJ, Striano P, Mei D, Watrin F, Lise S, Pagnamenta AT, Taylor JC, Kini U, Clayton-Smith J, Novara F, Zuffardi O, Dobyns WB, Scheffer IE, Robertson SP, Berkovic SF, Represa A, Keays DA, Cardoso C, Guerrini R. Periventricular heterotopia in 6q terminal deletion syndrome: role of the C6orf70 gene. Brain. 2013;136(Pt 11):3378-94.
6. Mancuso M, Orsucci D, Angelini C, Bertini E, Carelli V, Comi GP, Minetti C, Moggio M, Mongini T, Servidei S, Tonin P, Toscano A, Uziel G, Bruno C, Caldarazzo Ienco E, Filosto M, Lamperti C, Martinelli D, Moroni I, Musumeci O, Pegoraro E, Ronchi D, Santorelli FM, Sauchelli D, Scarpelli M, Sciacco M, Spinazzi M, Valentino ML, Vercelli L, Zeviani M, Siciliano G. Phenotypic heterogeneity of the 8344A>G mtDNA "MERRF" mutation. Neurology. 2013 May 28;80(22):2049-2054.
7. Kasperaviciute D, Catarino CB, Matarin M, Leu C, Novy J, Tostevin A, Leal B, Hessel EV, Hallmann K, Hildebrand MS, Dahl HH, Ryten M, Trabzuni D, Ramasamy A, Alhusaini S, Doherty CP, Dorn T, Hansen J, Krämer G, Steinhoff BJ, Zumsteg D, Duncan S, Kälviäinen RK, Eriksson KJ, Kantanen AM, Pandolfo M, Gruber-Sedlmayr U, Schlachter K, Reinthaler EM, Stogmann E, Zimprich F, Théâtre E, Smith C, O'Brien .
8. TJ, Meng Tan K, Petrovski S, Robbiano A, Paravidino R, Zara F, Striano P, Sperling MR, Buono RJ, Hakonarson H, Chaves J, Costa PP, Silva BM, da Silva AM, de Graan PN, Koeleman BP, Becker A, Schoch S, von Lehe M, Reif PS, Rosenow F, Becker F, Weber Y, Lerche H, Rössler K, Buchfelder M, Hamer HM, Kobow K, Coras R, Blumcke I, Scheffer IE, Berkovic SF, Weale ME; UK Brain Expression Consortium, Delanty N, Depondt C, Cavalleri GL, Kunz WS, Sisodiya SM. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. Brain. 2013 Oct;136(Pt 10):3140-50.
9. Ramachandran N, Munteanu I, Wang P, Ruggieri A, Rilstone JJ, Israelian N, Naranian T, Paroutis P, Guo R, Ren ZP, Nishino I, Chabrol B, Pellissier JF, Minetti C, Udd B, Fardeau M, Tailor CS, Mahuran DJ, Kissel JT, Kalimo H, Levy N, Manolson MF, Ackerley CA, Minassian BA. VMA21 deficiency prevents vacuolar ATPase assembly and causes autophagic vacuolar myopathy. Acta Neuropathologica. 2013 Mar;125(3):439-57.
10. De Fusco M, Vago R, Striano P, Di Bonaventura C, Zara F, Mei D, Kim MS, Muallem S, Chen Y, Wang Q, Guerrini R, Casari G. The α_{2B} adrenergic receptor is mutant in cortical myoclonus and epilepsy. Ann Neurol. 2013 Oct 1. doi: 10.1002/ana.24028. [Epub ahead of print].

11. Suls A, Jaehn JA, Kecskés A, Weber Y, Weckhuysen S, Craiu DC, Siekierska A, Djémié T, Afrikanova T, Gormley P, von Spiczak S, Kluger G, Iliescu CM, Talvik T, Talvik I, Meral C, Caglayan HS, Giraldez BG, Serratosa J, Lemke JR, Hoffman-Zacharska D, Szczepanik E, Barisic N, Komarek V, Hjalgrim H, Møller RS, Linnankivi T, Dimova P, Striano P, Zara F, Marini C, Guerrini R, Depienne C, Baulac S, Kuhlenbäumer G, Crawford AD, Lehesjoki AE, de Witte PA, Palotie A, Lerche H, Esguerra CV, De Jonghe P, Helbig I; EuroEPINOMICS RES Consortium. De Novo Loss-of-Function Mutations in CHD2 Cause a Fever-Sensitive Myoclonic Epileptic Encephalopathy Sharing Features with Dravet Syndrome. Am J Hum Genet. 2013 Nov 7;93(5):967-75.

Translational centre of myology and neurodegenerative diseases

Director: Dr. Claudio Bruno

STAFF

Name	Position
Simona Baldassari	Biologist

RESULTS YEAR 2013

Research activity was carried out in the Laboratory di Muscular Pathology - Pediatric Neurology and Neuromuscular Disease unit (Prof. C. Minetti, Dr. F. Zara. Dr. E. Gazzerro) in collaboration with national and international centres.

We performed etiopathogenetic studies applied to the clinical practice to improve diagnosis and to provide accurate counselling and effective sociomedical care. In collaboration with national and international research centres, basic projects are ongoing aimed at the characterization of physiopathological mechanisms of muscular dystrophies and of some metabolic myopathies, based on the use of murine and zebrafish models.

In 2013, we developed i) outcome measures for patients with muscular dystrophy and spinal muscular atrophy, within national networks, ii) guidelines on safe anesthesia in the myopathic patient and on hyperCKemia, in collaboration with the Italian Association of Myology (AIM) and the ICU of the Istituto G. Gaslini.

Dr. Bruno is responsible for the projects of therapeutic trials for patients with muscular dystrophy and spinal muscular atrophy ("Multicentre, randomized, adaptive, double blind, placebo-controlled phase II study to evaluate the safety and efficacy of olesoxime (TRO19622) in patients with spinal muscular atrophy (SMA) aged between 3 and 35 years"; "Randomized, double blind, placebo-controlled. phase III clinical study on the use of tadalafil in Duchenne muscular dystrophy").

Dr. Bruno participates in national and international clinical networks in the field of neuromuscular and metabolic diseases. He is member of the European consortium "EUROMAC", a registry of patients with muscular glycogenosis (http://euromacregistry.eu/) and is partner of the Telethon project GSP13002: "Development of an Italian Clinical Network for Spinal Muscular Atrophy".

Main collaborations year 2013

- Dr. E. Bertini, Bambino Gesù hospital, Roma
- Prof. E. Mercuri, Cattolica University, A. Gemelli hospital, Roma
- Prof. E. Pegoraro, University of Padova, Padova
- Dr. F.M. Santorelli, Stella Maris Foundation, Pisa
- Dr. E. Zito, Mario Negri Institute, Milano
- Prof. S. DiMauro, Columbia University, New York (USA)
- Dr. F. Grassi, IRB, Bellinzona (SUI)
- Italian Association of Myology

PLANNED RESEARCH ACTIVITY YEAR 2014

Titolo: Study of the pathogenetic mechanisms of limb-girdle muscular dystrophy due to alpha-sarcoglycan deficiency (LGMD2A)

Objective: The project is aimed at analysing the role of extracellular ATP and of its activation pathway of purinergic receptors in the dystrophic process caused by alpha-sarcoglycan (a-SG) deficiency, responsible for a severe limb-girdle muscular dystrophy. In addition, the study will evaluate the therapeutic potential of the modulation of this signalling pathway through an antagonist of P2 purinergic receptor.

Description: Extracellular ATP (eATP), a molecule involved in the development of both adaptive and innate immune response, is released by cytosol of degenerating cells and, in an initial phase of the immune response, it contributes to the activation of antigen-presenting cells and of T lymphocytes, then facilitating immune response amplification.

Alpha-sarcoglycan (a-SG) presents a binding site for ATP in its extracellular portion and is characterized by ecto-ATPase activity allowing the control of eATP concentration on surface of cells expressing P2 receptors, thus reducing the amplitude and duration of the effect of this molecule.

The absence of a-SG and therefore the loss of ecto-ATPase activity on muscular sarcolemma could cause a persistent increase in eATP concentration, amplifying its effects and inducing intracellular calcium overload with ensuing death of myofibers.

We therefore hypothesize that purinergic/eATP pathway can be altered in muscular cells with a-SG deficiency and that signal inhibition using an antagonist of the purinergic receptor (oATO) can improve muscular tissue, decreasing inflammatory response and favouring the regeneration of the muscular fiber cell.

The study will be carried out on primary cell cultures of myoblasts from samples of skeletal muscle of patients and murine models with a-SG deficiency and the efficacy of an antagonist drug of P2 receptor (oATP) will be tested in an animal model of a-SG deficiency.

Our study will contribute to elucidate some pathogenetic aspects of muscular degeneration in LGMD2D and will facilitate the identification of a new therapeutic strategy aimed at improving muscular inflammation and calcium homeostasis in this disease.

External collaborations:

- Dr. F. Grassi, IRB, Bellinzona (SUI)

BEST PUBLICATIONS YEARS 2011-2013

1. Gazzerro E, Andreu AL, Bruno C. Neuromuscular disorder of Glycogen Metabolism. Curr Neurol Neurosci Rep 2013;13(3):333.
2. Garone C, Donati MA, Sacchini M, Garcia-Diaz B, Bruno C, Calvo S, Mootha V, Di Mauro S. Infantile mitochondrial encephalomyopathy due to a novel in ADAD9. JAMA Neurol 2013; 8:1-3.
3. Pappalardo A, Pitto L, Fiorillo C, Alice Donati M, Bruno C, Santorelli FM. Neuromuscular disorders in zebrafish: state of the art and future perspectives. Neuromolecular Med 2013;15(2):405-19.
4. Pane M, Messina S, Bruno C, D'Amico A, Villanova M, Brancalion B, Sivo S, Bianco F, Striano P, Battaglia D, Lettori D, Vita GL, Bertini E, Gualandi F, Ricotti V, Ferlini A, Mercuri E. Duchenne muscular dystrophy and epilepsy. Neuromuscul Disord 2013;23(4):313-5.
5. Tasca G, Moro F, Aiello C, Cassandrini D, Fiorillo C, Bertini E, Bruno C, Santorelli FM, Ricci E. Limb-Girdle Muscular Dystrophy with α-Dystroglycan Deficiency and Mutations in the ISPD gene. Neurology 2013;80(10):963-5.
6. Natali A, Gastaldelli A, Camastra S, Baldi S, Quagliarini F, Minicocci I, Bruno C, Pennisi E, Arca M. Metabolic consequences of adipose triglyceride lipase deficiency in humans: an in vivo study in patients with neutral lipid storage disease with myopathy. J Clin Endocrinol Metab 2013;98(9):E1540-8.

7. Fiorillo C, Brisca G, Cassandrini D, Scapolan S, Astrea G, Valle M, Scuderi F, Trucco F, Natali A, Magnano G, Gazzerro E, Minetti C, Arca M, Santorelli FM, Bruno C. Subclinical myopathy in a child with neutral lipid storage disease and mutations in the PNPLA2 gene. Biochem Biophys Res Commun 2013;430(1):241-4.
8. Erol I, Alehan F, Alkan O, Bruno C. Involvement of the globus pallidus in giant axonal neuropathy. Pediatr Neurol 2012;47(5):382-4.
9. Fiorillo C, Moro F, Brisca G, Astrea G, Nesti C, Bálint Z, Olschewski A, Meschini MC, Guelly C, Auer-Grumbach M, Battini R, Pedemonte M, Romano A, Menchise V, Biancheri R, Santorelli FM, Bruno C. TRPV4 mutations in children with congenital distal spinal muscular atrophy. Neurogenetics 2012;13(3):195-203.
10. Giribaldi G, Doria-Lamba L, Biancheri R, Severino M, Rossi A, Santorelli FM, Schiaffino C, Caruso U, Piemonte F, Bruno C. Intermittent-relapsing pyruvate dehydrogenase complex deficiency: a case with clinical, biochemical, and neuroradiological reversibility. Dev Med Child Neurol 2012;54(5):472-6.

Child neuropsychiatry

Director: Professor Edvige Veneselli

STAFF

Name	Position
Maria Giuseppina Baglietto	University researcher
Laura Doria-Lamba.	Physician
Roberta Biancheri	Physician
Fabia Brera	Physician
Maria Elena Celle	Physician
Maria Margherita Mancardi	Physician
Elisabetta Zanotto	Physician
Paola Lanteri	Physician
Daniela Paola Rossi	Physician
Margherita Savoini	Psychologist
Lucia Sciarretta	Psychologist
Francesca Maria Battaglia	Psychologist
Elisa De Grandis	Physician – University researcher
Maria Pintaudi	Physician
Marisol Mirabelli Badenier	Physician
Michela Stagnaro	Physician
Giulia Prato	Physician
Alessandra Ploderl	Psychologist

CLINICAL PSYCHOLOGY

Vincenza Lertora	Clinical psychologist
Enrico Giuffra	Clinical psychologist – researcher
Ezio Casari	Clinical psychologist
Francesca Burro	Psychologist

RESULTS YEAR 2013

Epilepsy: We evaluated the outcome of seizures correlated to lesionectomy in series of children with epilepsy and glioneural tumors; we studied epileptic encephalopathy with continuous spike-waves during slow sleep in a series of subjects with periventricular leukomalacia. We collaborated in the international study "Exon-disrupting deletions of NRXN1" in idiopathic generalized epilepsy.

Neuroimmunology: for anti-N-methyl-D-aspartate receptor encephalitis, new cases have been described to better define research and diagnostic processes and to optimize patient management and follow-up; we described the neuroradiological aspect as marker of activity in chronic demyelinating inflammatory polyradiculoneuropathy and its usefulness in the therapeutic programme. In 2013, we also organized the congress "'Inflammatory and immune-mediated diseases in child neuropsychiatry" (Genova, Nov. 8, .2013) with national and international faculty members and chairmen.

Posterior cranial fossa diseases: molecular analysis yielded innovative results in case series of Joubert syndrome and J.-like syndrome, congenital cerebellar hypoplasia with impairment of anterior spinal cord horns, Dandy-Walker malformation, and Wisconsin syndrome (for this syndrome, participation in an international cooperative study); these studies included the

retrospective and prospective analysis of clinical and neuroradiological data and the correlation with genetic data.
Autistic spectrum disorders: we are analysing biological, genetic, and electroclinical data in a large series of patients in order to evaluate their role in the pathogenesis and clinical phenotype; we described the observation of 2q24.3 interstitial deletion including SCN2A and SCN3A genes in a non-epileptic autistic subject.
ADHD: a study was carried out in collaboration with other regional reference centres in Italy for advances in patient diagnostic and therapeutic process.
Rare neurological diseases: we also continued studies with advances in the clinical, neuroradiological, and genetic definition as well as in the phenotype-genotype correlation of different forms, including some leucoencephalopathies as hypomyelination and congenital cataract, Alexander disease, Pelizaeus-Merzbacher-like disease spectrum, and some polydystrophies as infantile ceroidolipofuscinosis. The role of SLC2A1 gene mutation (GLUT1) in Italian cases of alternating hemiplegia was not confirmed. Clinical and neuroradiological aspects in Brown-Vialetto-Van Laere syndrome were described.

