GASLINI

IRCCS - Istituto Giannina Gaslini

Scientific Report 2012
Ongoing Research 2013

SCIENTIFIC REPORT 2012
ONGOING RESEARCH 2013

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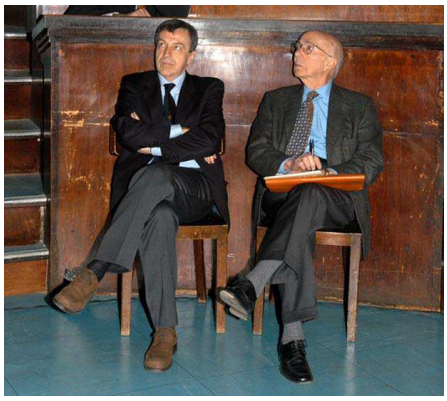
Some pictures of the Istituto Giannina Gaslini



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 of paediatricians and pediatric nurses on HSCT in children and adolescents

"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" (Gerolamo Gaslini)

Foreword

A recent publication by Via Academy - "Small is beautiful" – analyzed the quality of research carried out in different Italian universities and institutes. Small and medium-sized organizations with fewer than 100 principal investigators (PI) or university professors were extracted and in this ranking, based on the ratio of PI/TIS (Top Italian Scientists, Via Academy), Gaslini is ranked first, closely above the Humanitas Institute of Milan. This is a remarkable result and underscores once more the caliber of Gaslini's researchers, among whom 23 are TIS, equally distributed between basic and clinical investigators. Despite the critical period, scientific production remains at a high level, with more than 300 international publications over the last two years and an Impact Factor (IF) - a reliable index of the importance of journals - exceeding 1,650. Given the size of Gaslini, these results are excellent when considered as absolute values and even more so when normalized according to the number of PI.

In 2012, it was possible to take all necessary steps to fill vacancies for three permanent biologists and four temporary (5-year) positions. Three temporary posts for laboratory technicians were also created, and numerous contracts of excellence and three prizes for young researchers (authors of highly relevant publications) were awarded, always on a meritocratic basis, thanks to the generous and enlightened contribution of the Gaslini Foundation. It is also worth recalling that, over the last few years, Gaslini has funded four permanent positions of university researchers for three pediatricians and one geneticist, who are presently working in our Institute within the framework of the agreement between Gaslini and the University of Genoa. Another major development at Gaslini was the appointment of Francesco Frassoni, an internationally renowned hematologist, as director of the Laboratory of Postnatal Stem Cells and Cell Therapies and coordinator of Gaslini's activities in the field of hematology/oncology. The recruitment of qualified personnel is of vital importance - not only for the researchers/technicians who are hired - but also because it guarantees a generational turnover at Gaslini. It is our sincere hope that this marks a new trend, one that is more

focused on research, which is the essential mission of comprehensive health care centers like Gaslini and a key prerequisite to maintaining health care levels of excellence that require constant updating and refinement. To this end, the Ministry of Health contributed with funding that, thanks to co-funding from the Regione Liguria, allowed the purchase and/or upgrade of equipment of pivotal relevance for both research and advanced diagnostics. Instrumentation commonly used in our core facilities and managed by highly experienced professionals was preferred. It is undeniable that the presence of highly qualified researchers and the availability of state-of-the-art equipment are two essential elements for research; they are, however, only two of the necessary ingredients. Indeed, others are required that are mainly related to the *Italian system*, Italy being a country that is hardly inclined towards research: adequate financial resources assigned on a meritocratic basis, sufficient laboratory spaces and efficient infrastructures, less red tape, appropriate salaries for researchers, tax exemptions for research expenses, and the list goes on. Regretfully, Italy has always contributed very little to research (roughly 1% of its GDP, which ranks our country in the last positions among EU countries), and this meager support has often been poorly invested. In the midst of the recent economic crisis, the US and Germany have stimulated research with considerable investments. And the term *investment* could not be more appropriate! Indeed, too often our institutions and administrations consider research a *cost*. A recent American survey revealed that each dollar invested in research yielded 14 dollars! It is the sincere hope of all of Gaslini's researchers that our Institute will not in the future become emblematic of a country in decline! We strongly urge that research at Gaslini be supported and encouraged, as provided for by its very status of Ministry of Health-funded research institute. Research must be recognized as a value for the progress of our Institute, as its founder so insightfully envisaged. I like to quote what Gerolamo Gaslini wrote over half a century ago: "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".

Prof. Lorenzo Moretta
Scientific Director

ANNUAL REPORT 2012

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SCIENTIFIC PRODUCTION AND RESULTS

CONTRIBUTION OF UNITS TO SCIENTIFIC PRODUCTION IN 2012

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

Unit	N.	IF	Normalized IF
Pediatric Rheumatology	36	327.821	201.5
Oncology/Hematology and BMT	29	176.994	108.5
Pediatric Neurology and Muscular Diseases	36	137.069	144.5
Laboratory of Oncology	24	127.221	135.5
Clinical and Experimental Immunology	22	108.458	79
Pediatric Pneumology and Allergology	20	107.984	69
Infectious Diseases	20	94.479	65.2
Laboratory of Molecular Genetics	16	77.298	65
Pediatric Clinic	24	72.504	51.5
Child Neuropsychiatry	11	70.24	43
Nephrology, Dialysis and Transplantation	15	69.262	55.8
Laboratory of Clinical Chemical Analysis	15	48.013	64
Laboratory of Pathophysiology of Uremia	9	44.575	46
Laboratory of Molecular Biology	3	41.488	17.5
Centre of Genetic Diagnostics and Biochemistry of Metabolic Diseases	6	23.986	19
Neurosurgery	6	20.469	26
Surgery	10	16.591	40
Neuroradiology	6	13.775	22
Pathologic Anatomy	4	12.087	14
Pediatric Gastroenterology with Digestive Endoscopy	2	7.977	5
Neonatal Pathology	4	7.598	12
Laboratory of Hematology and Hemophilia	3	7.595	8
Epidemiology and Biostatistics	4	6.875	5
Orthopedics	4	5.715	9
Radiology	3	5.022	10
Cytogenetics	2	4.921	6
ICU/NICU	2	3.901	6
Cardiovascular Surgery	3	3.869	3.5
Cardiology	2	3.785	6
Emergency/Urgency	1	2.321	0.8
Obstetrics and Gynecology	1	1.495	1
Total	**343**	**1651.388**	**1339.3**

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 2012

Unit	N.	IF	Normalized IF
Pediatric Rheumatology	43	346.91	225.5
Oncology/Hematology and BMT	42	213.78	161
Laboratory of Oncology	31	149.981	159.5
Pediatric Neurology and Muscular Diseases	39	144.645	160.5
Clinical and Experimental Immunology	25	118.632	92
Pediatric Pneumology and Allergology	22	111.696	77
Nephrology, Dialysis and Transplantation	23	109.119	98.8
Infectious Diseases	27	105.492	81.2
Pediatric Clinic	32	100.414	86.5
Child Neuropsychiatry	20	95.444	81.2
Laboratory of Molecular Genetics	20	92.928	85
Laboratory of Clinical Chemical Analysis	23	71.293	98
Epidemiology and Biostatistics	23	65.659	76.5
Laboratory of Molecular Biology	6	52.966	33.5
Pathologic Anatomy	13	45.653	64
Laboratory of Pathophysiology of Uremia	9	44.575	46
Neuroradiology	14	43.738	64
Neurosurgery	10	31.463	44
Centre of genetic diagnostics and biochemistry of metabolic diseases	6	23.986	19
Laboratory of Hematology and Hemophilia	6	23.379	26
Surgery	12	19.847	46
Pediatric gastroenterology with digestive endoscopy	5	13.671	17
Radiology	6	12.029	19
Pharmacy	3	8.148	7.5
Orthopedics	6	8.124	13
Neonatal Pathology	4	7.598	12
Cytogenetics	3	7.249	8
ICU/NICU	4	6.604	12
Obstetrics and Gynecology	2	6.598	7
Cardiovascular Surgery	4	5.364	5.5
Dermatology	2	5.067	9
Cardiology	2	3.785	6
Emergency/Urgency	1	2.321	0.8
Clinical Psychology	1	2.123	4
Immunohematology and Transfusion Medicine	1	1.891	4
Ophthalmology	1	1.566	1
Management Control and Quality Office	1	1.253	2

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

	Area	H-index **
Lorenzo Moretta	(Immunology/Hematology)	110
Cristina Bottino	(Immunology)	64
Francesco Frassoni	(Cell Therapies/Hematology)	53
Roberto Biassoni	(Mol. Biology/Immunology)	52
Alberto Martini	(Rheumatology)	49
Mirco Ponzoni	(Oncology)	47
G. Marco Ghiggeri	(Nephrology)	43
Angelo Ravelli	(Rheumatology)	43
Luigi Varesio	(Molecular Biology)	42
Vito Pistoia	(Oncology)	40
Angela Pistorio	(Epidemiology and Biostatistics)	40
Claudia Cantoni	(Immunology)	40
Isabella Ceccherini	(Med. Genetics)	38
Giovanni Rossi	(Pneumology)	36
Claudio Bruno	(Neuromuscular Diseases)	35
Roberto Ravazzolo	(Med. Genetics)	35
Nicolino Ruperto	(Rheumatology)	35
Michela Falco	(Immunology)	34
Carlo Minetti	(Neromuscular Diseases)	33
JLV Galietta	(Med. Genetics)	32
Carlo Dufour	(Oncology/Hematology)	32
Bruno Azzarone	(Immunology)	32
Claudio Gambini	(Pathologic Anatomy)	31
Marco Gattorno	(Rheumatology)	31
	Total	**1027**

* H-index > 30
** ISI or Via Academy

Table 4 - Impact Factor-related data in the period 1999-2012

Year	N. Publications	Impact Factor	Normalized Impact Factor (according to ministerial indications)	IF/ Publication	Normalized IF/ Publication
1999	193	441.6	-	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

RESEARCH LINES

Number	Title
1	INNOVATIVE DIAGNOSTIC – THERAPEUTIC STRATEGIES
2	CLINICAL PEDIATRICS AND PERINATAL MEDICINE
3	IMMUNOLOGY AND RHEUMATOLOGY
4	ONCOLOGY AND HEMATOLOGY
5	NEUROMUSCULAR DISEASES
6	PEDIATRIC SURGERY