Main collaborations year 2013:

- Multiple sclerosis, dysimmune encephalitis, OMA, and other neuroimmunological disorders: A Vincent, Nuffield Department of Clinical Neurosciences-J Radcliffe Hospital Oxford, B Hero, University of Cologne;
- Epilepsy, tuberous sclerosis: DN Franz, Cincinnati Children's Hospital, USA;
- Leucoencephalopathies, Rett syndrome, Alternating Hemiplegia syndrome of infancy, other
- Rare Neurological diseases: O Boepsflug-Tanguy CHU Clermont-Ferrand, MS Van Der Knapp University Medical Center Amsterdam, A. Clarke Inst Medical Genetics University Hospital of Wales, B Ben Zeev Safra Ped. Hospital, Sheba Medical Center, Tel Hashomer, Ramat-Gan; MA MIkati Duke University, A Arzimanoglou CHU Lyon;
- ICP and other movement disorders: J Campistol, H Sant Joan de Déu Barcelona; Autism: G De Leo, Old Dominion University Norfolk, VA, USA.;
- Stress-induced post-traumatic disorders in developmental age: V Ardino, London School of Economics and Political Science;
- Somatoform and conduct disorders: Anna Freud Center, London.

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: New acquisitions in infantile neuropsychiatric diseases
Objective: Advances in the knowledge of clinical, neurophysiological, neuropsychological, and neuroradiological aspects in neuropsychiatric diseases in order to improve diagnostic procedures, management, treatment, and follow-up. In particular in genetic forms, improvement of characterization of phenotypes and genotype-phenotype correlation in order to reach also a better knowledge and identification of variants.
Description: We will continue the studies already started in 2013 concerning the following topics: *Epilepsies of developmental age*, in particular, study of patients operated for epileptogenic cortical lesions with minimum 2 years' follow-up; in parallel, genetic and electroclinical study of early epileptic encephalopathies; R*are neurological diseases,* with specific involvement in international studies on leucoencephalopathies, peripheral neuropathies, cerebellar disease, brain malformations, Rett syndrome, alternating hemiplegia;

Neuroimmunology diagnostic and therapeutic protocols in national and international network for multiple sclerosis and other demyelinating forms, immune-mediated encephalitis, Opsoclonus-myoclonus-ataxia, chronic demyelinating inflammatory polyradiculoneuropathy; *Complex disability and Infantile Cerebral Palsy*, in internal and national networks, with delineation or updating of diagnostic-therapeutic pathways in particular for intercurrent ictal manifestations, correlated to biological/psychological factors; *Autism:* analysis of biological, genetic, and electroclinical data aimed at excluding symptomatic forms with advanced techniques and at defining the biological contribution to the determination of the behavioural picture, and the correlation between clinical phenotype and neuropsychological profile; *Somatoform and conduct disorders;* evaluation of the role of attachment and emotional relationship.

Internal collaborations:

- *Epilepsies:* Laboratory of Neurogenetics and Neurosurgery unit;
- *Complex disabilities:* Physical Medicine and Rehabilitation unit and Orthopedics unit;
- *Rare Neurological Diseases:* Neuroradiology unit, Pediatric Neurology, Laboratory of Metabolic Diseases, Pediatric Clinic, Medical Genetics;
- *Neuroimmunology:* Pediatric Rheumatology unit, Hematology/Oncology unit, Laboratory of Molecular Biology.

External collaborations:

- *SM and other neuroimmunological disorders*: Neurologic Clinic AOUSM;
- *Epilepsy:* C Munari centre, Niguarda hospital, Milano, Lab. Genetics, Galliera hospital, Meyer Children's Hospital, Firenze, AIST;
- *Rare diseases*: Child Neuropsychiatry, Verona, Stella Maris Institute, Pisa, E. Bertini, Bambino Gesù hospital, Roma, San Paolo hospital, Milano, Medical Genetics, Gemelli hospital, Roma; AISEA, A Fragile X, AIR, Auxologic Institute, Milano, Child Neuropsychiatry and Medical Genetics, AOU Senese, Dept. Physiology and Biophyisics, Genova;
- *ICP and other movement disorders*: Besta Neurologic Institute, Milano;
- *Autism:* Robotics School, Genova;
- *Psychology -Psychiatry:* Psychiatric Clinic SPDC AOUSM, SISST Italian Society for the Study of Traumatic Stress, La Sapienza University, Roma, School of Educational Sciences, Genova, SS in Psychotherapy, Institute of Psychology and Cognitive-Behavioural Therapy, Genoese centre of Family Therapy, The Therapeutic Role of Genova; PsiBA Torino-Milano;
- *Neuropsychomotricity:* ANUPI, National Coordination CdS TNPEE, I N Mondino, Pavia.

BEST PUBLICATIONS YEARS 2011-2013

1. Biancheri R, Cassandrini D, Pinto F, Trovato R, Di Rocco M, Mirabelli-Badenier M, Pedemonte M, Panicucci C, Trucks H, Sander T, Zara F, Rossi A, Striano P, Minetti C, Santorelli FM. EXOSC3 mutations in isolated cerebellar hypoplasia and spinal anterior horn involvement. J Neurol. 2013 Apr 7.
2. Biancheri R, Rosano C, Denegri L, Lamantea E, Pinto F, Lanza F, Severino M, Filocamo M. Expanded spectrum of Pelizaeus-Merzbacher-like disease: literature revision and description of a novel GJC2 mutation in an unusually severe form. Eur J Hum Genet. 2013 Jan;21(1):34-9.

3. Celle ME, Cuoco C, Porta S, Gimelli G, Tassano E. Interstitial 2q24.3 deletion including SCN2A and SCN3A genes in a patient with autistic features, psychomotor delay, microcephaly and no history of seizures. Gene. 2013 Dec 15;532(2):294-6. doi: 10.1016. Epub 2013 Sep 28.
4. De Grandis E, Stagnaro M, Biancheri R, Giannotta M, Gobbi G, Traverso M, Veneselli E, Zara F. Lack of SLC2A1 (glucose transporter 1) mutations in 30 Italian patients with alternating hemiplegia of childhood. J Child Neurol. 2013 Jul;28(7):863-6. doi: 10.1177/0883073812452789. Epub 2012 Aug 16
5. Mirabelli-Badenier M, Morana G, Pinto F, Uccelli A, Veneselli E, Battaglia FM, Biancheri R, Baglietto MG, Vincent A, Mancardi MM. Anti-glutamic acid decarboxylase limbic encephalitis without epilepsy evolving into dementia with cerebellar ataxia. Arch Neurol - Chicago 2012;69(8):1964-1066.
6. Prato G, Mancardi MM, Baglietto MG, Janis S, Vercellino N, Rossi A, Consales A, Raso A, Garrè ML. Congenital Segmental Lymphedema in Tuberous Sclerosis Complex With Associated Subependymal Giant Cell Astrocytomas Treated with Mammalian Target of Rapamycin Inhibitors. J Child Neurol. 2013 Sep 20.
7. Heinzen EL, Swoboda KJ, Hitomi Y, Gurrieri F, Nicole S, de Vries B, Tiziano FD, Fontaine B, Walley NM, Heavin S, Panagiotakaki E; European Alternating Hemiplegia of Childhood (AHC) Genetics Consortium; Biobanca e Registro Clinico per l'Emiplegia Alternante (I.B.AHC) Consortium; European Network for Research on Alternating Hemiplegia (ENRAH) for Small and Medium-sized Enterpriese (SMEs) Consortium, Fiori S, Abiusi E, Di Pietro L, Sweney MT, Newcomb TM, Viollet L, Huff C, Jorde LB, Reyna SP, Murphy KJ, Shianna KV, Gumbs CE, Little L, Silver K, Ptáček LJ, Haan J, Ferrari MD, Bye AM, Herkes GK, Whitelaw CM, Webb D, Lynch BJ, Uldall P, King MD, Scheffer IE, Neri G, Arzimanoglou A, van den Maagdenberg AM, Sisodiya SM, Mikati MA, Goldstein DB. Nicole S, Gurrieri F, Neri G, de Vries B, Koelewijn S, Kamphorst J, Geilenkirchen M, Pelzer N, Laan L, Haan J, Ferrari M, van den Maagdenberg A, Zucca C, Bassi MT, Franchini F, Vavassori R, Giannotta M, Gobbi G, Granata T, Nardocci N, De Grandis E, Veneselli E, Stagnaro M, Gurrieri F, Neri G, Vigevano F, Panagiotakaki E, Oechsler C, Arzimanoglou A, Nicole S, Giannotta M, Gobbi G, Ninan M, Neville B, Ebinger F, Fons C, Campistol J, Kemlink D, Nevsimalova S, Laan L, Peeters-Scholte C, van den Maagdenberg A, Casaer P, Casari G, Sange G, Spiel G, Martinelli Boneschi F, Zucca C, Teresa Bassi M, Schyns T, Crawley F, Poncelin D, Vavassori R. De novo mutations in ATP1A3 cause alternating hemiplegia of childhood. Nat Genet 2012;44(9):1030-1033.
8. Santorelli FM, Garavaglia B, Cardona F, Nardocci N, Bernardina BD, Sartori S, Suppiej A, Bertini E, Claps D, Battini R, Biancheri R, Filocamo M, Pezzini F, Simonati A. Molecular epidemiology of childhood neuronal ceroid-lipofuscinosis in Italy. Orphanet J Rare Dis. 2013 Feb 2;8:19.
9. Ferraris A, Bernardini L, Sabolic Avramovska V, Zanni G, Loddo S, Sukarova-Angelovska E, Parisi V, Capalbo A, Tumini S, Travaglini L, Mancini F, Duma F, Barresi S, Novelli A, Mercuri E, Tarani L; Italian CBCD Study Group (Arrigoni F, Borgatti R, Romaniello R, Accorsi P, Fazzi E, Giordano L, Pinelli L, Biancheri R, Mirabelli Badenier M, Rossi A, Briguglio M, Tortorella G, Chiapparini L, D' Arrigo S, Moroni I, Pantaleoni C, Spaccini L, Uziel G, D' Amico A, Del Giudice E, Pichiecchio A, Signorini S, Battini R, Casarani M, Colafati S, Digilio MC, Leuzzi V, Micalizzi A, Romani M, Spalice A, Travaglini L, Vitiello G, Silengo M, Simonati A.) Bertini E, Dallapiccola B, Valente EM. Dandy-Walker malformation and Wisconsin syndrome: novel cases add further insight into the genotype-phenotype correlations of 3q23q25 deletions. Orphanet J Rare Dis. 2013 May 16;8:75.

10. Grillo E, Villard L, Clarke A, Ben Zeev B, Pineda M, Bahi-Buisson N, Hryniewiecka-Jaworska A, Bienvenu T, Armstrong J, Martinez AR, Mari F, Veneselli E, Russo S, Vignoli A, Pini G, Djuric M, Bisgaard AM, Mejaški Bošnjak V, Polgár N, Cogliati F, Ravn K, Pintaudi M, Melegh B, Craiu D, Djukic A, Renieri A. Rett networked database: an integrated clinical and genetic network of Rett syndrome databases. Hum Mutat 2012;33:1031-1036.

Physical medicine and rehabilitation

Director: Dr. Paolo Moretti

STAFF

Name	Position
Luca Doglio	Physician
Chiara Tacchino	Physician
Anna Ronchetti	Physician
Carla Guenza	Physical therapist
Isa Blanchi	Physical therapist
Paola Durand	Therapist of Childhood Neuro- and Psychomotricity
Carla Ferrari	Physical therapist
Antonietta Spanò	Physical therapist
Nicoletta Orsini	Physical therapist
Daniela Spina	Physical therapist
Roberta Mantero	Physical therapist
Ottavia Melluso	Physical therapist
Christian Savio	Physical therapist
Cinzia Scano	Physical therapist
Carlo Gaccioli	Physical therapist
Enrica Pastorino	Physical therapist
Carlotta Rossi	Speech therapist
Federica Defranchis	Psychologist
Ludovica Primavera	Psychologist
Valentina Lanzillotta	Physical therapist
Anna Provvidenti	Physical therapist
Riccarda Barbieri	Therapist of Childhood Neuro- and Psychomotricity
Federica Lencioni	Occupational therapist

RESULTS YEAR 2013

Pilot study on the efficacy of olesoxime and on tests, comparison of two types of corset in spinal neurogenic atrophy, and development and evaluation of outcome measures in Duchenne muscular dystrophy in collaboration with the Department of Pediatric Neurology of the Università Cattolica of Roma and the Neuromuscular and Neurodegenerative Disease unit of the Istituto G. Gaslini.

Launch of the project for the implantation and use of infusion pumps for the intrathecal administration of baclofene in patients with generalized spasticity in collaboration with the Neurosurgery unit of the Istituto Gaslini.

Study on therapy with perception of action by eye and ear in the rehabilitation of the paretic upper limb in children with infantile cerebral palsy in collaboration with the Italian Institute of Technology.

Study on instrumental analysis of preterm newborn movement in collaboration with the Neonatal Disease unit and the Neuroradiology unit of the Istituto G. Gaslini, the Italian Institute of Technology, and the University of Hiroshima.

Study of talocrural joint modelling with the instrumental analysis of movement in juvenile rheumatoid arthritis in collaboration with the Pediatric Rheumatology unit of the Istituto Gaslini and the Rehabilitation unit of the Bambin Gesù Hospital of Roma.

Main collaborations year 2013

- Italian Institute of Technology
- Department of Pediatric Neurology, Catholic University, Roma

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Action and movement analysis in the recovery from sensory-motor disability
Objective: Development of reliable and simple systems for action and movement analysis in order to improve the early identification of potentially disabling conditions and to plan and implement effective rehabilitation programmes.
Description: The presently available systems of movement analysis are complex and invasive, and can therefore be used to a limited extent in the clinical-rehabilitative practice. For this reason, we carried out a series of studies aimed at improving objective instruments able to support rehabilitation both in terms of early identification of disabling conditions and of support in the choice and implementation of rehabilitation treatment:

- Development of a simple and little invasive system of movement analysis in the newborn and in the small child to favour early rehabilitative intervention.
- Development of a protocol of movement analysis combined with MR examination for the study of ankle-foot complex in order to early identify bio-mechanical alterations in juvenile rheumatoid arthritis and start immediately rehabilitation treatment.
- Study on action perception in infantile cerebral palsy aimed at highlighting the activation of "mirror" system and at exploiting optimally the multisensorial component in order to favour the restoration of the function of the paretic upper limb.
- Development of interactive and movement-sensitive environments in order to favour, through direct feed-back, ecological recovery interventions in the disabled child.