SCIENTIFIC PRODUCTION YEAR 2012 FOR RESEARCH LINE

Figure 1 – Impact Factor for Main Research Lines 2012

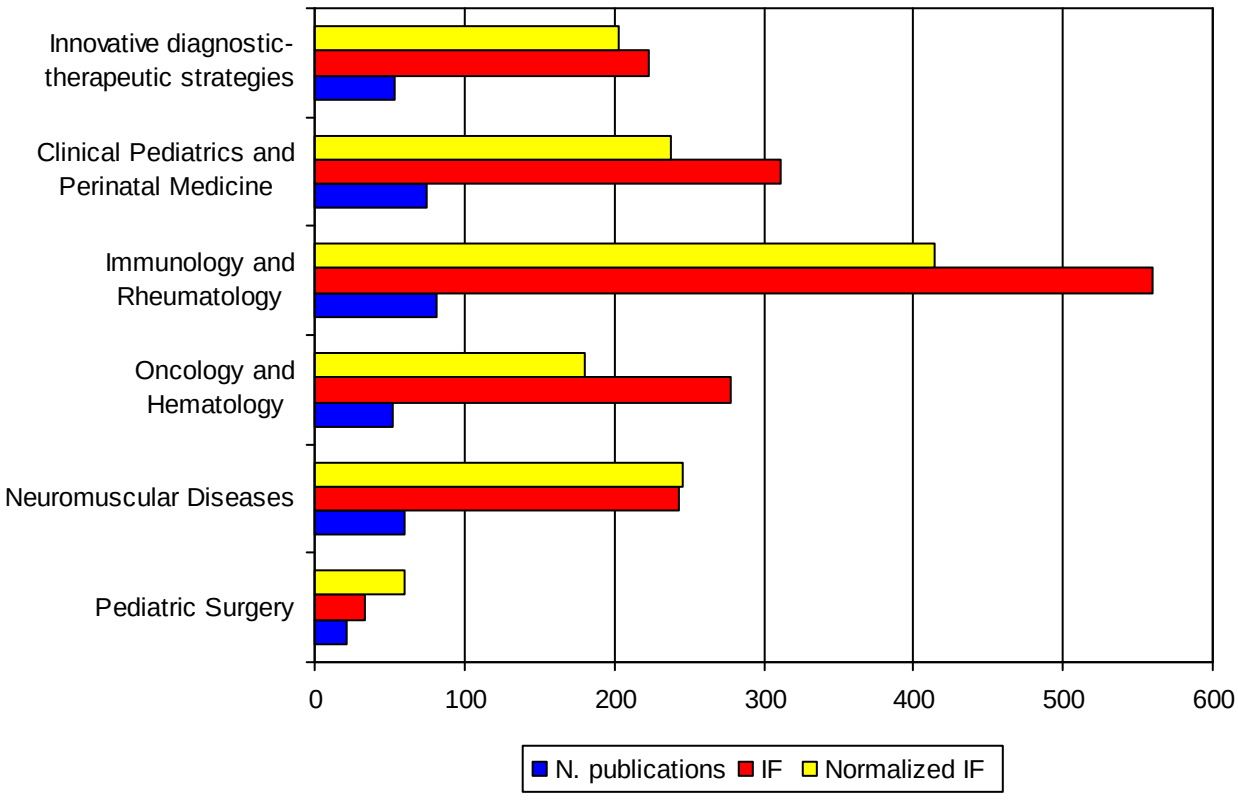


Figure 2 – Number of Publications

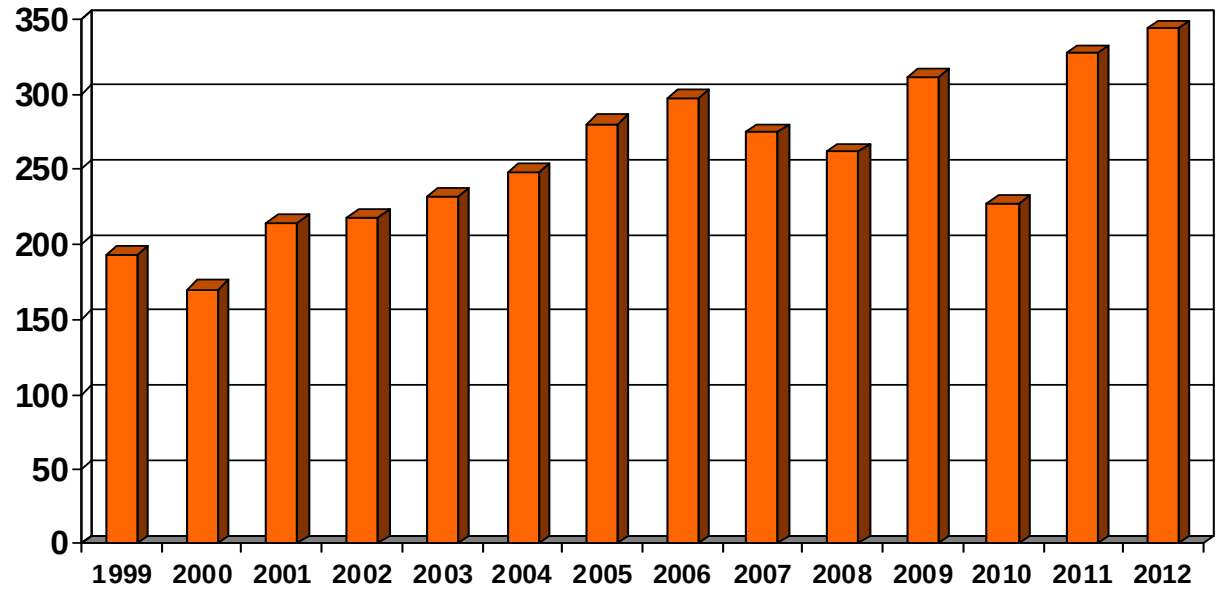
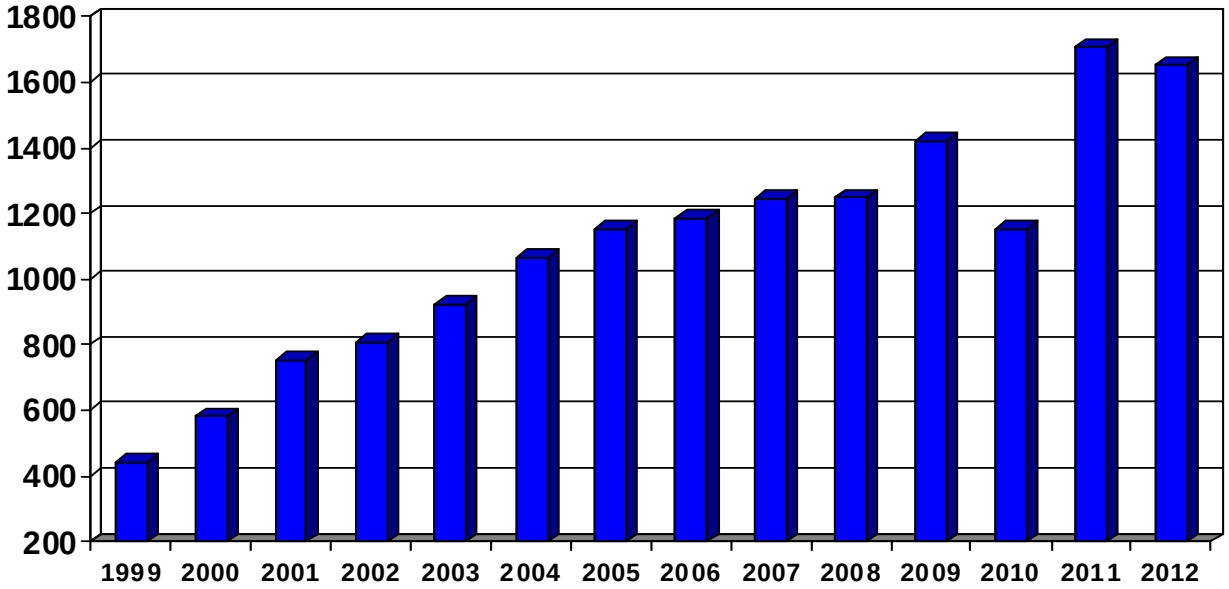


Figure 3 - Impact Factor



RESEARCH LINES AND PUBLICATIONS 2012

Research line 1
Innovative diagnostic-therapeutic 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, Dr. Giovanni Melioli, Dr. Claudio Gambini

Project description (outline and objectives)
General objective of the project was to identify innovative strategies to be translated into the medical practice, in terms of new diagnostic methods and new options for therapies and/or treatments of pediatric diseases, through a variety of approaches resulting from the specific skills of the different groups involved in the project. Common element was the logical process that, starting from in-depth study of disease mechanisms, leads to the development of diagnostic and therapeutic products. Methods used: given the different skills and methods of participating groups, techniques in the following fields were used: biology and molecular genetics, cellular biology, microbiology and virology, histology, biochemistry, imaging diagnostics, and epidemiology and biostatistics.

Principal investigators
Dr. Claudio Gambini – Pathologic Anatomy
Dr. Luigi Varesio - Laboratory of Molecular Biology
Dr. Giovanni Melioli – Laboratory of Clinical Chemical Analysis
Dr. Mirella Filocamo - Centre of genetic diagnostics and biochemistry of metabolic diseases
Prof. Roberto Ravazzolo – Laboratory of Molecular Genetics and Cytogenetics
Prof. Francesco Frassoni - Laboratory of Postnatal Stem Cells and Cell Therapies
Dr. Gian Michele Magnano - Radiology
Dr. Rossella Rossi - Pharmacy
Dr. Riccardo Haupt – Epidemiology and Biostatistics

Activity year 2012

Pathologic Anatomy - *Director: Dr. Claudio Gambini*

- Study of spontaneous abortion in the first trimester. Correlation between histomorphological aspects and chromosomal anomalies with FISH technique and cytofluorimetry.
- Study of Italian cases from the NB registry of neuroblastomas at onset in adolescents and adults with biomolecular characterization.
- Study of Italian cases from the NB registry of congenital neuroblastomas, morphological and biomolecular aspects.
- Study of atypical Spitz tumors.
- Study of minimal residual disease in patients with neuroblastoma (at onset and in different disease phases) through immunocytochemical investigation with anti-GD2 antibody on samples of bone marrow aspirate, peripheral blood, and apheretic collections.
- Clinical-patological immunohistochemical study and molecular characterization of mixed tumors/myoepitheliomas, juxtacortical bone tumors.
- Study of glucide metabolism in pregnancy: screening, diagnosis, etiopathogenesis, maternal and fetal follow-up; newborn management.
- Study of telomere length and telomerasic activity in oncologic and metabolic disease.

Laboratory of Molecular Biology - *Director: Dr. Luigi Varesio*
Two research lines were followed in 2012: the first one studied tissue microenvironment and the

impact of local signals, in particular hypoxia, on innate immune system cells (NK, DC, MN) and on endothelial and stromal tumor cells. On the basis of the data obtained, we defined molecular signatures specific of response to hypoxia of the different cell types on which the metabolic pathways involved in adaptation to tissue microenvironment will be based. These signatures were integrated with the hypoxic signature of neuroblastoma through a bioinformatic analysis which assigns a weight to each signature in order to balance the contribution of each cell type in the tumor system.
The second research line was focused on the generation of a new murine model of glycogenosis type 1 in which the glucose-6-phosphatase gene is deleted only in the liver at birth.
This model will allow the selective study of liver tissue alterations and the possibile treatment of liver dysfunction. We envisage that mean mouse life expectancy will increase, thus allowing a better experimentation compared to total KO mice. This model will be extended to selective gene deletion in kidney and/or intestine.

Laboratory of Clinical Chemical Analysis - *Director: Dr. Giovanni Melioli*
The identification of reference values (RV) for the results of laboratory investigations performed in pediatric patients becomes every day more and more important. In fact, we calculated that about half RV in pediatrics changes statistically according to age. In particular, some parameters change few days after birth, while others change over a longer time. Actually, the clinical use of non specific RV of a given age can lead to gross diagnostic mistakes. Until a few years ago, the pediatric patient was classified according to arbitrary age ranges. We observed that RV can be calculated more accurately when age is considered a continuous variable: in that case, RV is extremely more usable. In addition, it is possible to modulate RV specificity and sensitivity by using different percentiles: for instance, the 10th and the 90th percentile show increased sensitivity but lower specificity, while 2.5^{th} and 97.5^{th} percentiles show a worse sensitivity but an improved specificity.

Centre of Genetic Diagnostics and Biochemistry of Metabolic Diseases - *Director: Dr. Mirella Filocamo*
Research interests of the Centre include genetics of lisosomal diseases (LD) and genetics of some white matter disorders. Another research line includes the activity and regulation of genetic biobanks.
Among LD, Gaucher disease, due to glucocerebrosidase defect (GBA), is the focus of different projects. In particular, studies are being carried out to elucidate molecular mechanisms underlying bone disease, using zebrafish as animal model (Genzyme Generation Program), and to evaluate molecular mechanisms that can modulate the response to enzyme substitution therapy: among possible factors, the role of LIMP-2 (receptor involved in trafficking of GBA endogenous enzyme) in uptake of GBA exogenous recombinant enzyme is being evaluated.
Among white matter disorders, hypomyelinating leukodystrophies are a topic of great interest for the Centre (FP7-Health EU project). Genotype-phenotype correlation studies were performed, based on *in silico* functional characterization of mutated protein sequences in Pelizaeus-Merzbacher (PMD)-like disease. In the same project, antisense oligonucleotides were used to correct *in vitro* a mutant allele causing an altered splicing pattern in a patient with the classic form of PMD.
Concerning a second research line, the Centre with its genetic biobank supported internal and external 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. Finally, it has continued the monitoring of specific indicators of Biobank regulations.

Laboratory of Molecular Genetics and Cytogenetics - *Director: Prof. Roberto Ravazzolo*
Research was mainly focused on rare genetic diseases and in particular on the following:
- identification of genes responsible for monogenic hereditary diseases;
- development of diagnostic methods for monogenic hereditary diseases;

- development of new diagnostic methods using Next Generation Sequencing;
- studies on the pathogenetic mechanisms of monogenic hereditary diseases;
- studies on functional genomic approaches to identify interrelations among disease genes;
- studies on innovative therapeutic approaches for rare genetic diseases;
- studies on cytogenetic anomalies responsible of rare genetic diseases;
- studies on genomic imbalances by Comparative Genomic Hybridization.

Results have been recently obtained in the following fields: cystic fibrosis, congenital central hypoventilation syndrome; Hirschsprung disease; Alexander disease; progressive ossifying fibrodysplasia; intestinal innervation defects; congenital anomalies of kidney and urinary tract (CAKUT); recurrent fever of genetic cause; congenital limb anomalies; Poland syndrome; animal model of cerebellar ataxia; Nail Patella syndrome.

Laboratory of Postnatal Stem Cells and Cell Therapies - *Director: Prof. Francesco Frassoni*

In 2012, studies were carried out on gene expression (Card analysis) of hemopoietic stem cells (CD34+) from cord and medullary blood before and after transplantation. In addition, the technique of expansion of mesenchymal stem cells (MSC) from the umbilical cord was developed and the protocol of MSC expansion from medullary blood was validated.

Radiology - *Director: Dr. Gian Michele Magnano*

- MR in juvenile idiopathic arthritis allows a direct evaluation of the inflammatory process and bone and cartilage articular damage. For the study of joint cartilages, we further implemented the sequences for T2 mapping and T1 mapping (dGEMRIC), which allow *in vivo* quantitative analysis of collagen/proteoglycans, with the demonstration of early macromolecular alterations (i.e. without morphologic correspondence). We have also demonstrated that synovial CE can be quantified with semiquantitative evaluation (synovitis scoring system) and also with the calculation of synovial volume, and that it can be used for disease monitoring.
- Data obtained using Whole Body MR (diagnostic tool in systemic inflammatory diseases and in particular in the follow-up of JDM thanks to the simultaneous visualization of all body areas) showed a good correlation between disease activity and muscular signal alteration and new aspects related to the distribution of muscular involvement not predictable on the basis of clinical-laboratory evaluation alone.
- URO MR with functional analysis is a non irradiating diagnostic technique for renal morpho-functional evaluation and represents an alternative to dynamic renal scintigraphy in the study of urologic disease. A multicentre comparative study fMRU-DRS is being conducted in collaboration with the group of the University of Rouen, directed by Prof Dacher. About 150 FMRU examinations were performed; among them, 30 performed in our Institute and 30 performed by the URO MR French group, including functional evaluation (postprocessing analysis with dedicated software - “MRU version 5.0 of ImageJ) were selected and compared with the results of sequential dynamic scintigraphy. Results are still being processed and seem to show a good quantitative correlation between fRMU e DRS data, DRS being still considered the gold standard.

Pharmacy - *Director: Dr. Rossella Rossi*

Research activity included the following projects:

- Weekly high dose liposomal amphotericin B for secondary prophylaxis of invasive fungal disease in immunocompromised children: experience in a series of pediatric cases.
- Treatment 3. Etanercept in Fanconi’s anemia; US and Italian experience.
- Response to rituximab in 3 children with opsoclonus-myoclonus syndrome resistant to conventional treatments.

Epidemiology and Biostatistics - *Director: Dr. Riccardo Haupt*

In 2012, the following research projects were carried out:

- Methodological-statistical activity for the analysis of data from clinical trials or observational studies in infectivology, hemato-oncology, endocrinology, metabolic diseases, and neonatology.
- Italian Neuroblastoma Registry (RINB). Clinical and anatomopathological data on children and

adolescents with diagnosis of neuroblastoma from AIEOP centres (Associazione Italiana Ematologia Oncologia Pediatrica) are collected and processed. Over 3,000 cases were included in the Registry and about 120 new cases are added every year.

- Off-therapy Registry (OTR). Data on children treated for tumor in AIEOP centres who have completed their therapeutic programme are collected and processed. Over 14,000 cases were included in the Registry.
- International registry on the association between Langerhans cell histiocytosis (LCH) and malignant tumor.
- Collaboration with the Rheumatology unit a) for the analysis of data from clinical trials (RCT) studying 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 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.
- Application of bivariate and multivariate biostatistical methods in clinical epidemiology of rheumatic or oncologic rheumatic diseases in the child.

Publications year 2012

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IF: 2.164 Norm. IF: 2.

5) Benzi Fabio, Vanni I., Cassina G., Ugolotti Elisabetta, Di Marco Eddi, Cirillo Carmelina, Cristina Emilio, Morreale Giuseppe, Melioli Giovanni, Malnati M., Biassoni Roberto.
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IF: 3.969 Norm. IF: 4.

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The role of basophil activation test in special populations with mastocytosis and reactions to hymenoptera sting.
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NUCLEIC ACIDS RES 2012; 40(11): e84.
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A validated HPLC method for the monitoring of thiopurine metabolites in whole blood in paediatric patients with inflammatory Bowel disease.
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IF: 2.991 Norm. IF: 6.

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Research line 2
Clinical Pediatrics and Perinatal Medicine

Title
Clinical-translational studies on perinatal and pediatric diseases with genetic or immunologic basis

Coordinators
Prof. Renata Lorini, Prof. Giovanni Rossi, Prof. Pasquale Di Pietro, Prof. Giorgio Bentivoglio

Project description (outline and objectives)
In this research line, translational research concerns the transfer of basic research results to the clinical practice in the pediatric field. These studies are the result of continuing education and of the discovery of diagnostic and therapeutic procedures at the Istituto Gaslini, which include and combine elements from different scientific areas and considerably large series of cases with perinatal and pediatric diseases having a genetic or immunologic basis.
In some cases, effective and promising research is carried out, well guided by clinical needs (genetic diagnostics of highly frequent diseases; development of new disease biomarkers; application to the study and therapy of pediatric diseases; applications in the field of solid organ transplantation), thanks to wide scientific knowledge that is important for the understanding of experimental mechanisms and of the considerable impact, in a reasonable time, on the therapy of pediatric diseases.