Internal collaborations:

- Pediatric Rheumatology unit
- Neurosurgery unit
- Neonatal Disease unit
- Neuroradiology unit
- Radiology unit
- Child Neuropsychiatry unit
- Neuromuscular Disease unit

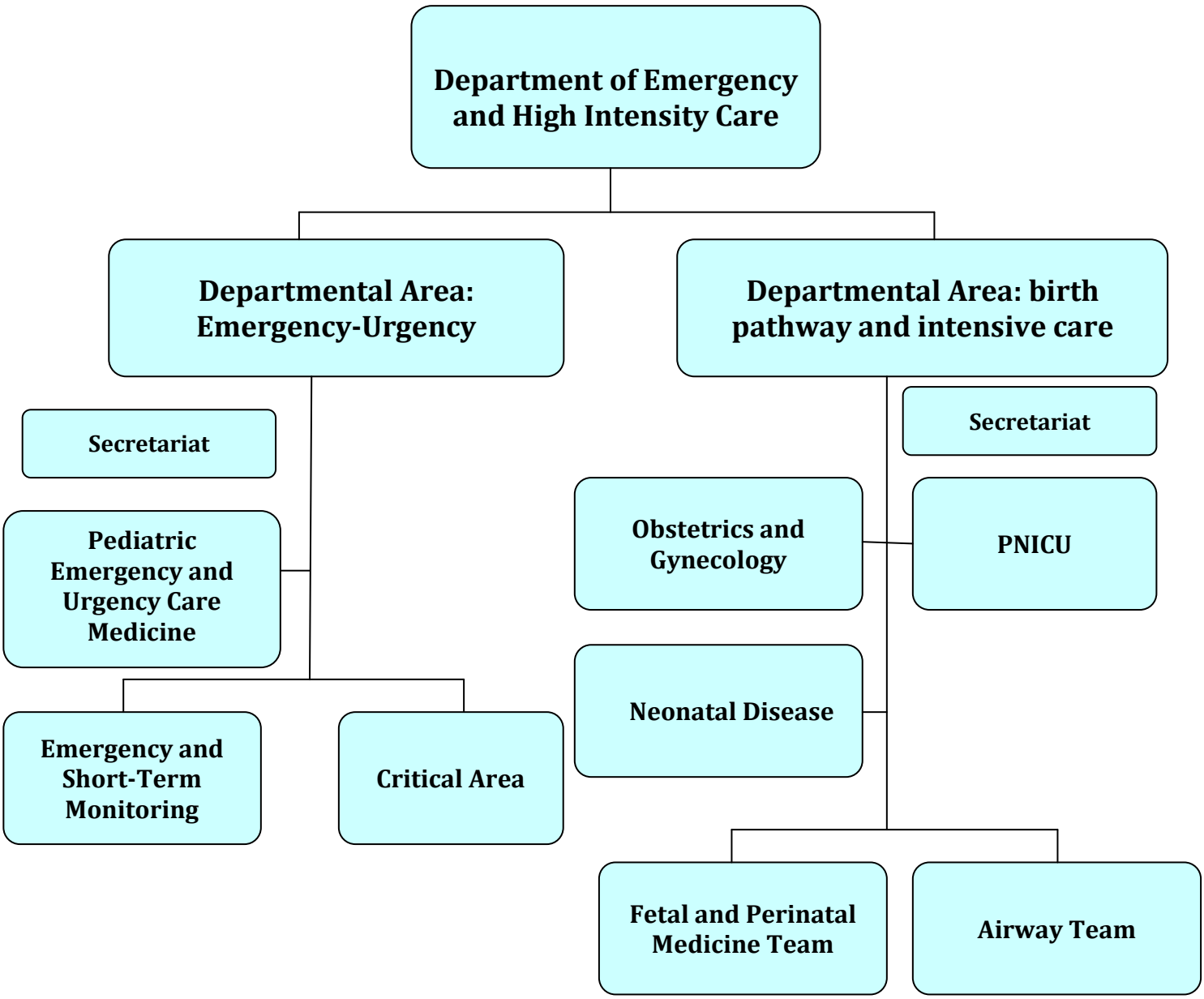
External collaborations:

- Italian Institute of Technology
- University of Hiroshima
- DIBRIS University of Genova
- Department of Pediatric Neurology, Università Cattolica, Roma
- Bambino Gesù Children's Hospital, Roma

BEST PUBLICATIONS YEARS 2011-2013

1. Mazzone ES, Pane M, Sormani MP, Scalise R, Berardinelli A, Messina S, Torrente Y, D'Amico A, Doglio L, Viggiano E, D'Ambrosio P, Cavallaro F, Frosini S, Bello L, Bonfiglio S, De Sanctis R, Rolle E, Bianco F, Magri F, Rossi F, Vasco G, Vita G, Motta MC, Donati MA, Sacchini M, Mongini T, Pini A, Battini R, Pegoraro E, Previtali S, Napolitano S, Bruno C,

2. Politano L, Comi GP, Bertini E, Mercuri E.Correction: 24 Month Longitudinal Data in Ambulant Boys with Duchenne Muscular Dystrophy. PLoS One. 2013 Nov 11;8(11). doi: 10.1371/annotation/cbe611fe-cda9-4d98-9574-0ac18e109daa.
3. Mazzone ES, Pane M, Sormani MP, Scalise R, Berardinelli A, Messina S, Torrente Y, D'Amico A, Doglio L, Viggiano E, D'Ambrosio P, Cavallaro F, Frosini S, Bello L, Bonfiglio S, De Sanctis R, Rolle E, Bianco F, Magri F, Rossi F, Vasco G, Vita G, Motta MC, Donati MA, Sacchini M, Mongini T, Pini A, Battini R, Pegoraro E, Previtali S, Napolitano S, Bruno C, Politano L, Comi GP, Bertini E, Mercuri E. 24 month longitudinal data in ambulant boys with Duchenne muscular dystrophy. PLoS One. 2013;8(1):e52512. doi: 10.1371/journal.pone.0052512. Epub 2013 Jan 11.
4. Doglio L, Pavan E, Pernigotti I, Petralia P, Frigo C, Minetti C. 2011 Dec;47(4):587-94. Epub 2011 Sep 13. Early signs of gait deviation in Duchenne muscular dystrophy. Eur J Phys Rehabil Med.
5. Mazzone E, Vasco G, Sormani MP, Torrente Y, Berardinelli A, Messina S, D'Amico A, Doglio L, Politano L, Cavallaro F, Frosini S, Bello L, Bonfiglio S, Zucchini E, De Sanctis R, Scutifero M, Bianco F, Rossi F, Motta MC, Sacco A, Donati MA, Mongini T, Pini A, Battini R, Pegoraro E, Pane M, Gasperini S, Previtali S, Napolitano S, Martinelli D, Bruno C, Vita G, Comi G, Bertini E, Mercuri E. Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study. Neurology. 2011 Jul 19;77(3):250-6. doi: 10.1212/WNL.0b013e318225ab2e. Epub 2011 Jul 6.


Department of Emergency and High Intensity Care
Departmental Area: Emergency-Urgency
Departmental Area: birth pathway and intensive care
Secretariat
Pediatric Emergency and Urgency Care Medicine
Emergency and Short-Term Monitoring
Critical Area
Secretariat
Obstetrics and Gynecology
PNICU
Neonatal Disease
Fetal and Perinatal Medicine Team
Airway Team

Pediatric Emergency and Urgency Care Medicine

Director: Professor Pasquale Di Pietro

STAFF

Name	Position
Emanuela Piccotti	Physician
Salvatore Renna	Physician
Ornella Bellagamba	Physician
Simona Costabel	Physician
Maria Cristina Diana	Physician
Silvia Fontanazza	Physician
Carla Debbia	Physician
Piero Gianiorio	Physician
Ilaria Negro	Physician
Antonella Palmieri	Physician
Daniela Pirlo	Physician
Barbara Tubino	Physician
Marta Vandone	Physician
Giovanna Villa	Physician
Donatella Passalaqua	Nurse
Marta Costa	Nurse

RESULTS YEAR 2013

The Pediatric Emergency/Urgency unit represents a privileged observatory of complex or particular clinical cases, deserving to be reported in the literature, such as a recent case of neonatal encephalitis due to Parechovirus (HPeVs: a new family of neurotropic viruses able to cause CNS infections in the neonatal period similar to meningoencephalitides due to enterovirus) with favourable outcome. HPeVs infection is generally associated with mild respiratory or gastroenteric symptoms and the association with severe diseases, such as flaccid paralysis and encephalitis/encephalomyelitis, has been described only recently in the literature (largest case series: 10 cases of HPeVs encephalitis reported in a Dutch paper).

Main collaborations year 2013:

- Children's Hospital of Boston for 1) pain sedation and management in the Department of Emergency (ED); 2) organizational aspects in ED and Trauma Center; 3) nutrition in the critical patient; 4) teleconference programmes in pediatric intensive care
- Institute of Pathologic Anatomy and Legal Medicine of Genova, ASR and Health Department and Social Services, Regione Liguria (SIDS)
- Dept. of Genetics, Istituto Gaslini, Neonatology unit, Meyer hospital (FI), Pediatric Clinic (VA), SIDS center, Sant'Anna hospital (TO), Dept. of Genetics (PR), Pneumology unit, Bambino Gesù children's hospital (RM) (ALTE-SIDS)
- Advanced Pediatric Simulation Project in collaboration with the State University of Moscow and La Sapienza University of Rome on training based on simulation
- MAREA Project Multicenter Study – Monitoring of antibiotic safety in children with bronchopneumonia, pharyngotonsillitis, and acute otitis media of Regione Liguria – Pharmacovigilance in Pediatrics, Regione Liguria

- SINIACA (system of collection of epidemiologic data on home accidents) and DATIS (system of collection of epidemiologic data on road accidents), both in collaboration with ISS and the Ministry of Health – national multicenter groups
- JAMIE: system of collection of epidemiologic data on all accidents (traumas, intoxication, violence) in collaboration with ISS and Ministry of Health – European multicentre group
- PERN Study-Toxic surveillance international study – intercontinental multicentre group
- Urgency Medicine, Toronto hospital for Patient Family Center Care

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: evaluation of the efficacy of communication in the prevention of SIDS - Regione Liguria
Objective: observation, prevention, care, and management of SIDS events as well as care for patients with ALTE are part of the activity of a Regional Centre that Regione Liguria has assigned to the Emergency Department of Gaslini. To this end, the project is aimed at overviewing the present state of communication for prevention in Liguria, starting first from Genoa city.
Description: this objective is part of the monitoring activity of the Regional Centre on Sudden Infant Death Syndrome – Apparent Life Threatening Event (SIDS-ALTE), which also functions as epidemiologic observatory. The project includes the creation of an ad hoc questionnaire for the evaluation of efficacy of the SIDS prevention campaign in the Genoese population.
A subsequent step will be represented by planning of an improvement project of the education/information network.

External collaborations:
Family pediatricians, counseling, Italian Sociey of Neonatology.

BEST PUBLICATIONS YEARS 2011-2013

1. S. Renna, L. Bergamino, D. Pirlo, A. Rossi, M. Furione, A. Piralla, M. Mascaretti, E. Cristina, M.G. Marazzi, P. Di Pietro. "A case of neonatal human parechovirus encephalitis with a favourable outcome" Brain Dev. 2013 Jan 21. pii: S0387-7604(12)00322-1. doi: 10.1016/j.braindev.2012.12.006. [Epub ahead of print]
2. Chiappini E, Principi N, Mansi N, Serra A, Masi S, Camaioni A, Esposito S, Felisati G, Galli L, Landi M, Speciale AM, Bonsignori F, Marchisio P, de Martino M, Italian Panel on the Management of Pharygitis in Children (ancknowledgments: Di Pietro P). "Management of acute pharyngitis in children: summary of the Italian National Institute of Health guidelines". Clin Ther. 2012 Jun; 34(6): 1442-1458.e2.
3. De Florentiis D, Parodi V, Orsi A, Rossi A, Altomonte F, Canepa P, Ceravolo A, Valle L, Zancolli M, Piccotti E, Renna S, Macrina G, Martini M, Durando P, Padrone D, Moscatelli P, Orengo G, Icardi G, Ansaldi F. "Impact of influenza during the post-pandemic season: epidemiological picture from syndromic and virological surveillance." J Prev Med Hyg. 2011 Sep;52(3):134-6.
4. Ascone G., Bacigalupo A., Corsello G., Dallapiccola B., Di Pietro P., Fava A., et al. Quaderni del Ministero della Salute "Promozione e tutela della salute del bambino e dell'adolescente: criteri di appropriatezza clinica, tecnologica e strutturale" ISS n. 16 luglio-agosto 2012
5. Panatto D, Amicizia D, Giacchino R, Tacchella A, Natalizia AR, Melioli G, Bandettini R, Di Pietro P, Diana MC, Gasparini R. "Burden of rotavirus infections in Liguria, northern Italy: hospitalisation and potential saving by vaccination". Eur J Clin Microbiol Infect Dis 2011 Aug; 30(8): 957-64.

6. Italian Multicenter Study Group and Vaccine Safety in Children (Di Pietro P. Renna S.). “Effectiveness and safety of the A-H1N1 vaccine in children: a hospital-based case-control study”.
7. Ansaldi F, de Florentis D, Canepa P, Bandettini R, Diana MC, Martini M, Durando P, Icardi G. “Epidemiological changes after PCV7 implementation in Italy. Perspective for new vaccines”. Hum Vaccin. 2011 Jan-Feb; 7 Suppl: 7: 211-6. Review.

Urgency Medicine Critical Area

Director: Dr. Salvatore Renna

STAFF

Name	Position
Emanuela Piccotti	Physician
Ornella Bellagamba	Physician
Simona Costabel	Physician
Maria Cristina Diana	Physician
Silvia Fontanazza	Physician
Carla Debbia	Physician
Piero Gianiorio	Physician
Ilaria Negro	Physician
Antonella Palmieri	Physician
Daniela Pirlo	Physician
Barbara Tubino	Physician
Marta Vandone	Physician
Giovanna Villa	Physician
Donatella Passalaqua	Nurse

RESULTS YEAR 2013

Within the framework of multicentre studies, we published the results of research on complications affecting the upper gastrointestinal tract (UGIC: Upper GastroIntestinal Complications) following the use of drugs in pediatric age, on Stevens-Johnson syndrome (SJS) associated with the use of medications and vaccines (The Italian Multicenter Study Group for Drug and Vaccine Safety in Children), and on the use of off-label antiemetic drugs (ondansetron) in the treatment of gastroenteritis (in collaboration with the Pharmacology unit of Burlo Garofalo Institute of Trieste).
The correlation between chronic use of FANS and bleeding of the gastrointerstinal tract is well-known: in the study funded by AIFA, in any case, the mean duration of the use of ibuprofen was 4 days, so that it was possible to document that UGIC can occur even after short-term therapy in pediatric age. In addition, the lower gastrotoxicity of paracetamol (the most largely used medication in the Italian pediatric population) compared to the other NSAIDs was also confirmed.