Principal investigators
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 Pneumology and Allergology
Prof. Pasquale Di Pietro – Pediatric Emergency/Urgency
Prof. Giorgio Bentivoglio – Obstetrics and Gynecology
Dr. Luca Antonio Ramenghi – Neonatal Pathology

Activity 2012

Pediatric Clinic - *Director: Prof. Renata Lorini*
In the Laboratory of Diabetology of the Pediatric Clinic in 2012, molecular analysis was performed by direct sequencing of genomic DNA of 67 subjects with: occasional hyperglycemia, diabetes mellitus (DM) or glycosuria in the absence of antibodies against autoimmune beta cell (DM1 marker). Differential diagnosis based on clinical and metabolic data included MODY (*GCK, HNF1a, HNF1b*), Wolfram 1 syndrome and Wolfram 2 syndrome (*WFS1, ZCD2*), neonatal diabetes (*GCK*, *KCNJ11*) and familial renal glycosuria (*SLC5A2*). Of the 67 requests of genetic analysis, 36 were made by the Istituto Gaslini and 31 by other institutions. *GCK* gene analysis, performed in 37 subjects (17 from Gaslini), showed mutations in 16 patients. *HNF1a* gene analysis, performed in 7 subjects (6 from Gaslini), showed mutations in 2 patients. *HNF1b* gene sequencing performed in 5 subjects (4 from Gaslini) did not show any mutations. *KCNJ11* gene analysis performed in a patient with neonatal diabetes and in 1° and 2° degree relatives showed mutations in the proband and in the mother. This allowed the suspension of insulin therapy and its substitution with sulphonylurea. *SLC5A2* gene analysis performed in 2 patients with glycosuria in the absence of hyperglycemia and in their relatives (4 subjects from Gaslini) showed a variant in the two siblings and in the father. *WFS1* gene analysis, performed in 5 subjects from other institutions, showed a mutation in homozygosis in 1 patient and mutations in heterozygosis in 3 parents. *ZCD2* gene analysis, performed in 1 patient with Wolfram syndrome and peptic disease and in her relatives, showed deletion in homozygosis in the proband and in heterozygosis in her relatives.

Laboratory for the standardization and check of screening of endocrine and metabolic diseases
In 2012, the following studies were carried out:

- Development and validation of *2nd tier test* applied to extended neonatal metabolic screening (Regione Liguria): *2nd tier tests* performed on the same blood spot screening card are able to assay analytes that cannot be identified by 1st tier tests, being their presence strongly suggestive of a specific metabolic disease. This makes it possible to filter positives at the first test, lowering recall threshold and, most of all, assuring the identification of all affected subjects and reducing the number of recalled subjects and consequently the psychological impact on the families.
- Kuvan Adult Maternal Paediatric European Registry-Kamper: Some forms of phenylketonuria can be responsive to BH4 cofactor of phenylalanine hydroxylase enzyme. Sapropterin (Kuvan) is the synthetic version of BH4 existing in nature. Primary objective of the study involving 9 European countries is the evaluation of long-term safety in treated subjects, trying to obtain further information on growth indicators in subjects with phenylketonuria treated with the drug, on the degree of adherence to therapy and possible diet, and on the long-term sensitivity of sapropterin therapy.
- Psychometric validation of questionnaires assessing the impact of phenylketonuria on patients' and parents' quality of life - PKU-QOL: Diet therapy is the essential therapy of phenylketonuria. However, due to the type of food used and, in particular, of amino acid mixtures lacking phenylalanine, it is often difficult to follow, especially by adolescents and adults. Objective of the study was to evaluate the impact of phenylketonuria and of the effects of treatment on the quality of life.

Dermatology - *Director: Dr. Corrado Occella*
In 2012, we studied neurocutaneous melanosis (NCM – a rare, non-familial, congenital, neurocutaneous syndrome), characterized by melanocytic nevi and excessive proliferation of melanocytes in the CNS. In particular, we examined the pathologic surgical characteristics of a lesion in the right temporal lobe in a 3-year-old child with NCM and complex partial seizures. The study of this case confirms that NCM must be listed among the possibile causes of chronic drug-resistant partial epilepsy. Surgical resection should be considered for the treatment of this type of lesion.

Pediatric gastroenterology with digestive endoscopy - *Director: Dr. Arrigo Barabino*
We retrospectively analyzed the patient records of all children who, from May 1997 to March 2012, presented a severe attack of ulcerative colitis, defined on the basis of an international clinical score, refractory to first line treatment with i.v. steroid, and who therefore underwent rescue therapy with i.v. and oral cyclosporine. Objective of the study was to evaluate the efficacy and safety of the drug, in order to avoid colectomy on an urgency or delayed basis. The study was concluded and presented as an abstract in occasion of the last national congress of SIGENP. We identified 42 children with 43 severe attacks. In 27% of cases, treatment was ineffective and it was necessary to perform colectomy on an urgency basis after mean 6 days. In 73% of cases, clinical treatment was effective after mean 6 days, with no need for surgery. In the long-term, among this patient group, 32% underwent early colectomy (on average within one year from the severe attack), while 68% maintains the colon at mean 3.5 years (range 2.8-9.8 years). In 8 patients (18%), side effects were observed and their severity required the suspension of treatment in 5 of them (11%). The study still lacks statistical analysis for the search for elements of outcome predicitivity.
The scope of the study, which is still ongoing, is very topical in pediatric gastroenterology since 1) it has been recently dealt with in guidelines of international scientific associations; 2) cyclosporine is opposed to biological Infliximab; 3) at present, only about 90 cases of children treated with this drug have been published.

Nephrology, Dialysis and Transplantation - *Director: Dr. Gian Marco Ghiggeri*
We studied different cell populations potentially involved in the activation and regulation of mechanisms that determine the onset of idiopathic nephrotic syndrome (iNS).

In monocytes, isolated from peripheral blood of patients with iNS, we evaluated the membrane expression of urokinase Plasminogen Activator Receptor (uPAR). The study was carried out also in normal controls and in patients with other renal diseases of different etiologic origin, in order to evaluate the specificity of the marker as iNS causative agent and to correlate its expression with disease severity, in particular with response to drugs and with remission of proteinuria. The presence of the receptor in soluble form (sUPAR) in the patients' serum was investigated and the possible mechanisms determining its release and remote action were evaluated. The role of regulatory T cells (Tregs) in iNS patients and the possible induction of these cells in response to different therapeutic protocols were studied. The contribution of Tregs is still being studied, in particular concerning their potential capacity to modulate the course of iNS, by using transgenic mice. In them, the disease was induced through the inoculation of LPS, which presumably activates oxidative burst and therefore the real causative role of this mechanism was studied in parallel in a defective animal strain lacking expression of P2X7, the main receptor activated by ATP, which is known to trigger the inflammatory process. This animal model allows an easy visualization of Tregs in peripheral blood and in the main lymphoid organs, and therefore their activation after different *in vivo* treatments. Experiments aimed at *in vitro* preactivation of autologous Tregs, previously activated by cell sorting, are ongoing in order to strengthen their activity and ability to regulate *in vivo* in the experimental animal the pathogenetic mechanisms of iNS.

Pediatric Pneumology and Allergology - *Director: Prof. Giovanni A. Rossi*
In 2012, the following studies were carried out:

- We evaluated *in vitro* the effect of drugs able to increase [cAMP]i levels on repair processes of bronchial epithelium exposed to cigarette smoke. Using human bronchial epithelial cell line (BEAS-2B), we demonstrated that preincubation of cells with cAMP analogue, Salmeterol or Roflumilast N-oxide (a selective inhibitor of PDE4), induced a significant increase in BEAS-2B migration to fibronectin. A significant reduction of the distance between wound margins was observed. Therefore, drugs normally used in the clinical practice as bronchodilators can favour *in vivo* tissue repair processes in allergic or infectious respiratory diseases.
- In order to evaluate bronchial reactivity (BHR) in children/adolescents practising competitive sports, we enrolled 30 subjects playing tennis or soccer and 32 subjects practising swimming. BHR and asthma-like symptoms were more frequent in swimmers alone and FEV_1 and Tiffenau index correlated with the duration of competitive activity, suggesting that this activity could improve especially lung volume. The higher frequency of BHR in swimmers could be due to higher irritability of airways due to exposure to chloride.
- To evaluate the reliability of the Visual Analogic Scale "VAS" in the screening of pediatric asthma, 703 children [mean age 10.3 years (range 8.3–12.6)] were recruited. In the analysis of the whole population, the frequency of bronchial obstruction was limited to 6.5%. Therefore, to have a balanced sample of subjects with and without bronchial obstruction, the analysis was performed in a sample including all subjects with bronchial obstruction (N=46) and only some of the subjects without bronchial obstruction (N=92) (1:2 ratio). VAS correlated with FEV_1 (r=0.47) and/or $FEF_{25–75}$ (r=0.42). VAS value equal to 6 resulted a reliable cutoff to distinguish children with bronchial obstruction [sens: 80.4, spec: 69.6, AUC: 0.8 (0.8–0.9), diagnostic OR: 9.4 (4.0–22.1)].

Pediatric Emergency/Urgency - *Director: Prof. Pasquale Di Pietro*
In 2012, the following studies were carried out:

- SONDO (research activity supported by AIFA – Italian Medicines Agency).
- AIFA: Monitoring of safety and evaluation of appropriateness of antibiotic use in children with bronchopneumonia, pharyngotonsillitis, and acute otitis media of Liguria region.
- SINIACA (National Informative System of Accidents in Citizens' Houses) – JAMIE.

Obstetrics and Gynecology - *Director: Prof. Giorgio Bentivoglio*
In 2012, the following studies were carried out:

- In the colposcopy outpatient service, cervical biopsies were investigated not only for dysplasia

but, in women persistently HPV-positive and diagnosed with L-SIL or ASC-US, the presence of p16 protein in cytology samples was evaluated.
- In collaboration with the Pediatric Clinic, controls of glucide metabolism were performed by GCT/OGTT, serial echographies, evaluation of delivery, and subsequent newborn controls.
- RNA study (RNA-based non invasive aneuploidy): an LTD laboratory developed test was concluded for single pregnancy with optimal results (our centre resulted first in Europe and second in the world for number of referred cases). Further studies are ongoing on medically assisted conception and twin pregnancies and pregnancies in the normal population.
- Breast carcinoma in pregnancy. Besides following the only three cases of breast carcinoma during pregnancy and at delivery and evaluating the anatomopathological aspects of the placenta and newborn health and development, many pregnant women were selected for anamnestic or actual risks and referred for echographic examination to the Cancer Research Institute. Cancer was not found in any of them.

Neonatal Pathology - *Director: Dr. Luca Antonio Ramenghi*

In 2012, the following studies were carried out:
- Treatment of hypotension in highly preterm newborns (multicentre randomized controlled study).
- SLI – Sustained Lung Inflation in highly preterm newborns in the delivery room (multicentre randomized controlled study).
- Non-invasive brain monitoring of high-risk newborns by cerebral function monitoring.
- Supplementation of maternal diet with omega 3 fatty acids (DHA) in the first month of breast feeding.
- Oxidative stress and lipid emulsions in the preterm newborn.
- Lung oxygenation in the newborn.
- Perinatal and postnatal diagnostic and therapeutic approach to neonatal lymphatic dysplasias.
- Volume guarantee ventilation in the early phase and during weaning of the newborn with RDS.
- Monitoring of vital parameters and integration with respiratory mechanics parameters during neonatal mechanical ventilation.

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Research line 3
Immunology and Rheumatology

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

Coordinators:
Prof. Lorenzo Moretta, Prof. Alberto Martini, Dr. Vito Pistoia

Project description (outline and objectives)
Overall, objective of the project was to analyze the physiopathological aspects of different pediatric diseases and correlate the data obtained with the patients' clinical picture. In particular, hematologic and non-hematologic tumors such as leukemias and neuroblastoma, autoinflammatory syndromes and autoimmune diseases such as juvenile idiopathic arthritis, juvenile dermatomyositis, and diabetes type I. Methodology: Results were obtained with basic research techniques using material derived *ex vivo* from patients and healthy donors, *in vivo* experimental models using immunodeficient mice and collection of clinical data: long-term follow up of patients (diagnosis, active disease, remission, minimal residual disease), quality of life, and response to innovative biological therapies.

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

Activity year 2012

Clinical and Experimental Immunology - *Director*: *Prof. Cristina Bottino*
In 2012, the following studies were carried out:
- Study of KIR repertoire in hemopoietic stem cell (HSC) donors and statistical correlation with post-transplant clinical data of leukemic patients (survival, relapse).
- Analysis of the role of cytomegalovirus (HCMV) infection in the function/maturation of natural killer (NK) cells after HSCT from umbilical cord blood.
- Characterization of the interaction between NK cells and macophages of healthy subjects or tumor patients (tumor-associated macrophages - TAM)
- Analysis of the ability of soluble factors produced by tumor cells to modulate the function and phenotype of NK cells
- Characterization of new serological markers of autoimmune diseases

Pediatric Rheumatology - *Director: Prof. Alberto Martini*

In 2012, the following studies were performed:
- Definition of the disease status that is considered acceptable by the parent and by the patient in juvenile idiopathic arthritis
- Opinion poll conducted among international pediatric rheumatologists for the identification of the most useful diagnostic parameters for the identification of macrophage activation syndrome.
- Development of cut-off values of the Juvenile Arthritis Disease Activity Score (JADAS) that identify disease activity states in juvenile idiopathic arthritis.
- Identification of factors associated with the achievement of remission in children with juvenile idiopathic arthritis treated with etanercept (the project was funded by Wyeth-Pfizer).
- Evaluation of the efficacy of methotrexate in preventing the onset of uveitis in children with juvenile idiopathic arthritis.
- NMR study of the main pathologic aspects that can be observed in juvenile idiopathic arthritis (JIA): the study was concluded with the standardization of the image acquisition protocol and with the development and preliminary validation of a semiquantitative score for the evaluation of the importance of the inflammatory process and of the structural damage. In parallel, a research

study is carried out for the development of a software for the automated quantitative evaluation of NMR. To date, software has been developed and validated for the quantitative analysis of enhancement curves after administration of contrast medium and for the automated evaluation of synovial volume. Software is being validated for the automated reading of the progression of erosion damage and for functional-ultrastructural evaluation of constitutive macromolecules of the cartilaginous matrix. A score has been recently developed and validated for the evaluation of disease activity using total body NMR in patients with juvenile dermatomyositis.

In 2012, the following aspects of autoinflammatory diseases were evaluated:

1) Evaluation of the clinical impact of MEFV genotype in familial Mediterranean fever;
2) Long-term follow-up of CAPS patients treated with anti-IL-1 monoclonal antibody (Canakinuma);
3) Role of TH17 in CAPS syndrome (in collaboration with the Istituto di Ricerca in Biomedicina, Bellinzona);
4) Role of autophagia in the pathogenesis of TRAPS syndrome (in collaboration with the Laboratory of Molecular Genetics);
5) Study of the mechanisms of IL-1 production in familial Mediterranean fever (Ricerca Corrente, Telethon).

Laboratory of Oncology - *Director: Dr. Vito Pistoia*

- The family of HLA class Ib molecules includes HLA-G, HLA-E, HLA-F, and HLA-H. These molecules that, unlike those of HLA class Ia, have a low degree of polymorphism, are expressed not only on the surface of different cell types, but also in soluble form in biological fluids. The physiological role of HLA-G is to create a tolerogenic environment at the materno-fetal interface by inhibiting immune response to fetal tissues. HLA-G exerts different immunoregulatory functions: 1) inhibition of cytotoxicity mediated by cytotoxic T lymphocytes and NK cells; 2) induction of apoptosis of $CD8^+$ T lymphocytes and NK cells; 3) downregulation of the expression of some chemokine receptors on T lymphocyte surface and inhibition of chemotaxis at corresponding ligands; 4) modulation of the release of cytokines and pro-angiogenic factors by $CD56^{bright}$ NK cells. HLA-G molecules exert these functions by interacting with at least four different inhibiting receptors: immunoglobulin-like transcript (ILT)2 (expressed by T, B, NK cells and monocytes), ILT4 (on monocytes), KIR2DL4 (on NK cells), and CD160 (on T, NK, and endothelial cells).

  The main function of HLA-E is the presentation of peptides deriving from the leader sequence of HLA class Ia molecules to NK cells through the interaction with the CD94/NKG2A complex, allowing NK cells to monitor HLA class I molecule expression levels. The interaction between HLA-E/peptide complex and CD94/NKG2A inhibits NK cytotoxicity.

  Little information is available on HLA-F and HLA-H. Intracellular expression of HLA-F was demonstrated in resting lymphocytes, while surface expression was identified after cellular activation, suggesting that HLA-F is a potential marker of immunological activation. In addition, HLA-F is expressed irrespective of the association with peptides and HLA-F heavy chain interacts with heavy chains of HLA-Ia molecules, suggesting a role of HLA-F in the control of expression and function of HLA-Ia molecules.

  Objective of this project is to characterize the expression and function of HLA-Ib molecules in patients with autoimmune and inflammatory diseases or tumors. The role of HLA-G in tumor mechanisms has been largely characterized. The expression of surface HLA-G is upregulated in different human tumors and molecule concentration in the serum of tumor patients is higher than in normal subjects. Conversely, the concentration of soluble HLA-G (s) in the serum of patients with different autoimmune diseases (such as rheumatoid arthritis, multiple sclerosis, and systemic lupus eryhtematosus) is lower than that found in normal subjects, suggesting that low sHLA-G levels can cause a persistent activation of the immune system that predisposes to these diseases.

  However, information is lacking on HLA-G function, HLA-G-modulated intracellular signaling pathways, and possibile regulation of microRNA (miRNA) expression induced by HLA-G. In addition, the role of HLA-E and HLA-F in tumors and chronic inflammatory diseases with autoimmune pathogenesis is still not well-known today.

The project is aimed at filling this gap by focusing on neuroblastoma as a model of tumor and multiple sclerosis as a model of inflammatory autoimmune disease.
Last year a study was conducted on the role of miRNA in the regulation of gene expression induced by sHLA-G in CD4+ activated human lymphocytes. The specifically analyzed function was modulation induced by sHLAG of CXCR3 chemokine receptor. We demonstrated that miR 451 is downregulated, while miR 210 is upregulated in CD4+ cells incubated with sHLA-G; none of the two miRNAs is involved in the regulation of CXCR3 expression. Analysis of miR210 and miR451 target genes demonstrated an increased expression of *OSR-1 (odd*-skipped related 1) and HBP-1 (HMG-box transcription factor 1), and a decreased expression of CXCL16 (chemokine C-X-C motif ligand 16) and C11orf30 (chromosome 11 open reading frame 30) in CD4+ lymphocytes treated with sHLA-G.

- Neuroblastoma (NB) is a pediatric tumor that, in about half cases, appears as metastatic disease at diagnosis; two thirds of these patients does not survive 5 years in spite of the use of the most advanced therapies. Immunotherapy of NB with non HLA-restricted lymphocyes is an interesting perspective since this tumor expresses very low or no levels of HLA class I molecules. Circulating γδ T lymphocytes belong prevalently to Vδ2γ9 subset lysing tumor cells through mechanisms depending on T cell receptor (TCR) or on NKG2D stimulatory molecule of cytotoxicity. In both cases, recognition of tumor cells does not depend on HLA restriction. Biphosphonates are inhibitors of bone reabsorption used for therapy of osteoporosis and bone metastases. A particular aminobiphosphonate, zoledronate (ZOL), causes an accumulation in target cells of IPP metabolite that is recognized by TCR of Vδ2γ9 T lymphocytes. These latter are activated to proliferate and expand from zoledronate. Therefore, we have developed a preclinical model of immunotherapy of NB based on the combination of Vδ2γ9 T lymphocytes and ZOL. First we demonstrated the feasibility of *in vitro* expansion of Vδ2γ9 T lymphocytes from peripheral blood of normal donors and patients with metastatic NB by stimulation with ZOL. Subsequently, we developed an orthotopic model of human NB and we implanted HTLA-230 NB cell line in the adrenal gland of immunodeficient mice that were then treated with systemic administration of *in vitro* expanded Vδ2γ9 T lymphocytes, ZOL, Vδ2γ9 T lymphocytes with ZOL and diluent. The results obtained demonstrated a significant improvement in terms of survival only for the combination Vδ2γ9 T lymphocytes plus ZOL. Histological and immunohistochemical analyses in animals treated with this latter combination showed an inhibition of the proliferation and induction of apoptosis of tumor cells combined with inhibition of angiogenesis. Tumors were infiltrated by Vδ2γ9 T lymphocytes, i) cytotoxic since positive for the antigen associated with Tia-1 cytotoxic granules and ii) expressing IFN-γ, which in turn induced an intense expression in tumor cells of CXCL10 anti-angiogenic chemokine, but not of CXCL9. On the other hand, inoculated Vδ2γ9 T lymphocytes expressed CXCR3, CXCL10 receptor, suggesting that CXCL10 can be involved in their recruitment in the tumor mass. These studies, that must be continued to optimize timing and schedule of the association Vδ2γ9 T lymphocytes + ZOL, lay the foundations for the design of a phase I study on NB.