Twenty-nine children with diagnosis of SJS and 1362 with neurological problems were admitted between November 1, 1999 and October 31, 2012 in 9 of the main Italian children's hospitals: antiepileptic drugs were the medications with higher OR (Odds Ratio: 26.8%), for antibiotics, OR resulted 3.3%, even though the limited power of the study did not make it possible to establish differences among the main 3 classes (penicillins, cephalosporins, and macrolides), for the other medications, a statistically significant higher risk was observed for paracetamol and corticosteroids, with OR between 3.2 and 4.2. No increased risk was observed after the use of vaccines.
The study on the use of antiemetic drugs in pediatric age, carried out in the Emergency Departments of 8 main Italian cities, showed in at least 30% the use of off-label medications (the only antiemetic that can be used is domperidone, since both metoclopramide and ondansetron result off-label for age range and indications for use).

In agreement with the law in force, off-label medications should be prescribed only in the presence of predominant potential beneficial effects compared to potential toxic effects, with consequent legal risk for the prescribing physician in case of onset of side effects and compulsory informed consent by the family. Hence, the need to start clinical trials and/or retrospective studies able to define the appropriate use of off-label antiemetic drugs.

Main collaborations year 2013:

- Italian Multicenter Study Group for Drug and Vaccine Safety in Children, funded by AIFA (Italian Drug Agency) for multicentre studies on the safety of medications in pediatrics and pharmacovigilance
- Multidisciplinary Working Group on Noninvasive Ventilation
- Italian Group for Italian Registry of Infantile Thrombosis (GIRTI)

PLANNED RESEARCH ACTIVITY IN 2014

Title: Stroke in pediatric age
Objective: the peculiarity of stroke in pediatric age requires an accurate observation of the phenomenon and the awareness that, though rare, this disease needs a multidisciplinary and synergic approach by different professionals with proved experience in the treatment of pediatric patients. Primary objective is the evaluation of the incidence in the regional pediatric population and the identification of ranges at risk.
Description: besides data collection (creation of a regional epidemiologic observatory interacting with the Italian Registry of Infantile Thrombosis), the project is aimed at reviewing protocols for emergency-urgency management of stroke starting from the territory until possible transfer to the reference centre, in consideration of the opportunity of clinical management in the different pediatric facilities in the Liguria region.
Training courses on stroke in pediatric age (e.g. "Stroke in età pediatria", a course organized in 2013 with the support of AINR – SIN – SIP - SIMEUP) and in depth studies with experts are aimed at creating synergic and homogeneous behaviour in emergency-urgency with the creation of a regional network with the Emergency/Urgency Department of Gaslini as reference centre.

Internal collaborations:

Hemorrhagic Disease Centre

External collaborations:

- Hemophilia Regional Centre
- Family doctors and family pediatricians
- 118 Emergency Call Service – Liguria region
- Italian Group of Italian Registry of Infantile Thrombosis (GIRTI)

BEST PUBLICATIONS YEARS 2011-2013

1. Zanon D, Gallelli L, Rovere F, Paparazzo R, Maximova N, Lazzerini M, Reale A, Corsetti T, Renna S, Emanueli T, Mannelli F, Manteghetti F, Da Dalt L, Palleria C, Banchieri N, Urbino A, Miglietta M, Cardoni G, Pompilio A, Arrighini A, Lazzari C, Messi G ."Off-label prescribing patterns of antiemetics in children: a multicenter study in Italy". Eur J Pediatr. 2013; 172: 361-367.
2. M. Bianciotto, E. Chiappini, I. Raffaldi, C. Gabiano, PA. Tovo, S. Sollai, M. de Martino, F. Mannelli, V. Tipo, R. Da Cas, G. Traversa, F. Menniti-Ippolito, and the Italian Multicenter

Study Group for Drug and Vaccine Safety in Children. “Drug use and upper gastrointestinal complications in children: a case–control study” Arch Dis Child 2013; 98:218–221.

3. Raucci U, Rossi R, Da Cas R, Rafaniello C, Mores N, Bersani G, Reale A, Pirozzi N, Menniti-Ippolito F, Traversa G, Italian Multicenter Study Group For Vaccine Safety In Drug and Children. “Stevens-Johnson syndrome associated with drugs and vaccines in children: a case-control study”. PLOS One. 2013 Jul 16;8(7):e68231.

Emergency Room and Short-Term Monitoring

Director: Dr. Emanuela Piccotti

STAFF

Name	Position
Pasquale Di Pietro	Physician – Director
Salvatore Renna	Physician
Ornella Bellagamba	Physician
Simona Costabel	Physician
Maria Cristina Diana	Physician
Silvia Fontanazza	Physician
Carla Debbia	Physician
Piero Gianiorio	Physician
Ilaria Negro	Physician
Antonella Palmieri	Physician
Daniela Pirlo	Physician
Barbara Tubino	Physician
Marta Vandone	Physician
Giovanna Villa	Physician
Marta Costa	Nurse

RESULTS YEAR 2013

Particular attention was paid to the identification and correction of communication modalities between health care professionals of the Emergency Room and of the Urgency Medicine section. The process of patient's admission and management in the ER was divided into 5 phases: patient's arrival; definition of patient and family needs; patient's traceability; patient's transfer; patient's discharge. In a prospective study carried out from April 2008 to May 2009 in our ER involving 43 physicians and nurses and analysing 400 documents related to communications, the higher risks for frequency and possibility of causing damage resulted correlated to communication problems at the moment of patient's transfer or discharge. Mean RPN (Risk Priority Number) was 182 (values > 100 are considered significant for the implementation of corrective actions).

Child pain assessment and treatment in ER were neglected for too long. A questionnaire sent to 14 Italian Mother and Child hospitals and to 5 general hospitals with pediatric emergency sections showed that routine pain assessment at triage or in patient examination room is performed only in 26% of interviewed centres. About 1/3 do not use algometric scales and about 1/2 (47,4%) do not have local protocols for pain treatment. Only in 3 centres pain is reassessed after treatment and EMLA is used in 2. All interviewed centres allow the presence of parents during painful procedures, in 11 (57,9%) parents are allowed to hold the child in their arms during blood sampling. Mother and Child hospitals of northern Italy, that have a medical-surgical-traumatologic Emergency Department with short-term monitoring and round-the-clock triage resulted more able to report adequate measures of pain management both at triage and in patient examination room. To sum up, notwithstanding the availability of national and international guidelines, pain management is suboptimal in Italian Emergency departments. Multiple strategies, such as the development of local policies, educational programmes, and involvement of families in pain management should be implemented.

Main collaborations year 2013

- Multidisciplinary Working Group on Ill-Treatment and Abuse – Childhood Protection Project (Regina Margherita Children's Hospital (TO), Department of Health and Social Services - Regione Liguria, Direction of Social Policies – Municipality of Genoa)
- Multidisciplinary Working Group on Ill-Treatment and Abuse – Boston Children's Hospital
- Gaslini's Pain-Free Hospital group - PIPER (Pain in Pediatric Emergency Room) group

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: Multicentre project on abusive head trauma

Objective: identification of indicators of "non accidental event" for cranial lesions of the child aged < 2 years : retrospective study on admissions to pediatric ER for cranial trauma, with use of database for data collection on diagnostic pathway and possible neurosurgery. Analysis and statistical analysis of data. Preparation of a common diagnostic protocol.

Description: In USA, abuse is the third main cause of all cranial lesions (Bishop 2006).

The estimated incidence of abusive head trauma varies, but the range is between 20 and 30 cases per 100,000 children under 1 year of age (Keenan 2003, Leventhal 2008)

The estimated percentage of fatal cases for abusive head trauma is about 20% with significant outcome for about 2/3 of survivors (Dubraine 2008 e 2009).

Objective of the study is to collect significant Italian data, to identify indicators of "non accidental event" for cranial lesions of the small child, to standardize the diagnostic protocol

Essenzial references:

- Head Injury: triage, assessment, investigation and early management of head injury in infants, children and adults. National Collaborating Centre for Acute Care at The Royal College of Surgeons of England, 2007
- Multidisciplinary Guidelines on the identification, investigation and management of Suspected Abusive Head Trauma. Canadian Paediatric Society, 2012

Internal collaborations:

- Surgery unit
- Neurosurgery unit
- ICU

External collaborations:

- Italian pediatric ER/ED (including pediatric Neurosurgery with Neuroradiology, PICU)
- Children's Hospital of Boston

BEST PUBLICATIONS YEARS 2011-2013

1. Bagnasco A, Tubino B, Piccotti E, Rosa F, Aleo G, Di Pietro P, Sasso L, Donatella Passalacqua, Laura Gambino and all the nursing and medical staff of the Emergency and Urgency Department of the IRCCS Giannina Gaslini in Genova, Italy. "Identifying and correcting communication failures among health professionals working in the Emergency Department" Int Emerg Nurs (21) 2013:168-72.
2. Ferrante P, Cuttini M, Zangardi T, Tomasello C, Messi G, Pirozzi N, Losacco V, Piga S, Bernini F, for the PIPER Study Group. "Pain management policies and practices in pediatric emergency care: a nationwide survey of Italian hospitals". BMC Pediatrics 2013, 13: 139.

Obstetrics and Gynecology

Director: Professor Giorgio Bentivoglio

STAFF

Name	Position
Pierangela De Biasio	Physician
Marco Adriano	Physician
Irina Bruzzone	Physician
Davide Buffi	Physician
Massimo Foglia	Physician
Gianmario Ginocchio	Physician
Daniela Pastorino	Physician
Patrizia Ponte	Physician
Marco Tiesi	Physician
Emanuele Raviola	Physician
Giuseppe Vincelli	Physician
Giuseppe Villa	Physician
Rita Paoletti	Physician

RESULTS YEAR 2013

Besides the collaboration in the field of infectious diseases and immunology (see publications), we continue the thirty-year clinical-scientific research on early and prenatal diagnostics and on the identification and therapy of fetal diseases.

Main collaborations year 2013:

- Medical Genetics – Gaslini
- Hematology/Oncology – Gaslini
- Neonatal Disease – Gaslini
- Infectious Disease Clinic – S.Martino hospital
- HIV – European Coll. Study

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: IMPLANTATION, DEVELOPMENT AND ADAPTATION OF PLACENTA IN THE THIRD TRIMESTER
Objective: Definition of the role of extravillous trophoblast proliferation at the implantation site and characterization of the morphology of small-caliber placental vessel wall. Characterization of trophoblast populations involved in mechanisms of cell replication of proliferating villi. Correlation of normal and pathological morphological and phenotypical pictures with clinical and evolutive pictures of very premature newborns (< 32° GW).
Description: This translational research is aimed at studying extravillous trophoblast (EVT) and at understanding the physiopathological mechanisms underlying the implant, which depends on EVT ability to grow and invade the decidua. Thus, the study of EVT is focused on the evaluation of proliferation indexes and growth factors. Another aspect concerns the properties of trophoblastic cells and the ability to proliferate as isolated cells infiltrating decidual or myometral tissues, dissociating vessel coats with progressive substitution mechanism, or taking the place of their endothelium. Cell adhesion mechanisms are important for understanding this mechanism.

A second branch of this research is focused on the characteristics of the villous tree: 1) evaluation of villous proliferation and state of maturity, identification and immunohistochemical characterization of focal proliferating immature villi; 2) evaluation of morphofunctional characteristics of placental vessels and, in particular, leiomuscular components of vessel walls, especially in pathological or adaptive conditions in intermediate and terminal villi; 3) evaluation of placental phenotype, potentially variabile for mosacism phenomena.

Internal collaborations:

- Pathologic Anatomy unit
- Neonatal Disease unit
- Medical Genetics unit
- Laboratory of Cytogenetics
- Hematology/Oncology unit

External collaborations:

- Infectious Disease Clinic – S. Martino-IST hospital, Genova
- HIV – European Coll. Study

BEST SCIENTIFIC PUBLICATIONS YEARS 2011-2013

1. Aebi-Popp K, Mulcahy F, Glass TR, Rudin C, Martinez de Tejada B, Bertisch B, Fehr J, Grawe C, Scheibner K, Rickenbach M, Hoesli I, Thorne C; European Collaborative Study in EuroCoord; Swiss Mother & Child HIV Cohort Study: Thorne C, Bailey H, Giaquinto C, Rampon O, Mazza A, De Rossi A, Wörner I, Mok J, de José MI, Martínez B, Peña J, Garcia J, Lopez JR, Rodriguez MC, Asensi-Botet F, Otero MC, Pérez-Tamarit D, Scherpbier HJ, Kreyenbroek M, Godfried MH, Nellen FJ, Boer K, Navér L, Bohlin AB, Lindgren S, Kaldma A, Belfrage E, Levy J, Barlow P, Manigart Y, Hainaut M, Goetghebuer T, Brichard B, De Camps J, Thiry N, Deboone G, Waterloos H, Viscoli C, De Maria A, Bentivoglio G, Ferrero S, Gotta C, Mûr A, Payà A, López-Vilchez MA, Carreras R, Valerius NH, Rosenfeldt V, Coll O, Suy A, Perez J, Fortuny C, Boguña J, Savasi V, Fiore S, Crivelli M, Viganò A, Giacomet V, Cerini C, Raimondi C, Zuccotti G, Alberico S, Maso G, Tropea M, Barresi V, Taylor G, Lyall EG, Penn Z, Buffolano W, Tiseo R, Martinelli P, Sansone M, Maruotti G, Agangi A, Tibaldi C, Marini S, Masuelli G, Benedetto C, Niemieç T, Marczynska M, Dobosz S, Popielska J, Oldakowska A, Aubert V, Barth J, Battegay M, Bernasconi E, Böni J, Brazzola P, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Cheseaux JJ, Drack G, Duppenthaler A, Egger M, Elzi L, Fehr J, Fellay J, Francini K, Furrer H, Fux CA, Gorgievski M, Grawe C, Günthard H, Haerry D, Hasse B, Hirsch HH, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kovari H, Ledergerber B, Martinetti G, de Tejada B, Metzner K, Müller N, Nadal D, Pantaleo G, Polli Ch, Posfay-Barbe K, Rauch A, Regenass S, Rickenbach M, Rudin C, Schmid P, Scheibner K, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Taffé P, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Wyler CA, Yerly S. Missed opportunities among HIV-positive women to control viral replication during pregnancy and to have a vaginal delivery. J Acquir immune Defic Syndr. 2013 Sep 1;64(1):58-65.doi: 10.1097/QAI.0b0!3e3182a334e3.

2. Bailey H, Townsend CL, Cortina-Borja M, Thorne C; European Collaborative Study in EuroCoord: Giaquinto C, Rampon O, Mazza A, De Rossi A, Grosch Wörner I, Mok J, de José MI, Larrú Martínez B, Peña JM, Gonzalez Garcia J, Arribas Lopez JR, Garcia Rodriguez MC, Asensi-Botet F, Otero MC, Pérez-Tamarit D, Scherpbier HJ, Kreyenbroek M, Godfried MH, Nellen FJ, Boer K, Navér L, Bohlin AB, Lindgren S, Kaldma A, Belfrage E, Levy J, Barlow P, Manigart Y, Hainaut M, Goetghebuer T, Brichard B, De Camps J, Thiry N, Deboone G, Waterloos H, Viscoli C, De Maria A, Bentivoglio G, Ferrero S, Gotta C, Mûr A, Payà A, López-Vilchez MA, Carreras R, Valerius H, Rosenfeldt V, Coll C, Suy A, Perez JM, Fortuny C, Boguña J, Savasi V, Fiore S, Crivelli M, Viganò A, Giacomet V, Cerini C, Raimondi C, Zuccotti G, Alberico S, Maso G, Airoud N, Taylor GP, Lyall EG, Penn Z, Buffolano W, Tiseo R, Martinelli P, Sansone M, Maruotti G, Agangi A, Tibaldi C, Marini S, Masuelli G, Benedetto C, Niemieç T, Marczynska M, Dobosz S, Popielska J, Oldakowska A. Improvements in virological control among women conceiving on combination antiretroviral therapy in Western Europe AIDS 2013 Sep 10;27(14):2312-5.doi: 10.1097/qad.0b013e32883678e4.
3. Lotta LA, Wu HM, Cairo A, Bentivoglio G, Peyvandi F. Drop of residual plasmatic activity of ADAMTS13 to undetectable levels during acute disease in a patient with adult-onset congenital thrombotic thrombocytopenic purpura. Blood Cells Mol Dis. 2013 Jan;50(1):59-60.doi: 10.1016/j.bcmd.2012.08.001. Epub 2012 Sep 11.No abstract available.
4. Lambert-Messerlian G, Kloza EM, Williams J 3rd, Loucky J, O'Brien B, Wilkins-Haug L, Mahoney MJ, De Biasio P, Borrell A, Ehrich M, van den Boom D, Bombard AT, Deciu C, Palomaki GE. Maternal plasma DNA testing for aneuploidy in pregnancies achieved by assisted reproductive technologies. Genetics in Medicine 2013 Oct 3. doi: 10.1038/gim.2013.149.
5. Morotti M[1], Podestà S, Musizzano Y, Venturini PL, Bentivoglio G, Fulcheri E, Ferrero S. Defective placental adhesion in voluntary termination of second-trimester pregnancy and risk of recurrence in subsequent pregnancies. J Matern Fetal Neonatal Med. 2012 Apr;25(4):339-42. doi: 10.3109/14767058.2011.576722. Epub 2011 May 24.
6. Marras F, Bozzano F, Bentivoglio G, Ugolotti E, Biassoni R, Moretta L, De Maria A. Receptor modulation and functional activation of human CD34+ Lin- -derived immature NK cells in vitro by Mycobacterium bovis Bacillus Calmette-Guerin (BCG). Eur J Immunol. 2012 Sep;42(9):2459-70. doi: 10.1002/eji.201242375. Epub 2012 Jul 25
7. De Marco P, Merello E, Calevo MG, Mascelli S, Pastorino D, Crocetti L, De Biasio P, Piatelli G, Cama A, Capra V. Maternal periconceptional factors affect the risk of spina bifida-affected pregnancies: an Italian case-control study. 1. Childs Nerv Syst. 2011 Jul;27(7):1073-81. doi: 10.1007/s00381-010-1372-y. Epub 2011 Jan 5.

Neonatal and Pediatric Intensive Care

Director: Dr. Pietro Tuo

STAFF

Name	Position
Nicola Disma	Physician
Giovanni Montobbio	Physician
Leila Mameli	Physician
Victoria Bosio	Physician
Clelia Zanaboni	Physician
Gabriele De Tonetti	Physician
Claudia Grattarola	Physician
Silvia De Benedetto	Physician
Mirta Della Rocca	Physician
Caterina Forcheri	Physician
Lara Petrucci	Physician
Enrica Zamorani	Physician
Francesca Catani	Physician
Chiara Balzarini	Physician
Svetlana Kotzeva	Physician
Miriam Tumolo	Physician
Elisabetta Lampugnani	Physician
Franco Puncuh	Physician
Gabriella Bottari	Physician
Alessandro Simonini	Physician
Alessia Franceschi	Physician
Sara Frontalini	Physician
Silvia Buratti	Physician
Andrea Moscatelli	Physician
Franco Lerzo	Physician
Francesco Grasso	Physician
Andrea Dato	Physician
Gaia Giribaldi	Physician
Daniela Tronconi	Nurse
Daniela Spennato	Nurse

RESULTS YEAR 2013

"Multi-site RCT comparing regional and general anaesthesia for effects on neurodevelopmental outcome in infants - The GAS study" (Ricerca finalizzata 167/GR-2009-1476067). Randomized, controlled, prospective, open, multicentre international study. Patients below 60 weeks of postconceptional age, scheduled for surgery for inguinal hernia, were randomized into two arms of the study to receive general anesthesia with sevoflurane or regional anesthesia without sedatives. Patients receive follow-up at 2 and 5 years of age to evaluate whether the different anesthesias result in the same neurocognitive development. Neurocognitive follow-up at 2 years of correct age was performed by means of pediatric examination, Bayley scale and McArthur test. Neurocognitive follow-up at 5 years of chronological age includes the following: pediatric examination, WPPSI-III Full Scale IQ (FSIQ), NEPSY-II Selected Subtests,

WIAT-II Screening Test, BRIEF-P Parent Questionnaire, ABAS Parent Questionnaire, CBCL Caregiver Questionnaire. On January 31, 2013, the sample included 722 patients from 28 participating centres. 167 patients were recruited in the three Italian centres (Genova: 81; Bergamo: 38; Milano: 48), with a final contribution of 23%. Data on the incidence of post-anesthesia apnea and postsurgical outcome are being analysed and will be available for publication by the end of 2013.

Main collaborations year 2013

- Murdoch Research Children's Institute & Dept of Anesthesia and Pain Management Royal Melbourne Children's Hospital, Melbourne, Australia.
- Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital & Harvard Medical School, Boston, MA, USA.
- Paediatric Anaesthesia Unit, Geneva Children's Hospital, University Hospitals of Geneva, Switzerland.

PLANNED RESEARCH ACTIVITY YEAR 2014

Title: PK/PD and pharmacogenomics of tranexamic acid in pediatric craniostenosis.
Objective: Determination of clinical efficacy in reducing bleeding during surgical correction of craniostenosis in pediatric age by comparison of low and high doses of tranexamic acid (TXA); determination of pharmacokinetic curve for TXA. Determination of polymorphism in the pediatric population with the study of PAI-1 gene and PAI-1 plasma levels.
Description: 52 patients aged between 3 months and 6 years scheduled for surgical treatment of craniostenosis will be randomized into two groups (double blind study). The first group will receive the current protocol, i.e. i.v. infusion of high-dose TXA (50 mg/kg/15 minutes followed by continuous infusion at the dose of 5 mg/kg/h), while the second group will receive low-dose TXA (10 mg/kg/15 minutes followed by continuous infusion at the dose of 5 mg/kg/h).
Seriate samplings for measurement of TXA plasma and urine levels will be used to determine dose response pharmacokinetic curve (PK) in the pediatric population receiving craniofacial surgery with low and high doses of TXA. In addition, we will study the genetic polymorphism of PAI-1 gene region and how high plasma concentrations of PAI-1 can interfere with the clinical response to TXA administration. In fact, insertion/deletion -675 4G/5G polymorphism and the presence of 4G allele are factors associated with high plasma levels and higher activity of PAI-1 , and the subjects with this polymorphism could respond differently to therapy with TXA.

Internal collaborations:

- Pediatric Neurosurgery (Dr Cama)
- Clinical Genetics (Prof Ravazzolo)
- Hematology/Oncology (Dr Molinari)
- Laboratory of Analysis (Dr Tripodi)
- Pharmacy (Dr Barabino)
- Clinical Pharmacology (Dr Della Casa)

External collaborations:

- Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital & Harvard Medical School, Boston, MA, USA

BEST PUBLICATIONS YEARS 2011-2013

1. Disma N, Frawley G, Mameli L, Pistorio A, Alberighi OD, Montobbio G, Tuo P. Effect of epidural clonidine on minimum local anesthetic concentration (ED50) of levobupivacaine for caudal block in children. Paediatr Anaesth. 2011 Feb;21(2):128-35.
2. Disma N, Mameli L, Pini-Prato A, Montobbio G. One lung ventilation with Arndt pediatric bronchial blocker for thoracoscopic surgery in children: a unicentric experience. Paediatr Anaesth. 2011 Apr;21(4):465-7.
3. Montobbio G, Pini-Prato A, Guida E, Disma N, Mameli L, Avanzini S, Scali R, Tuo P, Jasonni V, Mattioli G. Provisional unicentric experience with an electronic incident reporting form in pediatric anesthesia. Paediatr Anaesth. 2012 Mar 16.
4. Pini Prato A, Rossi V, Fiore M, Avanzini S, Mattioli G, Sanfilippo F, Michelazzi A, Borghini S, Disma N, Montobbio G, Barabino A, Nozza P, Ceccherini I, Gimelli S, Jasonni V. Megacystis, megacolon, and malrotation: a new syndromic association? Am J Med Genet A. 2011 Aug;155A(8):1798-802.
5. Davidson A, MacCann ME, Morton N, Disma N *et al*. Protocol 09PRT/9078: A multi-site RCT comparing regional and general anaesthesia for effects on neurodevelopmental outcome and apnoea in infants: The GAS study (ACTRN12606000441516, NCT00756600). The Lancet 2012.

Neonatal Diseases and Intensive Care

Director: Dr. Luca Ramenghi

STAFF

Name	Position
Carlo Bellini	Physician
Matteo Bruschettini	Physician
Francesco Campone	Physician
Maria Rita Caviglia	Physician
Sara Mangini	Physician
Alessandro Parodi	Physician
Francesco Risso	Physician
Andrea Sannia	Physician
Antonella Savelli	Physician
Fabio Scopesi	Physician
Cristina Traggiai	Physician
Lucia Trail	Physician
Teresa Asprea	Nurse
Roberta Da Rin Della Mora	Nurse
Simona Serveli	Nurse

RESULTS YEAR 2013

Scientific research was focused on perinatal neurology. In particular, we described relevant aspects of intracranial bleeding in the preterm newborn, including germinal matrix, intraventricular, and cerebellar bleeding. We studied the potentialities and the limits of transfontanellar and mastoid US examination, also for low-grade bleeding. We also compared the level of prematurity with different risks of brain damage. In addition, we correlated the presence of lesion with possible long-term outcome. We continued imaging diagnosis activity, by collecting brain MR data in hundreds of newborns (data not published).
Other research aspects included ventilation in the preterm newborn (also through a multicentre study comparing two different techniques of neonatal resuscitation) and the characteristics of fetal-neonatal diseases such as those of the lymphatic system, with many publications in 2013.
Finally, about a hundred of samples were collected for the study of hematopoietic cells of some cell lines in umbilical cord blood: preliminary results will be published in occasion of the congress in 2014 of the *Pediatric American Societies*.

Main collaborations year 2013:

- PREVENTROP: Study on prevention of retinopathy in preterm newborns – in collaboration with the University of Lund (Sweden) (or Goteborg)
- Brain MR in very low weight newborns – in collaboration with the Neuroradiology unit directed by Andrea Rossi
- "Phenotypic and functional evaluation of hemopoietic and non hemopoietic progenitors in blood and umbilical cord of fullterm and preterm newborns" - in collaboration with the Lab. of Postnatal Stem Cells directed by prof. Frassoni. An abstract with preliminary results (100 of 200 expected samples have already been collected) was submitted to the congress of *Pediatric American Societies* 2014

– Publication of systematic reviews – in collaboration with the *Cochrane Neonatal Review Group*

PLANNED ACTIVITY YEAR 2014

Title: Project on the prevention and study of cerebral bleeding in high-grade preterm newborns. **Objective**: main objective is the study of cerebellar bleeding, which is little known in inner pathogenetic mechanisms, similarly to existing knowledge on germinal matrix-intraventricular bleeding in the preterm newborn. In addition to diagnostics, pathologic anatomy aspects will be investigated, as well as correlations with prematurity placental disease.
Description: pathologic anatomy: it is not clear at what level cerebellar bleeding occurs; it would seem to affect external granulation tissue, but vascularization of this tissue and the analogy with germinal matrix bleeding have not been demonstrated especially in the supposed venous genesis, i.e. in the venous circulation. Both are in inverse relation, as risk at preterm gestational age. Neuroradiology: in general, cerebellar disease and even more mild forms can be diagnosed exclusively by US examination of the brain through the mastoid fontanelle and/or with MR, which is more sensitive, which at Gaslini is used in highly preterm newborns.