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Research line 4
Oncology and Hematology

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

Coordinators:
Dr. Giorgio Dini, Dr. Elio Castagnola

Project description (outline and objectives)
General objectives: - Study of new diagnostic modalities in infectious diseases, including monitoring of etiology of bacterial and fungal infections in children undergoing antineoplastic chemotherapy or bone marrow transplantation, focusing on the onset of drug-resistant strains. – Phase III study of new antifungal and antiviral drugs in infectious diseases. – Development of new therapeutic approaches in pediatric solid tumors. – Clinical follow-up of off-therapy subjects previously affected by a pediatric-onset tumor. – Physiopathology of allogenic HSCT: clinical and immunological aspects. – Extension of home care to patients with non-hematologic diseases. – Bone marrow failure in pediatrics. – New diagnostic-therapeutic tools. – Evaluation of immunomodulating effects of apheretic procedures. – Comparison between healthy subjects and patients with autoimmune diseases. – Applied methodology: Monitoring of the etiology of bacterial and fungal infections in children undergoing antitumoral chemotherapy or bone marrow transplantation, with particular reference to the appearance of drug-resistant strains. – Development of new therapeutic approaches in pediatric solid tumors. – Development of second lline protocols; Ethics Committee approval. – Recruitment of eligible patients. – Clinical follow-up of off-therapy subjects previously affected by a tumor in pediatric age – Definition of a scheme for paper and electronic filing of a short clinical history and exposure to chemotherapy or radiotherapy or surgery of each subject who has completed electively the therapeutic programme. – Development of a “passport” to be given to each subject who completes electively the therapeutic programme. This document must also contain recommendations for follow-up on the basis of guidelines. – Physiopathology of allogenic HSCT: clinical and immunological aspects. – Development of second line protocols; Ethics Committee approval. Recruitment of eligible patients. – Evaluation of the possibility to extend new health care delivery modalities (home care) to non-hematology/oncology patients. Survey of non-hematological diseases that could benefit from home care. Calculation of costs and needs. – Bone marrow failure in children. New diagnostic and therapeutic approaches. – Development of second line protocols; Ethics Committee approval. Recruitment of eligible patients. – Evaluation of immunomodulating effects of apheretic procedures. – Comparison between healthy subjects and patients with autoimmune diseases. – Study of leukocyte subpopulation and of plasma levels of TGFβ1, sHLA class I and soluble Fas ligand from peripheral blood sampling before, immediately after, and at 7 and 14 days from the apheretic procedure performed for donation or therapy (chronic inflammatory disease).

Principal investigators
Dr. Giorgio Dini – Oncology, Hematology and Bone Marrow Transplantation
Dr. Elio Castagnola – Infectious Diseases
Dr. Gino Tripodi - Immunohematology and Transfusion Medicine

Activity year 2012

Oncology, Hematology and Bone Marrow Transplantation - *Director*: *Dr. Giorgio Dini*
In 2012, the following studies were carried out:

- Off-therapy project: management of medium- and long-term sequelae induced by treatment, surveillance for second tumor, in collaboration with other units.
- Bone marrow failure: study of mechanisms underlying bone marrow injury; leukemias; study of genetic-metabolic factors favouring the development of disease and negative prognostic markers.

- Characterization of antiphospholipid antibodies in pediatric age; identification and prevention of venous thrombotic risk; non-invasive prenatal diagnosis; epidemiologic study of genetic and acquired risk factors correlated to thromboembolic diseases.
- Study of manignant tumors in patients aged < 3 years; intracranial germ cell tumors and cerebral rhabdoid tumors.
- Neuroblastoma: prognostic factors and innovative therapeutic modalities; phase I and II studies and new antiblastic drugs in pediatrics.
- Prospective study on the incidence and evolution of hepatic venocclusive disease after HSCT: role of defibrotide prophylaxis; phase II prospective study on treatment of graft-versus-host disease (GVHD) refractory to cortisone treatment.
- Evaluation of the possibility to create a new system for payment of home care delivery services.
- In addition, several activities were carried out which have significantly improved the efficiency and quality of the diagnosis of rare diseases and, indirectly, of treatment efficacy, namely:

  Genotype-phenotype analysis (cellular, somatic and hematological) of 90 Italian patients with Fanconi's anemia (data from national database at our unit) (completed)

  Analysis of immunological phenotype of 25 Italian patients with Fanconi's anemia (completed).

  Molecular analysis of 5 Italian patients with congenital dyskeratosis (completed).

  Molecular analysis of 5 Italian patients with genetic neutropenia (data from the Italian Registry of Neutropenias at our unit) (completed).

  Analysis of the infectious clinical profile of 73 neutropenic patients (data from the Italian Registry of Neutropenias at our unit) (completed).

  Analysis of the infectious profile of Italian aplastic patients (completed).

  Clinical hemato-immunological database of patients with immunological cytopenias (started).

  Analysis of pharmacological inhibition of P38MAPK in bone marrow hematopoietic cells of patients with Fanconi's anemia (implemented).

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

Monitoring of epidemiology of infections in children undergoing antitumoral chemotherapy or HSCT was continued: invasive bacterial and fungal infections. This activity has led to the development of local tailored therapeutic protocols based on type of underlying disease and the different therapeutic phases. In addition, it allowed the participation in national and international cooperative studies evaluating this type of infections and their management (see enclosed references) and in international study groups for the development of guidelines for the treatment of febrile neutropenia in children (J Clin Oncol. 2012 Sep 17. [Epub ahead of print]) and for the management of Candida infections (Clin Microbiol Infect 2012; 18, suppl. 7: 1-77).

Data have been collected on the efficacy and toxicity of treatment protocols for particular infectious conditions such as indwelling CVC-related bacteremias and invasive fungal infections that are presently undergoing statistical analysis.

Data have been collected on the performance of diagnostic tests for invasive fungal infections in children (search for 1-3-beta-D-glucan) who will undergo statistical analysis in the next future.

Immunohematology and Transfusion Medicine - *Director: Dr. Gino Tripodi*

We evaluated CD4+ and CD8+ lymphocytes, neutrophils, and monocytes sampled before, immediately after, and at 7 and 14 days from the apheretic procedure performed for donation (healthy subjects) or for therapy (patients with autoimmune disease) for three successive procedures with 2-week interval from each other. Evaluated parameters were the following: absolute count, cell cycle and phenotype, intracellular concentration of $TGF\beta_1$ (protein and mRNA). Simultaneously, we evaluated the plasma levels of $TGF\beta_1$, sHLA class I and soluble FasL both in samples obtained directly from donors and, subsequently, in plasma present in circuits at the end of apheretic procedures. We demonstrated that the significant increment (lasting over time) of $TGF\beta_1$ concentrations in neutrophils, monocytes and $CD8^+$ lymphocytes

after the apheretic procedure is reproducible at each procedure in both groups. In the donor group, plasma levels of $TGF\beta_1$ and sHLA-I result significantly increased up to fourteen days after the apheretic procedure, but the increase results significantly higher in patients. Plasma vaIues of FasL in donors do not show any significant changes while in patients there is a progressive and steady increase both after each procedure and when apheresis is repeated. Similarly to what has been demonstrated after transfusion, it is possible to hypothesize that, even during the apheretic procedure, there is an immunomodulating effect correlated with the capacity to induce transcriptional and post-transcriptional modulation of $TGF\beta_1$ following interactions of leukocytes with high concentrations of sHLA-I observable in circuits. This effect appears much more significant in the patient group, in which FasL and $TGF\beta_1$ levels appear much higher and show a progressive increment correlated with repetition of the apheretic procedure.

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Research line 5
Muscular and Neurologic Diseases

Title
Genetic-functional, morphological and clinical-rehabilitation studies in pediatric neurologic and muscular diseases

Coordinators
Prof. Carlo Minetti, Dr. Armando Cama

Project description (outline and objectives)
General objectives include the implementation of clinical, morphological, and genetic-functional studies on patients and experimental models in the field of neurologic and neuromuscular diseases. Applied methodology includes both clinical and neuroradiological evaluation of patients with pediatric neurological diseases and functional studies on in vivo and in vitro experimental models.

Principal investigators
Prof. Carlo Minetti – Pediatric Neurology and Muscular Diseases
Dr. Armando Cama - Neurosurgery
Prof. Edvige Veneselli – Child Neuropsychiatry
Dr. Andrea Rossi - Neuroradiology
Prof. Ezio Casari – Clinical Psychology
Dr. Paolo Moretti – Physical Therapy and Rehabilitation

Activity year 2012

Pediatric Neurology and Muscular Diseases - *Director: Prof. Carlo Minetti*
In 2012, the following studies were carried out:

- *Clinical and molecular characterization of a new leukoencephalopathy due to hyccin deficit*
  After the initial identification of patients with hypomyelinization and congenital cataract, we described 6 new cases with new mutations. Data show that, in spite of a higher clinical variability compared to the first description, the neuroradiological picture at MR is constant in all patients and therefore distinguishes this leukoencephalopathy from other hypomyelinating forms. In parallel, the laboratory generated hyccin knock-out mice and analyzed their neurological phenotype. In this model, deletion of the hyccin gene causes a delayed myelinization at the level of the CNS, with a reduction of myelinized fibers and axonal caliber.
- *Genotype-phenotype correlation in Neurofibromatosis type 1*
  In order to identify genetic factors modifying the clinical picture of neurofibromatosis, we identified 10 parent-child discordant couples. These couples will undergo exome sequencing for the identification of genetic factors specifically associated with mild or severe NF1 picture.
- *Study of functional molecular mechanisms in the pathogenesis of primary myopathies: perspectives of new therapeutic approaches*
  In order to identify which components of the proteasome system are specifically involved in degradation of the dystrophin complex in Duchenne muscular dystrophy, we determined a specific upregulation of E3 ubiquitin-protein ligase TRIM32 in a cohort of genetically confirmed DMD patients. Induction of TRIM32 was confirmed in degenerating muscular fibers and this induction correlates with disease severity. TRIM32 increase is specific for DMD since it is not present in muscular dtstrophies caused by other genetic defects (merosin, dysferlin, sarcoglycans).
- *Identification of genomic rearrangements involving neuronal ion channels in generalized idiopathic epilepsies*
  We performed a screening of about 400 genes coding for neuronal ion channels in 150 cases of generalized idiopathic epilepsy and in 150 controls for the identification of genomic rearrangements significantly associated with epilepsies. The study showed that the cumulative incidence of rearrangements does not differ in the two groups.

However, the subjects with epilepsy present a higher number of rearrangements, larger in size ($p< 0.0001$), involving exon regions of candidate genes ($p< 0.003$).