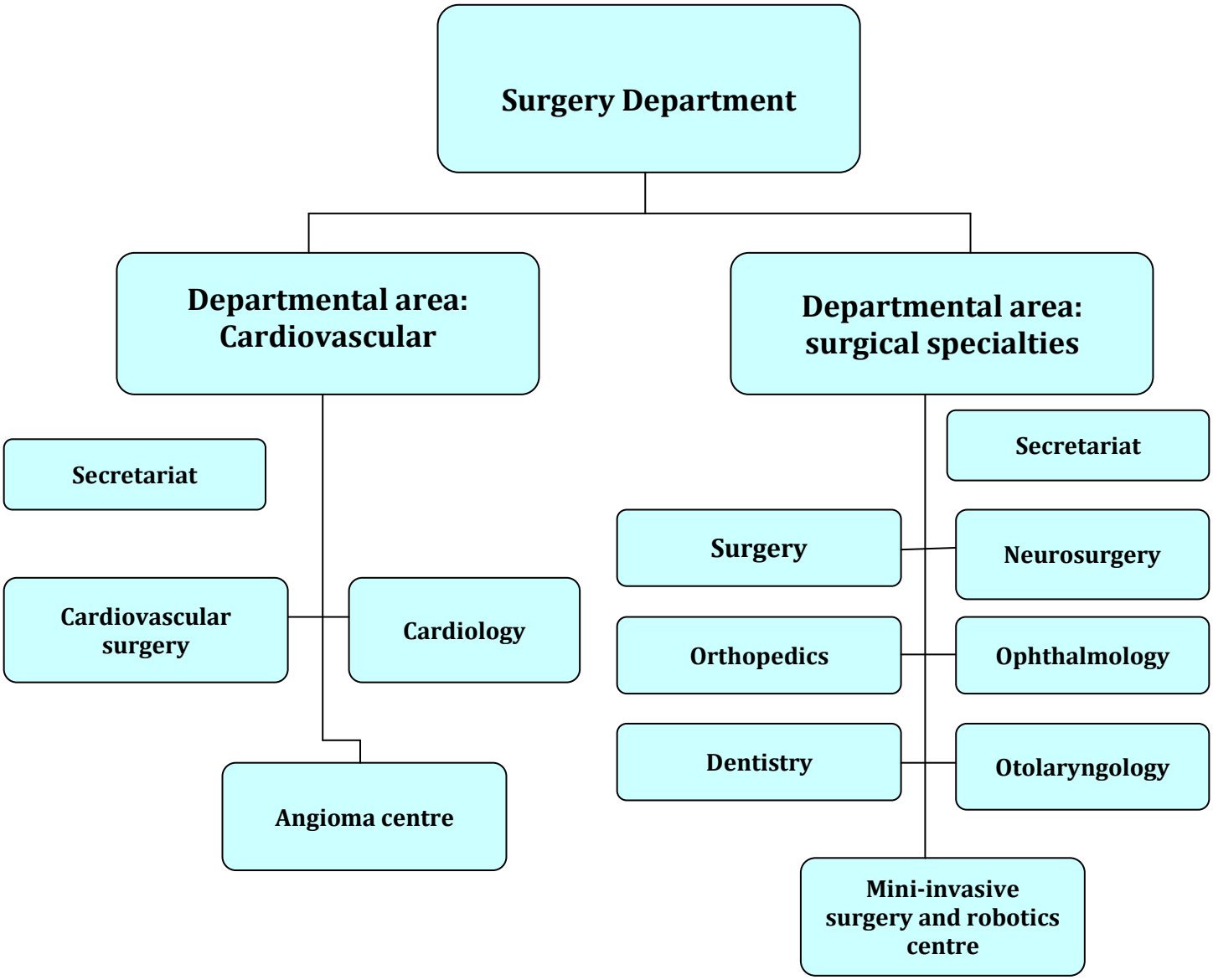
Internal collaborations
A continuous collaboration with the Neuroradiology unit allows the study of these highly preterm newborns when they reach the correct fullterm age. In addition, a collaboration with Prof. Fulcheri has already been started for the study of correlations with placental disease.

External collaborations
Collaborations with the Institute of Neurosciences of Rotterdam and with the Neonatology unit of Rotterdam have already been started in the already described study fields.

BEST PUBLICATIONS YEARS 2011-2013

1. Bellini C. Cited or read? Lancet 2012;379(9813):314-314.
2. Ramenghi LA, et al. Germinal matrix hemorrhage: intraventricular hemorrhage in very-low-birth-weight infants the independent role of inherited thrombophilia. Stroke 2011;42(7):1889-1893.
3. Van den Hove DL, Kenis G, Brass A, Opstelten R, Rutten BP, Bruschettini M, et al. Vulnerability versus resilience to prenatal stress in male and female rats; Implications from gene expression profiles in the hippocampus and frontal cortex. European neuropsychopharmacology 2013;23(10):1226-1246.
4. Fumagalli M, Ramenghi LA, et al. Total body cooling: skin and renal complications. Archives of disease in childhood-fetal and neonatal edition 2011;96(5):F377-F377.
5. Cavallaro G, Filippi L, Cristofori G, Colnaghi M, Ramenghi LA, et al. Does pulmonary function change during whole-body deep hypothermia? Archives of disease in childhood-fetal and neonatal edition 2011;96(5):F374-F377.
6. Rutherford MA, Ramenghi LA, et al. Neonatal stroke. Archives of disease in childhood-fetal and neonatal edition 2012;97(5):F377-F384.
7. Arrigoni F, Parazzini C, Righini A, Doneda C, Ramenghi LA, et al. Deep Medullary Vein Involvement in Neonates with Brain Damage: An MR Imaging Study. American journal of neuroradiology 2011;32(11):2030-2036.

8. Cangemi G, Storti S, Cantinotti M, Fortunato A, Emdin M, Bruschettini M, et al. Reference values for urinary neutrophil gelatinase-associated lipocalin (NGAL) in pediatric age measured with a fully automated chemiluminescent platform. Clinical chemistry and laboratory medicine 2013;51(5):1101-1105.


Surgery Department
Departmental area: Cardiovascular
Departmental area: surgical specialties
Secretariat
Cardiovascular surgery
Cardiology
Angioma centre
Secretariat
Surgery
Neurosurgery
Orthopedics
Ophthalmology
Dentistry
Otolaryngology
Mini-invasive surgery and robotics centre

Cardiovascular surgery

Director: Dr. Lucio Zannini

STAFF

Name	Position
Giuseppe Cervo	Physician
Elena Ribera	Physician
Alfredo Virgone	Physician
Giuseppe Panizzon	Physician
Pietro Dalmonte	Physician
Nadia Vercellino	Physician
Lauralba Di Sabato	Nurse
Gabriella Magioncalda	Nurse
Daniela Leonardini	Administrative

RESULTS YEAR 2013

Title: Gene expression profile in advanced decompensated heart failure: identification and validation of new biomarkers.

Objective: Objective of the project is to identify new biomarkers starting from the analysis of gene expression profile of the cardiac muscle in children with cardiac decompensation in congenital cardiopathies and undergoing surgery in the Cardiovascular Surgery unit of Gaslini.

Description: The identification of new biomarkers having higher sensitivity and specificity is essential to improve the management of cardiac decompensation. They allow the optimization of current therapeutic approaches with beneficial effects for the patient and reduction of hospitalizations. Pediatric patients with selected congenital cardiopathies and submitted to surgery were enrolled. In collaboration with the Laboratory of Molecular Biology, where the collected material is studied, the centralization of collected samples in the biobank-BIT of Gaslini is being continued. The collected material is studied by analysis of gene expression profile of the cardiac muscle by microarray technology.

Since the number of available samples is still insufficient, it is necessary to continue the collection of cardiac tissue during cardiovascular surgery for the study of gene expression profiles by microarray.

Main collaborations year 2013:

- Prof. Pascal Vouhé - Hôpital Necker, Paris: Surgery of congenitally corrected transposition of the great vessels (double Switch); surgery of the aorta (Ross technique); surgery of pulmonary atresia with DIV and MAPCA in neonatal age.
- Prof Patrick Diner – Hôpital Trousseau, Paris: Maxillofacial reconstructive plastic surgery for cervico-facial malformative vascular disease.
- Prof Claude Laurian - Hopital Saint Joseph, Paris: Surgery of complex musculoskeletal vascular malformations.
- Dr Michel Wassef- Hopital Lariboisiere, Paris: Pathologic anatomy and cytology of complex vascular malformations
- Dr J. C. Gutierrez - Hospital Universitario La Paz, Madrid: phantom bone disease (Gorham Stout syndrome)

Cooperative projects 2012

- Training of clinical/nursing staff and execution of cardiovascular surgery interventions
- Kossovo Pediatric Cardiology - Pristina Hospital and Kossovo Ministry of Health
- Kurdistan Sulimania University Hospital and Kurdistan Ministry of Health (in collaboration with Le Scotte hospital of Siena)
- Marocco Centre hopitalier IBN Sina, Rabat PROF Cherti Chef de Service de la Cardiologie.

PLANNED RESEARCH ACTIVITY YEAR 2014

Angioma centre

Title: Multicentre epidemiological study of phantom bone disease (Gorham Stout syndrome).
Objective: to establish a diagnostic-therapeutic protocol for this rare disease, whose treatment is still controversial.
Description: Gorham Stout syndrome is a rare and complex vascular malformation characterized by spontaneous and massive osteolysis associated with intraosseous local proliferation of small vessels of prevalently lymphatic nature, which determines the progressive destruction and reabsorption of bone. In affected sites, the lesion also infiltrates soft tissues (skin, subcutaneous tissue, muscles); in case of thoracic localization, it is associated with chylothorax.
It is a rare, sporadic condition of unknown etiology, generally affecting children and adolescents, equally males and females, with progressive evolution and invalidating. About 300 cases have been described in the international literature.
The management of these children is complex and multidisciplinary.

Internal collaborations:

- Pediatric Clinic unit (bone metabolism)
- Neuroradiology and Radiology unit (diagnostic instrumental approach and interventional radiology procedures)
- Physiotherapy and Orthopedics (monitoring and treatament of osteolysis)
- Pediatric Rheumatology unit (medical therapy)
- Laboratory of Molecular Genetics and Cytogenetics

External collaborations:
- Lymphatic Centre, University of Genova (Director prof C. Campisi)
- Dr J. C. Gutierrez (Hospital Universitario La Paz, Madrid): some years ago, joint management of the most difficult cases was started and genetic collaboration is being evaluated.

Cardiovascular Surgery

Title: Evaluation of autologous regeneration of Cor-Matrix patch (extracellular matrix graft) in pediatric cardiovascular surgery
Objective: Evaluation of cell regeneration and growth of Cor-Matrix extracellular matrix patch used for correction of congenital cardiopathies and vascular replacement in pediatric patients.
It is a new material in use for some years, certified and authorized for use in pediatric cardiovascular surgery, composed of decellularized extracellular matrix from bovine

intestine, which should provide the host with substrate for recellularization, guaranteeing plastic ability and size growth potentiality.

Description: clinical and instrumental evaluation of patients in whom extracellular matrix patch was used and histological analysis of explanted patch fragments when possible (e.g. in case of staged and palliative interventions waiting for correction).

Internal collaborations:

- Dr. G. Trocchio, Cardiovascular Dept. for imaging (US, angioCT and angioMR of heart)
- Dr P.Nozza, Pathologic Anatomy unit (histology)

BEST PUBLICATIONS YEARS 2011-2013

1. Nadia Vercellino, Maria Victoria Romanini, Monica Pelegrini, Alessandro Rimini, Corrado Occella, Pietro Dalmonte. The use of propranolol for complicated infantile capillary hemangiomas. Int Journal Dermatol 2013;52:1140-1146.
2. Parodi A, Gandolfo C, Palombo S, Zannini L, Ghiggeri GM. A. challenging case of renovascular hypertension. Vasc Med 2013; 18:318-9.
3. Dalmonte P, Granata C, Fulcheri E, Vercellino N, Gregorio S, Magnano G. Intra-articular venous malformations of the knee. J Pediatr Orthop 2012 32:(4):394-8.
4. Carinci S, Tumini S, Consilvio NP, Cipriano P, Di Stefano A, Vercellino N, Dalmonte P, Chiarelli F.A case of congenital hypothyroidism in PHACE syndrome. J Pediatr Endocrinol Metab. 2012;25(5-6):603-5.
5. Bondanza S, Derchi M, Marasini M. Selective pulmonary artery embolization in two patients with single ventricle and acquired pulmonary vein occlusion. Catheter Cardiovasc Interv. 2012 Jul 1;80(1):101-6. doi: 10.1002/ccd.23272. Epub 2011 Dec 12.
6. Bondanza S, Derchi M, Tuo G, Zannini L, Marasini M. Use of a telescopic system for transcatheter radiofrequency perforation and balloon valvotomy in infants with pulmonary atresia and intact ventricular septum. Cardiol Young. 2013;23(2):203-8.
7. C Bellini, Z. Ergaz, M. Radicioni, I. Forner-Cordero, M. Witte, G. Perotti, T. Figar, L. Tubaldi, P. Camerini, B. Bar-oz, I. Yatsiv, I. Arad, F. Traverso,T. Bellini, F. Boccardo, P. Dalmonte, N. Vercellino, C. Campisi, S. Manikanti, E. Bonioli. Congenital fetal and neonatal visceral chylous effusions: neonatal chylothorax and chylous ascites revisited. A multicenter retrospective study. Studio multicentrico - Cardiovascular Department (PD, NV), IRCCS Gaslini, Genoa, Italy Lymphology 2012; 45:91-102.
8. Tuo G, Volpe P, Bondanza S, Volpe N, Serafino M, De Robertis V, Zannini L, Pongiglione G, Calevo MG, Marasini M. Impact of prenatal diagnosis on outcome of pulmonary atresia and intact ventricular septum.. J Matern Fetal Neonatal Med. 2012;25(6):669-74.
9. Lerzo F, Peri G, Doni A, Bocca P, Morandi F, Pistorio A, Carleo AM, Mantovani A, Pistoia V, Prigione I. Dexamethasone prophylaxis in pediatric open heart surgery is associated with increased blood long pentraxin PTX3: potential clinical implications. Clin Dev Immunol. 2011:730828 Epub 2011 Jul 9.

Surgery

Director (pro-tempore): Dr. Piero Buffa

Staff

Name	Position
Girolamo Matttioli	Physician
Giuseppe Martucciello	Physician
Stefano Avanzini	Physician
Giovanni Maria Bisio	Physician
Fabio Faranda	Physician
Silvio Ferretti	Physician
Giuseppe Fratino	Physician
Cinzia Mazzola	Physician
Alberto Michelazzi	Physician
Ludovico Muller	Physician
Alessio Pini Prato	Physician
Fabio Sanfilippo	Physician
Piero Scarsi	Physician
Michele Torre	Physician
Marcello Carlucci	Physician
Maria Grazia Faticato	Physician
Lorenzo Leonelli	Physician
Luca Pio	Physician
Valentina Rossi	Physician
Manuela Mosconi	Biologist
Catarina Holm	Nurse

Results year 2013

Title: Characterization of phenotype variability of Hirschsprung disease and role of ret proto-oncogene in immune and microbial homeostasis of human and murine intestine

In 2013, we continued the enrolment of patients with Hirschsprung disease, who were included in a complex programme of phenotype screening (abdominal US, transfontanellar US, echocardiography, cardiologic examination, electrocardiogram, eye examination, audiometric examination in case of surgery) and genotype screening (screening of mutations and haplotypes of Ret protooncogene). Stool samples were collected from all patients for the metagenomic study (ongoing at the laboratories of NIH – Bethesda) and from those undergoing surgery; intestinal tissue and peripheral DNA were collected for the study of the expression of Ret and other genes potentially involved in inflammation. All this is aimed at elucidating the complex correlation between genotype and phenotype of Hirschpsrung disease and at formulating pathogenetic hypotheses explaining more accurately the main complication of the disease, i.e. enterocolitis. Until Nov. 30, 2013, overall 155 patients were enrolled, 115 of them underwent full screening and therefore were included in the study aimed at the definition of phenotype variability in Hirschsprung disease, at genotype/phenotype correlation, and at the identification of possible risk factors for the development of enterocolitis. The results obtained in the first 106 patients were published in Orphanet Journal of Rare Disease (Pini Prato A et al. *A prospective observational study of associated anomalies in Hirschsprung's disease*. Orphanet J Rare Dis. 23;8(1):184, 2013).