Neurosurgery - *Director: Dr. Armando Cama*

In 2012, the following studies were carried out:

- *Identification of candidate genesi involved in the pathogenesis of Neural Tube Defects (NTD)*
  Neural Tube Defects present a complex inheritance mechanism, due to the interaction of genetic factors with environmental factors, characterized by incomplete penetrance and phenotype variability within the same family. Genetic predisposition to NTD is modulated by the effect of multiple genetic variations, both common and rare, that can play a role in individual risk. It has been demonstrated that genes of Planar Cell Polarity (PCP) signalling pathway, also named non canonical *Wnt* signalling pathway, a cascade of molecular events ultimately aimed at directional polarization of cells within the plane of an epithelium, are involved in NTD pathogenesis both in animal models and in humans. Over the last few years, in collaboration with Dr. Kibar (CHU Sainte Justine Research Center and University of Montreal, Montreal, Canada), our group identified, in overall 629 patients, 74 rare mutations (mainly missense) in 7 essential genes of this signalling pathway, including *VANGL1, VANGL2*, *PRICKLE1*, *CELSR1*, *FZD6, DVL2, and DVL3,* and in a regulatory gene (*FUZ*), all being absent in analyzed controls. In 51 of these rare variants, we demonstrated a pathologic effect on the function of the encoded protein both using predictive software and *in vitro* and *in vivo* biological testing. These mutations can account for 8-10% of NTD cases, both open and closed. These data confirm an NTD inheritance model in which rare multiple variants in genes of the same signalling pathway have a synergic effect on the risk threshold for NTD.
- *Genetic–molecular study of pediatric brain tumors.*
  The study is mainly focused on pediatric low-grade glial tumors. Even though they are benign tumors, at least 12% of affected patients show disease progression. It was demonstrated that a genetic polymorphism of *TP53* gene is associated with negative prognosis in those cases who did not undergo complete resection. In addition, functional studies on primary tumor cell lines allowed the investigation of the possible pathogenicity and drug-resistance of these tumors.

Child Neuropsychiatry - *Director: Prof. Edvige Veneselli*

In 2012, the following studies were carried out:

- *Genetic neuropathies-CMT with infantile onset without known genetic marker: clinical-electrophysiological and genetic correlations*
  Recruitment of patients with pediatric onset genetic neuropathy, selected according to a specific clinical and electrophysiological flow chart. Genetic definition:
  Selection of patients with very early onset neuropathy (congenital-first year of life).
  Our clinical research study is aimed at the definition of molecular diagnosis of forms of genetic neuropathy, applying the already proposed methodology, with the recruitment of new cases as candidates for a targeted molecular analysis study based on clinical and electrophysiological phenotype and on associated clinical signs.
- *Genetic defects of metabolism and creatine transport in autistic spectrum disorders*
  Considering the recent report of cases with genetic defects of metabolism and creatine transport presenting autism, severe language impairment, delayed psychomotor development and epilepsy, and the fact that, for some forms, specific treatment is available, we examined a sample of 200 subjects (152 males, 48 females; age range 7.5 years) with Pervasive Developmental Disorder according to DSM IV criteria. They were enrolled between March 2006 and June 2010 on the basis of a diagnostic protocol including measurement of urine concentration of creatinine, repeated in case of positive result; assay of creatine/GAA ratio in urine; measurement of urine creatine, repeated in case of positive result once in males and twice in females; MR with spectroscopy, in hospitalized patients, in case of positive results in controls.
  In our series, there was no incidence of genetic disorders of metabolism and creatine transport.

Therefore, given the possibility of phenotypic traits ascribable to the autistic spectrum in subjects with a wider range of symptoms, on the basis of our experience we think it necessary to search these diseases, not simply through a general screening, but investigating all those subjects who present a compatible neuropsychic phenotype.

- *Neurophysiological and neuropsychological study of patients with epileptogenic cortical lesions: presurgical and longitudinal evaluation of epilepsies secondary to early brain injuries*

  Last year, we defined the presurgical approach to patients with drug-resistant epilepsy candidates for possible surgical exeresis of the epileptogenic area. The activity of identification and definition of the epileptogenic area involves a multidisciplinary staff composed of child psychiatrists and neurologists, with specific competences in the fields of epileptology and neurophysiopathology, a neuropsychologist for the study of correlations between epileptogenic focus and cognitive functions, neuroradiologists, and neurosurgeons. In operated patients, the post-surgical approach was defined, which involves child neuropsychiatrist, neuropsychologist and, from last year, physiatrist for clinical, electroclinical, cognitive-behavioural, and therapeutic follow-up.

  Compared to previous years, an increment in the frequency of candidates for neurosurgery and vagus stimulator implant was obtained. Objectives for next year are (i) the selection of new cases for electrophysiologic monitoring and multidisciplinary presurgical study (neuroimaging; neuropsychology); (ii) the study of clinical, electrophysiological, and neuropsychological outcome of operated patients with a minimum follow-up of 2 years; (iii) the statistical analysis of results and the production of scientific publications; (iv) the increment of therapeutic trials of new antiepileptic drugs; the development of multicentre studies.

  In parallel, in collaboration with the Neurooncology section, we started a review of the series of patients with epilepsy and brain tumors, focusing on type of epilepsy, drug-resistence, type of tumor, type of chemotherapy and radiotherapy used, and underlying disease progression for each patient. On the basis of retrospectively collected data, we will be able to start a second phase including a prospective evaluation of patients in order to define an approach to tumor-related epilepsy from a diagnostic, therapeutic, and rehabilitative perspective, to improve management of patients requiring integrated treatment (chemotherapy-radiotherapy-surgery), and to develop an interdisciplinary approach.

  This research can also be part of a multicentre study.

- *Study of immune mediated encephalitides in pediatric age, with particular reference to anti-N-methyl-D-aspartate (NMDA) receptor encephalitis*

  As an update of previously reported data, a study has been published on a patient with limbic encephalitis due to anti-GAD antibodies with atypical clinical characteristics (Mirabelli-Badenier M et al. Anti-glutamic acid decarboxylase limbic encephalitis without epilepsy evolving into dementia with cerebellar ataxia. Arch Neurol. 2012 Aug;69(8):1064-6.) This study allowed an extension of the clinical phenotype of anti-GAD limbic encephalitis, reporting for the first time in the literature the possibility of presentation without epilepsy and with cerebellar signs. In addition, the description of a further case of anti-NMDA encephalitis is being reviewed, the patient having been previously diagnosed as affected by Hashimoto encephalitis (Mirabelli et al. Hashimoto's encephalopathy and anti-NMDAR encephalitis: a near-miss diagnosis). These studies allowed the reevaluation of diagnostic and therapeutic aspects of these rare forms, in order to optimize the diagnostic workup and the therapeutic programme and follow-up, with particular focus on paraneoplastic forms.

- *Epileptic genotype-phenotype correlation in Rett syndrome*

  From the multicentre study on 165 patients, we continued our research on epilepsy in Rett syndrome, which had already yielded a publication (*Pintaudi M et al, Epilepsy in Rett syndrome: Clinical and genetic features. Epilepsy Behav. 2010 Nov;19(3):296-300).*

  In the same cohort, a retrospective study was performed to evaluate drugs and their efficacy in the treatment of epilepsy in these patients. The results of this study, started the previous year, underwent statistical analysis. Valproate resulted to be the more frequently used drug as first choice, followed by carbamazepine. Lamotrigine resulted as the most effective drug for patients with late epilepsy onset, while barbiturate proved to be poorly effective.

Valproate and carbamazepine showed quite good efficacy with few side effects and therefore, together with lamotrigine, can be proposed as first choice drugs at onset. Among the drugs used at follow-up, the association valproate plus lamotrigine resulted as the most effective. The results of this study are in press.

- *Advances in the diagnostic-therapeutic management of Infantile Cerebral Palsies*
  For subjects with Infantile Cerebral Palsy and other movement disorders, a database has been created for the input of clinical, electrophysiological, neuroradiological, and therapeutic data from the over 400 patients studied. This database is constantly updated, as well as the processing of data concerning motor and cognitive symptomatology, with particular reference to diplegic and tetraplegic forms, correlating with neuroradiologic picture, in order to delineate early significant parameters for prognosis (Carelli et al: MRI and motor impairment in Cerebral Palsy: which predictive factors?, presentato al IV International Cerebral Palsy Conference, Pisa 2012). In addition, electroencephalographic features and, when present, the type of epilepsy are being studied in a subgroup of patients with neuroradiological picture of periventricular leukomalacia.
  In particular, the incidence of electrical activation during sleep and its impact on motor and psychomotor skills are being evaluated (Carelli et al: Periventricular leukomalacia and Encephalopathy with electrical status epilepticus during slow sleep, LICE meeting 2012).
  In dystonic forms, CSF neuromediators were studied to identify possible targeted drug therapies. Some peculiar syndromes, characterized by predominantly motor expression, have been specifically studied: De Grandis et al: De Grandis et al: Lack of SLC2A1 (Glucose Transporter 1) Mutations in 30 Italian Patients With Alternating Hemiplegia of Childhood, J Child Neurol 2012; Cerebrospinal fluid alterations of the serotonin product, 5-hydroxyindolacetic acid in neurological disorders, J Inherit Metab Dis 2010; De Grandis et al: Paroxysmal dyskinesia with interictal myoclonus and dystonia, Park Relat Disord 2008.

Concerning the organization of services, follow-up of preterms and/or newborns with neurological distress has been functionally reorganized, early diagnosis has been improved, and continuity of care between hospital and territory has been developed through a regional multidisciplinary approach.

Neuroradiology - *Director*: *Dr. Andrea Rossi*
In 2012, the following studies were carried out:

- Validation of MR as adjuvant methodology in prenatal diagnosis of CNS disease : in 2012, 40 patients underwent fetal MR at 20 to 34 weeks of gestational age; in 7 cases, follow-up was performed at 3-4 weeks for a total of 47 examinations. Main indications were ventriculomegaly and search for congenital malformations. Besides traditional Ssh/TSE T2 dependent sequences, experimental sequences were performed in 42 cases, including: 42 diffusions (DWI), 2 tractographies (DTI), 8 dynamic studies of fetal movements (Dyn), and 7 spectroscopies (MRS). Examinations were interpretable in all cases, with the exception of tractographic examinations, providing additional or confirmed indications compared to echography.
  The DWI study was validated and inserted in the protocol for the evaluation of the development of the cortical mantle in the early phases (29-25 weeks) and for the recognition of disruptive lesions (ischemia/hemorrage) in the late phases (26-35 weeks).

Clinical Psychology - *Director: Prof. Ezio Casari*
In 2012, the following studies were carried out:

- Psychodiagnostic evaluation for specific problems or discomfort areas in developmental age.
- Evaluation of maladjustment and adjustment in chronic pediatric diseases: psychological support (counseling), first visits and follow-up according to operational protocols in agreement with single units.
- Evaluation of somatoform disorders in developmental age, anxiety and mood disorders in developmental age(moderate-mild).
- Evaluation of recurrent abdominal disorders.