Title: Miniinvasive approach in pediatric surgery: clinical audits, risk management, and guidelines

In 2013, we created a complex database able to include all main demographic and clinical data, intraoperative technical details, outcome measures, and possible complications. This database, adapted specifically for each disease, was initially applied to a selected patient population (oesophageal atresia) undergoing miniinvasive surgery at Gaslini. The audit was extended to all national units in order to define the main epidemiological features, surgical attitudes, and short- and long-term outcome of this rare congenital disease. We enrolled 147 patients treated in the 53 national Pediatric Surgery units in Italy, representative of all eligible patients. A paper summarizing the exceptional results obtained is being prepared and will be submitted to an international journal with high I.F. Preliminary results were presented in occasion of the National Joint Congress of the Italian Society of Pediatric Surgery in Ferrara, Italy, October 2013.

The same database, adapted for another disease (ulcerative colitis), is presently used for collection of data on patients undergoing surgery, also in this case extending data collection to many national centres.

Title: Hirschsprung disease as a model of neuro-immune dysfunctions in the gut: role of the ret proto-oncogene in the correct development and maintenance of microbial homeostasis

On Nov. 30, 2013, the 3rd year of the three-year project (to be extended for 1 year up to Nov. 30, 2014) was completed. Since Dec. 1, 2010 (start year) we enrolled overall 155 patients, 48 of them undergoing sampling of a portion of intestine for immunological study, 125 sampling of peripheral blood for DNA extraction (63 trios = proband + both parents), and 100 sampling of peripheral blood for the study of gene expression on circulating immune cells. In 2013, we published in the international journal *Plos-One* a paper describing the results of the study, focusing on the evaluation of RET proto-oncogene expression on different cell lines of circulating immunity in patients with Hirschsprung disease, and of the effect in these patients of RET stimulation on up- or down-regulation of some inflammation genes (Rusmini M et al. *Induction of RET dependent and independent pro-inflammatory programs in human peripheral blood mononuclear cells from Hirschsprung patients*. PLoS One. 2013;8(3):e59066).

PLANNED RESEARCH ACTIVITY YEAR 2014

TitLE: Oncologic risk for patients with Hirschsprung disease

BACKGROUND – Hirschsprung disease is a rare multifactorial congenital disease characterized by absence of myenteric and submucous plexus ganglia and involving the last tract of the intestine with variable extension and prevalently affecting left colon. The main disease gene is RET proto-oncogene whose mutations were described in up to 50% of familial cases and in 7-35% of sporadic cases of the disease. In 2013, Luo and colleagues demonstrated that RET can act as tumor suppressor in colorectal cancer and described a series of somatic mutations in some tumor cell lines. It is very interesting to observe that at least half these mutations have already been reported as germinal mutations in patients with Hirschsprung disease.. Colorectal cancer has never been investigated prospectively in patients with this rare disease. Our study is aimed at analyzing the possible role of Hirschsprung disease in predisposing colorectal cancer.

MATERIALS AND METHODS – The study was approved by Gaslini's Etics Committee in November 2013. In order to increase the study population, a multicentre project was started. However, in consideration of the extreme difficulty in recruiting patients aged > 50 years (maximum risk of developing colorectal tumor in the general population), we decided to

adopt a multimodal approach including 3 different steps: 1) analysis of prevalence of colorectal tumor in the relatives of all patients treated in our Institute with reliable diagnosis of Hirschsprung's disease (a superimposable number of healthy subjects will be used as control, with epidemiological data reported in the literature or in disease registries), 2) retrospective collection of all clinical records of patients aged > 40 years (in order to include also subjects with early tumor onset) who underwent surgical treatment and survived to date (from 1950, year of first effective treatment, to 1973). These patients will be contacted and interviewed about the onset of colorectal tumor. In case effective direct contacts are not feasible, patients will be recruited from disease registries or through cross-references with the analysis of regional DRG codes for the definition of comorbidity of colorectal tumor and Hirschsprung disease, 3) analysis of history of patients with colorectal tumor to define the anamnestic prevalence of Hirschsprung disease in this population.
FEASIBILITY – The Istituto Giannina Gaslini is one of the main Italian chidlren's hospitals and is national reference centre for Hirschsprung disease. The involvement of other national and international centres will increase the probability to reach a sufficient number of cases for the definition of the relative risk of developing colorectal tumor. The expected duration of the project is 1 to 3 years depending on the results that will be obtained in the different steps described above.
EXPECTED RESULTS – We expect to confirm the predisposition of patients with Hirschsprung's disease to colorectal cancer. This will allow us to propose a specific follow-up to obtain optimal and personalized prevention and monitoring of these patients, otherwise receiving preventive measures generally proposed for the general population.

Main collaborations:

- Professor Paolo De Coppi, Great Hormond Street Hospital – London, UK
- Mr Gordon Alexander MacKinlay, Royal Hospital for Sick Children – Edinburgh, UK
- Prof. Prem Puri, Our's Lady Hospital, Dublin, Ireland
- Dr William Pavan, NIH – Bethesda – USA
- Dr. John Hudson – Royal Children's Hospital – Melbourne, Victoria, Australia
- Dr. Andrew Davidson – Royal Children's Hospital – Melbourne, Victoria, Australia
- Dr. Sebastian King – Royal Children's Hospital – Melbourne, Victoria, Australia

Nest publications years 2011-2013

1. Pini Prato A, Rossi V, Mosconi M, Holm C, Lantieri F, Griseri P, Ceccherini I, Mavilio D, Jasonni V, Tuo G, Derchi M, Marasini M, Magnano G, Granata C, Ghiggeri GM, Priolo E, Sposetti L, Porcu A, Buffa P, Mattioli G. A prospective observational study of associated anomalies in hirschsprung's disease. Orphanet J Rare Dis. 2013 nov 23;8(1):184.
2. Rusmini M, Griseri P, Lantieri F, Matera I, Hudspeth KL, Roberto A, Mikulak J, Vanzini S, Rossi V, Mattioli G, Jasonni V, Ravazzolo R, Pavan WJ, Pini-Prato A, Ceccherini I, Mavilio D. Induction of ret dependent and independent pro-inflammatory programs in human peripheral blood mononuclear cells from hirschsprung patients. Plos one. 2013;8(3):e59066.
3. Pini Prato A, Castagnola E, Micalizzi C, Dufour C, Avanzini S, Pio L, Guida E, Mattioli G, Jasonni V, Disma N, Mameli L, Montobbio G, Buffa P. Early diverting colostomy for perianal sepsis in children with acute leukemia. J pediatr surg. 2012 oct;47(10):e23-7.
4. Montobbio G, Pini-Prato A, Guida E, Disma N, Mameli L, Avanzini S, Scali R, Tuo P, Jasonni V, Mattioli G. Provisional unicentric experience with an electronic incident reporting form in pediatric anesthesia. Paediatr anaesth. 2012 mar 16.

5. Mattioli G, Guida E, Pini-Prato A, Avanzini S, Rossi V, Barabino A, Coran AG, Jasonni V. Technical considerations in children undergoing laparoscopic ileal-j-pouch anorectal anastomosis for ulcerative colitis. Pediatr surg int. 2012 apr;28(4):351-6.
6. Torre M, Rapuzzi G, Carlucci M, Pio L, Jasonni V. Phenotypic spectrum and management of sternal cleft: literature review and presentation of a new series. Eur j cardiothorac surg. 2012 jan;41(1):4-9.
7. Pini Prato A, Rossi V, Fiore M, Avanzini S, Mattioli G, Sanfilippo F, Michelazzi A, Borghini S, Disma N, Montobbio G, Barabino A, Nozza P, Ceccherini I, Gimelli S, Jasonni V. Megacystis, megacolon, and malrotation: a new syndromic association? Am j med genet a. 2011 aug;155a(8):1798-802.
8. Mattioli G, Pini-Prato A, Barabino A, Gandullia P, Avanzini S, Guida E, Rossi V, PioL, Disma N, Mameli L, Mirta DR, Montobbio G, Jasonni V. Laparoscopic approach for children with inflammatory bowel diseases. Pediatr surg int. 2011 aug;27(8):839-46.
9. Pini Prato A, Rossi V, Avanzini S, Mattioli G, Disma N, Jasonni V. Hirschsprung's disease: what about mortality? Pediatr surg int. 2011may;27(5):473-8.
10. Torre M, Guida E, Bisio G, Scarsi P, Piatelli G, Cama A, Buffa P. Risk factors for renal function impairment in a series of 502 patients born with spinal dysraphisms. J pediatr urol. 2011 feb;7(1):39-43.

Neurosurgery

Director: Dr. Armando Cama

STAFF

Name	Position
Maria Luisa Garrè	Physician
Valeria Capra	Physician
Patrizia De Marco	Researcher – Biologist
Elisa Merello	Researcher - Biologist
Alessandro Raso	Researcher - Biologist
Samantha Mascelli	Researcher - Biologist

RESULTS YEAR 2013

Aim of the project was: (1) sequencing of the whole exome (WES, Whole exome sequencing) of 7 families of patients with Neural Tube Defects (NTD) in order to identify rare mutations (CNVs, SNVs and InDels) that can confer susceptibility to NTD; (2) Biological characterization of medulloblastoma stem cells and identification of molecular features related to drug resistance.

(1) In compliance with the specifications of Illumina/Solexa platform, a library of genomic DNA fragments was prepared, associated with selective enrichment of regions, followed by PCR generation of mllions of clonal clusters sequenced by synthesis through the use of dideoxy-reversible terminators. Analysis of data includes 5 phases: 1) transformation of raw data into reads; 2) quality control of reads and their alignment on a reference genome; 3) annotation of variants and their filtering using public databases; 4) study of segregation of variants within families according to different inheritance patterns; 5) validation (Gold Standard methods). Phases 1-3 have been concluded; at present, we are focusing on the analysis of CNVs by EXCAVATOR, a new tool for the identification of CNVs from WES data.

(2) Considering the most recent advances in the field of biology of medulloblastoma, with the introduction of 4 molecular groups for classification of this tumor, the study showed the groups in which there is a higher proportion of tumor initiating cells (TICs). The result can justify the more aggressive progression of some tumor forms related to the presence of TICs, with higher ability to metastasize and resist to chemo/radiotherapy. In addition, the study is highlighting specific activation pathways linked to the *self-renewal* ability of these cells in the differentiation process. These investigations are ongoing, as well as the genetic analysis of a larger case series, in order to validate the data obtained to date.

MAIN COLLABORATIONS YEAR 2013

- Zoha Kibar, Ph.D., University of Montreal, Department of Obstetrics and Gynecology, CHU Sainte Justine Research Center, Montreal, Canada
- Merce Garcia-Barcelo, Department of Surgery, University of Hong Kong, Hong Kong, China and Centre for Reproduction, Development and Growth, University of Hong Kong, Hong Kong, China
- Dr. Guido Frosina, National Cancer Research Institute, Department of Epidemiology, Prevention and Special Functions, Section of Molecular Mutagenesis and DNA repair, Largo Rosanna Benzi 10, 16132 Genova
- Professor Stefan Pfister, German Cancer Research Center, Heidelberg, Germany
- Professor Dominique FIGARELLA BRANGER, Laboratoire d'anatomie pathologique-neuropathologique - Hôpital de la Timone, Marseille.
- Michael D. Taylor, The Hospital for Sick Children, Toronto, Canada

PLANNED RESEARCH ACTIVITY IN 2014

Title: Next generation sequencing (NGS) in neurosurgical patients.
Objective: Through next generation sequencing, identification of mutations and causative genes that can confer susceptibility to NTD and of possible alterations in pathways related to stem cell phenotype of a specific molecular subgroup of medulloblastomas. In addition, continuation of the analysis and validation of variants identified in multigenerational families with NTD and validation of data obtained on stem cell phenotype lines of medulloblastoma.
Description: We will continue the analysis of SNVs and InDels obtained from data of sequencing of the exome of families with NTD. The presence of SNVs will be evaluated by GATK UnifiedGenotyper through multisample approach (including all dataset samples). Data analysis will be performed with the discrete filtering system based on cross referencing between SNPs present in the study sample and those found in exomes of healthy individuals, assuming that SNPs in common are not pathologic. For further filtering of residual SNPs, those that are not compatible with ascertained transmission modalities are excluded. Then, we will evaluate which SNPs are within known genes involved in diseases with similar phenotype or in biological processes related to the studied disease and we will evaluate how residual mutations segregate in the patient's parents.
A series of pediatric medulloblastoma tissues (N=45) will be analyzed by WES, again using Illumina technology. For the analysis, coverage of DNA sequence will be at least 20X, while mean on-target coverage for the whole exome will be 30x. Tumor tissues will be classified according to their molecular group and tumors belonging to the group with the highest possibility of stem cell phenotype will be used for comparison with the results obtained in TICs cells.

Internal collaborations:

- Dr. Roberto Biassoni, Molecular Medicine unit
- Dr. Paolo Nozza, Pathologic Anatomy unit

External collaborations:

- Dr. Z. Kibar, Department of Obstetrics and Gynecology, CHU Sainte Justine Research Center and University of Montreal, Montreal, Canada;
- Dr. A. Magi and Dr L. Tattini (University of Florence)
- Prof. Dr. Stefan Pfister, German Cancer Research Center, Heidelberg, Germany
- Prof. Dominique FIGARELLA BRANGER, Laboratoire d'anatomie pathologique-neuropathologique - Hôpital de la Timone, Marseille.
- Michael D. Taylor, The Hospital for Sick Children, Toronto, Canada

BEST PUBLICATIONS YEARS 2011-2013

1. Allache R, Lachance S, Guyot MC, De Marco P, Merello E, Justice M, Capra V; Kibar Z. Mutations in Lrp6 orthologues in mouse and human neural tube defects affect dosage-sensitive Wnt canonical β catenin-dependent and non canonical planar cell polarity pathways. Hum Mol Genet. 2013 Nov 18. [Epub ahead of print]
2. Mascelli S, Barla A, Raso A, Mosci S, Nozza P, Biassoni R, Morana G, Huber M, Mircean C, Fasulo D, Noy K, Wittemberg G, Pignatelli S, Piatelli G, Cama A, Garré ML, Capra V, Verri A. Molecular fingerprinting reflects different histotypes and brain region in low grade gliomas. BMC Cancer. 2013 Aug 15;13:387. doi: 10.1186/1471-2407-13-387.

3. Merello E, Kibar Z, Allache R, Piatelli G, Cama A, Capra V, De Marco P. Rare missense variants in DVL1, one of the human counterparts of the Drosophila dishevelled gene, do not confer increased risk for neural tube defects. Birth Defects Res A Clin Mol Teratol. 2013 97:452–455.
4. De Marco P, Merello E, Consales A, Piatelli G, Cama A, Kibar Z, Capra V. Genetic Analysis of Disheveled 2 and Disheveled 3 in Human Neural Tube Defects. J Mol Neurosci. 2013 Mar;49(3):582-588.
5. Samantha Mascelli , Alessandro Raso, Roberto Biassoni, Mariasavina Severino, Katrin Sak, Kairit Joost, Claudia Milanaccio, Salvina Barra, Filippo Grillo-Ruggieri, Irene Vanni, Alessandro Consales, Armando Cama, Valeria Capra, Paolo Nozza, Maria Luisa Garrè. Analysis of NADP+-dependent isocitrate dehydrogenase-1/2 gene mutations in pediatric brain tumors: report of a secondary anaplastic astrocytoma carrying the IDH1 mutation. J Neurooncol. 2012 Sep;109(3):477-84.
6. Raso A, Vecchio D, Cappelli E, Ropolo M, Poggi A, Nozza P, Biassoni R, Mascelli S, Capra V, Kalfas F, Severi P, Frosina G. Characterization of Glioma Stem Cells Through Multiple Stem Cell Markers and Their Specific Sensitization to Double-Strand Break-Inducing Agents by Pharmacological Inhibition of Ataxia Telangiectasia Mutated Protein. Brain Pathol. Brain Pathol. 2012 Sep;22(5):677-88.
7. De Marco P., Merello E., Rossi A., Piatelli G., Cama A., Kibar Z., Capra V. FZD6 is a novel gene for human Neural Tube Defects. Hum Mut 2012 Feb;33(2):384-390.
8. Bosoi CM, Capra V, Trinh VQH., De Marco P, Merello E, Drapeau P, Bassuk AG, Kibar Z. Identification and characterization of novel rare mutations in the planar cell polarity gene PRICKLE1 in human neural tube defects. Hum Mut 2011 Dec; 32(12):1371-1375.
9. A. Raso, S. Mascelli, R. Biassoni, P. Nozza, M. Kool, A. Pistorio, E. Ugolotti, C. Milanaccio, S. Pignatelli, M. Ferraro, M. Pavanello, M. Ravegnani, A. Cama, M. L. Garrè, V. Capra. High levels of PROM1 (CD133) transcript is a potential predictor of poor prognosis in medulloblastoma. Neuro-Oncology, 2011 May;13(5):500-8.

Orthopedics

Director (pro-tempore): Dr. Silvio Boero

STAFF

Name	Position
Antonio Andaloro	Physician
FlavioBecchetti	Physician
Nunzio Catena	Physician
Mauro Di Stadio	Physician
Paolo Famà	Physician
SandroGregorio	Physician
Giorgio Marrè Brunenghi	Physician
Beatrice Michelis	Physician
Simone Riganti	Physician
Filippo Senes	Physician

RESULTS YEAR 2013

New surgical technique for the correction of flexed elbow due to obstetric palsies: in 2013, we performed many surgical operations and the technique was presented at many national and international meetings (Switzerland and India). A national meeting on microsurgery chaired by Dr. Senes was organized (spring symposium of the Italian Society of Microsurgery). A paper on this topic was submitted for publication in J.Hand Surgery.
Use of guided growth technique in the correction of limb length discrepancies and axial deviations: even in this field, many operations were performed and the technique was presented at national and international meetings (Athens, Abu Dhabi). Results are being processed.
Vertebral tuberculosis in pediatric patients: we evaluated the different surgical treatment options, with or without instruments, for the treatment of vertebral deformities secondary to TBC.

Main collaborations year 2013

- Orthopedics unit of Careggi hospital for the treatment of musculoskeletal tumors
- Texas Scottish Rite Hospital for the application of techniques for limb lenghtening and correction of axial deviations with computer-assisted fixator
- CTO University of Torino – Interdepartmental group of microsurgery

PLANNED ACTIVITY YEAR 2014

Title: Sports traumatology in developmental age
Objective: Study of diseases and traumas correlated with sports activity and therapeutic options
Description: The increased spreading of sports activities and the decreased age at which competitive sports are started expose children to sports traumas once affecting adults and cause therapeutic problems, since treatment adopted in adults not always can be used in children.
The most significant skeletal districts will be studied in depth.

Internal collaborations:

Physical Therapy unit

BEST PUBLICATIONS YEARS 2011-2013

1. Catena N, Divizia MT, Calevo MG, Baban A, Torre M, Ravazzolo R, Lerone M, Sénès FM. Hand and upper limb anomalies in Poland syndrome: a new proposal of classification. J Pediatr Orthop. 2012 Oct-Nov;32(7):727-31.
2. Sénès FM, Catena N. Intramedullary osteosynthesis for metaphyseal and diaphyseal humeral fractures in developmental age. J Pediatr Orthop B. 2012 Jul;21(4):300-4.
3. Lanza C, Raimondo S, Vergani L, Catena N, Sénès F, Tos P, Geuna S. Expression of antioxidant molecules after peripheral nerve injury and regeneration. J Neurosci Res. 2012 Apr;90(4):842-8.
4. Sénès FM, Catena N. Correction of forearm deformities in congenital ulnar club hand: one-bone forearm. J Hand Surg Am. 2012 Jan;37(1):159-64.
5. Baban A, Torre M, Costanzo S, Gimelli S, Bianca S, Divizia MT, Sénès FM, Garavelli L, Rivieri F, Lerone M, Valle M, Ravazzolo R, Calevo MG. Familial Poland anomaly revisited. Am J Med Genet A. 2012 Jan;158A(1):140-9.
6. MB Michelis, S. Boero. Trattamento intraosseo di osteonecrosi asettica con concentrato piastrinico e cellulare autologo, ed osso sintetico: case report in età pediatrica. Touch briefing 2011 European Muscoloskeletal review supplement.

Ophthalmology

Director: Professor Paolo Capris

STAFF

Name	Position
Riccardo De Marco	Physician
Enrico Priolo	Physician
Simona Panarello	Physician
Carlo Sburlati	Physician
Paola Camicione	Physician
Enrica Spaletra	Orthoptist
Elisa Tassara	Orthoptist

RESULTS YEAR 2013:

From January 2013 to December 2013, we studied 3 patients with primary congenital glaucoma and 16 patients with glaucoma secondary to Sturge-Weber syndrome treated with Latanoprost. All patients underwent the following diagnostic examinations: corneal pachymetry, photograph of anterior and posterior segments, measurement of corneal diameters, and tonometry. All patients aged > 3 years underwent measurement of thickness of peripapillary retinal nerve fibers and analysis of macular retinal thickness by optical coherence tomography (OCT), Heidelberg Spectralis, and infrared retinography of optic papilla by laser scan ophthalmoscopy. In patients aged > 7 years, we also performed computerized visual field test (program 30-2, TOP strategy).
Topical monotherapy with Latanoprost proved effective in reducing intraocular pressure in 17% of patients, while in the remaining 83% combined topical therapy with beta blockers was necessary to obtain the correct pressure.

Main collaborations year 2013:

- Ophthalmology Clinic, University of Genova
- "David Chiossone" Institute for rehabilitation of blind and partially-sighted persons

PLANNED RESEARCH ACTIVITY YEAR 2014 :

Title: Study of retinal thickness in macular edema secondary to posterior uveitis
Objective: Correlation of macular retinal thickness with response to steroid therapy in macular edema secondary to posterior uveitis in the pediatric population
Description: enrolment of patients with macular edema secondary to posterior uveitis and measurement of macular retinal thickness by optical coherence tomography.

Internal collaborations:

- Pediatric Rheumatology unit
- Infectious Disease unit
- Pediatric Clinic

External collaborations:

- P. Herbort, La Source Eye Centre, University of Lausanne

BEST PUBLICATIONS YEARS 2011-2013

1. Arrigo Vittorio Barabino, Paolo Gandullia, Angela Calvi, Silvia Vignola, Serena Arrigo, Riccardo De Marco. Sudden blindness in a child with Crohn's disease.. World J Gastroenterol 2011 July 21; 17(31).
2. Francesco P. Bernardini, Juan O. Croxatto, Paolo Nozza, Andrea Rossi, Paolo Capris. Primary Diffuse Leptomeningeal Gliomatosis in Children: A Clinical Pathologic Correlation. OPHTHAL PLAST RECONS 2013;29(29:93-97.

Otolaryngology

Director: Vincenzo Tarantino

STAFF

Name	Position
Roberto D'Agostino	Physician
Andrea Melagrana	Physician
Adelina Porcu	Physician
Lucia Semino	Physician

Results year 2013

Title: Pediatric ENT diseases: clinical and epidemiological aspects.
Concerning the diagnosis and treatment of laryngeal and tracheal diseases, we continued the study on the incidence of laryngomalacia (LM) in newborns, on the number of children treated surgically (both as absolute and relative percentage), and on the association between best anesthesiological procedure and most effective and conservative surgical procedure.
To this end, thanks to the availability of a double laser instrument (CO2 and diods), we can evaluate prospectively the first results obtained in the treatment of a wide range of airway diseases using the two techniques, according to age, anatomical conditions, and usable anesthesiology techniques.
In addition, we proposed a classification of LM severity based on endoscopy to be associated with clinical classification in order to provide a more accurate endoscopic-symptomatological staging of LM, allowing a more objective identification of cases requiring surgery.

Main collaborations:

- Tracheal team
- Rheumatology unit (PFAPA)
- Physical Therapy unit – Radiology unit – Muscular Disease unit – Neurosurgery unit – ICU – Deglutition disorders
- ENT, Audiology and Phoniatry unit – University of Pisa- Prof. Stefano Berettini
- CHUV Lausanne – ENT Department – Prof. Philippe Monnier

Planned Research Activity year 2014

Title: Pediatric ENT diseases: clinical and epidemiological aspects
Objective: Identification of the etiopathogenesis of laryngotracheal malformative disease and new anesthesiological and surgical procedures.
Description: in view of the identification of the etiopathogenesis of these diseases, which is still not clear, we continue the administration to parents of newborns who developed LM of a specific questionnaire exploring many moments in life and behaviour of mother and fetus during pregnancy, in order to evaluate their possible impact on the onset of the problem. Patient enrolment will be continued.
Concerning the improvement of surgical techniques with further increase in patient safety and reduction of intra- and postoperative risk, we will evaluate the possible application of the jet-ventilation anesthesiological technique to laryngotracheal endoscopic surgery in children. This technique, which is not new, was improved by further acquisitions and modifications over the last few years, which however are presently applied in adults or patients older than our target age. We are waiting for the delivery of the dedicated equipment.

Best publications years 2011-2013

1. A.Raso, S.Mascelli, P.Nozza, R.Biassone, F. Negri, A.Garaventa, V.Tarantino. Detection of transplacental melanoma metastasis using quantitative PCR. Diagn. Mol. Pathol. 19.78.2010.
2. G. Motta, P.Cassano, S.Conticello, V.Tarantino et al. A multicentric study on: guidelines and (Adeno-)Tonsillectomy. Acta Otorhinolaringol. 5, 32, 2011.
3. M. Torre, M. Carlucci, V.Tarantino, R. D'Agostino et all. Gaslini's tracheal team: preliminary experience after one year of paediatric airway reconstructive surgery. It. J: of Ped. 37, 51, 2011.
4. G. Motta, V. Tarantino et al. BMC Ear, Nose and Throat Disorders 2013, 13:1. Effects of guidelines on adeno-tonsillar surgery on the clinical behaviour of otorhinolaryngologists in Italy. BMC Ear, Nose and Throat Disorders 2013, 13:1.

Dentistry

Director: Dr. Roberto Servetto

STAFF

Name	Position
Enrico Calcagno	Physician
Laura Ailunno	Head nurse

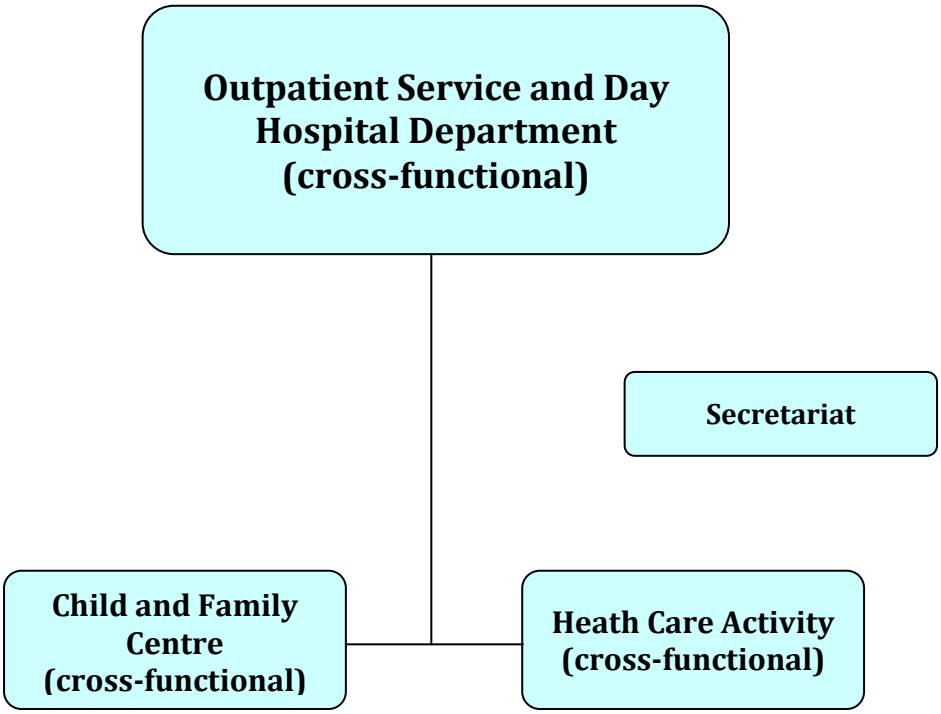
Activity year 2013

Research projects:

- Genetic syndromes, even rare, with alterations of the oro-dento-maxillofacial district
- Parodontal diseases and genetic diseases
- Parodontal diseases and nephropathies
- Study of temporo-mandibular joint in juvenile idiopathic arthritis
- Celiac disease and dental lesions
- Prosthesis with innovative material on fragile and disabled patients
- Research and testing with innovative orthodontic materials and techniques
- Research on beneficial effects/correlations between orthodontics and systemic diseases

Research programme for 2014

Research and development of new health care pathways related to dental prevention and conservative treatment in pediatric patients, including also fragile and disabled children, if necessary with hospitalization and general anesthesia if the child is not collaborating.


Outpatient Service and Day Hospital Department (cross-functional)
Secretariat
Child and Family Centre (cross-functional)
Heath Care Activity (cross-functional)