- Evaluation of gender identity disorders: psychotherapy until preadolescence.
- Evaluation of psychological support and psychotherapy for problems related to pregnancy and puerperium.

Physical Medicine and Rehabilitation - *Director: Dr. Paolo Moretti*
Intensive rehabilitation activity programs (implemented in a short time) and low intensity standard rehabilitation programs (implemented in a longer time) were carried out for the recovery of the upper limb in subjects with infantile cerebral palsy in developmental age. In addition, instruments for evaluation, both specific for the upper limb (AHA e Besta) and general, were adapted for a population of subjects in developmental age with multiple severe disabilities. All this was aimed at the evaluation of both basic requirements necessary to obtain effective results in the upper limb (in terms of severity of the disability, characteristics and type of associated disabilities, and patients' age) and the "amount" of treatment needed to obtain results in terms of reduction of hypertonus, improvement of muscular recruitment, and functional results.

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Research line 6
Pediatric Surgery

Title
Multidisciplinary translational research in the field of pediatric surgical diseases or diseases with surgical implications: from bench to bedside

Coordinators
Dr. Piero Buffa, Dr. Lucio Valerio Zannini, Dr. Girolamo Mattioli, Dr. Alessio Pini Prato

Project description (outline and objectives)
This project is aimed at combining clinical and basic research on selected pediatric diseases with surgical implications. In addition, the project is aimed at expanding the participation of surgeons specialized in different fields in the development of diagnosic and therapeutic pathways increasingly based on principles of safety, efficacy, appropriateness, and efficiency. This support to basic research is aimed at improving the understanding of the physiopathological basis of the main surgical diseases and, consequently, at providing the clinician with increasingly effective therapeutic instruments. The wide spectrum of selected diseases includes commonly detected clinical diseaes and rare diseases, in order to meet the needs of the general pediatric population, without exclusions and exceptions. Applied methodology: given the heterogeneity of the projects of this research line, methodology details are given in single projects.

Principal investigators
Dr. Pietro Tuo – ICU/NICU
Dr. Maurizio Marasini - Cardiology
Dr. Lucio Valerio Zannini – Cardiovascular Surgery
Dr. Piero Buffa - Surgery
Prof. Paolo Capris - Ophthalmology
Dr. Roberto Servetto - Dentistry
Dr. Silvio Boero - Orthopedics
Dr. Vincenzo Tarantino - Otolaryngology

Activity year 2012

ICU/NICU - *Director: Dr. Pietro Tuo*
In 2012, the following studies were carried out:
- Comparison between general and regional anesthesia for the evaluation of neuro-cognitive outcome post-anesthesia apnea: Randomized controlled multicentre study (The GAS Study). This study is aimed at determining whether general and regional anesthesia results in equivalent neuro-cognitive outcomes. Recruitment of patients started in 2008 and ended on January 31, 2013. 27 children's hospitals in 7 countries reached the target of 720 newborns. Neurocognitive evaluation is ongoing and will be performed at 2 and 5 years of age with standardized tests. Post-anesthesia apnea will be studied and the study results will be published.

Cardiology - *Director: Dr. Maurizio Marasini*
In 2012, the following studies were carried out:
- Diagnosis and non-surgical therapy in prenatal, neonatal, and pediatric cardiology
- Clinical study on the application of new techniques for the diagnosis and therapy of congenital cardiopathies, in particular in prenatal and neonatal periods.

Cardiovascular Surgery - *Director: Lucio Valerio Zannini*
In 2012, the following studies were carried out:
- *Effectiveness of fenoldopam mesylate in the control of splancnic ischemia during extracorporeal circulation in pediatric patients*
  Objective: to evaluate whether treatment with fenoldopam mesylate at the dose of 0.2 γ/Kg/min can improve perfusion of the splancnic district and limit the onset of lactic acidosis

during CPB in pediatric patients. The treatment will be considered effective if the percentage of patients with hyperlactatemia at the end of CPB will be reduced from about 40% (expected value according to our retrospective analysis) to 20%.
Description: The study enrolled 54 patients and was concluded in the first half of 2012. Recorded data were filed in a dedicated database and underwent statistical analysis. The study results are being analyzed and a paper is being prepared for publication.
The primary end point has been reached and no drug-related adverse events have been reported. The changes in hourly diuresis during CPB and the first 6 postoperative hours and the changes in plasma lactates during the first 6 postoperative hours will be evaluated as secondary objectives.

- *Gene expression profile in advanced heart failure: identification and validation of new biomarkers*
  Objective: To find new biomarkers starting from the analysis of gene expression profile of the cardiac muscle in pediatric patients with heart failure in congenital cardiopathies undergoing surgery in the Cardiovascular Surgery unit of Gaslini.
  Description: The identification of new biomarkers with higher sensitivity and specificity is essential to improve the management of heart failure. They allow the optimization of current therapeutic approaches, with a positive impact on the patient, and the reduction of hospitalizations. Pediatric patients with selected congenital cardiopathies were admitted to the Cardiovascular Surgery unit and underwent surgery. In collaboration with the Laboratory of Molecular Biology, where the collected material is studied, the centralization of samples in Gaslini's biobank-BIT is continued. The collected material is studied by analysis of the gene expression profile of the cardiac muscle using microarray technique.

Surgery - *Director: Dr. Piero Buffa*
In 2012, additional patients with Hirschsprung disease were enrolled and carefully investigated for family history of the disease, previous episodes of enterocolitis, and other useful data for the completion of a complex integrated database. All patients consecutively enrolled in our Institute were also inserted in a programme of genotype-phenotype screening plus sampling of intestinal tissue for immunological study (in case of surgery) and of stool for meta-genomic study (performed at NIH – Bethesda). Up to November 30, 2012, overall 139 patients were enrolled, and 98 of them underwent complete screening, thus being suitable for the definition of phenotype variability of Hirschsprung disease, for genotype/phenotype correlation, and for the detection of possible risk factors.

Ophthalmology - *Director: Prof. Paolo Capris*
In 2012, the following studies were carried out:

- Prospective, non interventional, longitudinal cohort study for the evaluation of long-term safety of treatment with Xalatan in the pediatric population.
- Study n. A6111143, Pfizer.
- Study on patients treated for congenital glaucoma (ongoing).
- Morphological evaluation of the papilla by optical coherence tomography in Sturge-Weber angiomatosis.

Dentistry - *Director: Dr. Roberto Servetto*
In 2012, the following studies were carried out:

- Genetic syndromes, even rare, with alterations of the oro-dento-maxillofacial district.
- Parodontal 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 in fragile and disabled patients
- Research and testing using innovative orthodontic materials and techniques
- Research on benefits/correlations between orthodontics and systemic diseases

Orthopedics - *Director: Dr. Silvio Boero*

In 2012, the following studies were carried out:

- *Medium-long-term review of the treatment of obstetrical brachial plexus palsies*

  The authors carried out and concluded a medium-term retrospective study on a group of 32 patients with obstetrical brachial plexus palsy treated with selective neurotization (use of a healthy nerve to revive a damaged nerve) of muscle groups that did not recover their function, both as first surgery during spontaneous recovery remaining incomplete or after primary nerve repair of the brachial plexus.

  The study is original in that operations for reinnervation of muscle groups were performed later than reported in the literature, exploiting the capability of nerve regeneration in the child, which allows delayed treatment of a nerve lesion compared to the adult.

  Statistical analysis, performed in collaboration with Prof. Ivano Repetto from the Department of Mathematics of the University of Genoa, Italy, showed that, among age groups of patients, age increase at surgery did not yield worse results, confirming surgical indication even long after the perinatal nerve lesion.

- *Retrospective study of axial corrections and limb lengthening in patients with osteochondrodysplasia*

  The study analyses a cohort of 46 patients aged between 8 and 19 years, including 25 patients with genetically confirmed diagnosis of achondroplasia and 21 control patients with congenital limb length discrepancy of lower limbs.

  Between January 1994 and December 2007, all the patients underwent surgical lengthening of lower llimbs by femoral and/or tibial osteotomy and distraction of the bone callus with Ilizarov or monoaxial external fixator.

  During surgery in selected patients of both groups, a sample of osteoblastic cells was cultured *in vitro* to study their differentiation process.

  The combined analysis of clinical and *in vitro* results showed that the significant differences between the two groups in terms of limb lengthening, consolidation time, and healing index should be ascribed not only to a chondrogenetic alteration present in achondroplastic patients, as universally recognized in the literature, but also to alterations in the processes of osteoblastic differentiation that would lead to an abnormal and early mineralization of the matrix in achondroplastic patients.

- *Study of the bone-metal interface in vertebral implants*

  Studies carried out in collaboration with the Department of Applied Mechanics (DI.MEC.) of the University of Genoa, Italy have been completed. These studies, aimed at the analysis of biocompatibility of vertebral implants, led to the clarification of some mechanisms triggering the breaking of implants, depending on the function of their structure and material. Research results, presented in occasion of international meetings, will be published.

- *Morphological changes of the cartilagineous and fibro-ligamentous components of the foot*

  For several years, in the Orthopedics unit of Gaslini, Ponseti method has been adopted for the correction of congenital clubfoot.

  From the anatomic pathology point of view, the deformity consists of malpositions of tarsal bones, which undergo extreme flexion, abduction, and inversion, all maintained by capsular, ligamentous, and tendineous retractions.

  The technique includes a progressive correction by reducing cavus deformity and talonavicular subluxation, and by recreating the correct talocalcaneal angle through weekly manipulations followed by the immediate application of immobilizations involving the whole lower limb.

  Bones and joints are remodeled at each new immobilization since, in very young subjects, the properties of connective tissue, cartilage, and bones allow a response to the exerted mechanical stimuli.

  Our study seems to confirm the good results obtained by Ponseti and other orthopedic surgeons who use his technique, provided that adherence to treatment is complete, with the use of a fixator, after reaching correction, for few hours a day until 3 to 4 years of age.

Otolaryngology - *Director: Dr. Vincenzo Tarantino*

In 2012, we carried out the following studies:

- Pediatric ENT diseases: clinical and epidemiological aspects
  In the field of diagnosis and treatment of laryngeal and tracheal diseases, we started a retrospective study on the incidence of laryngomalacia (LM) in newborns, on the number of surgically treated children (both as absolute and relative percentages), and on the association between best anesthesiological procedure and more effective and conservative surgical procedure. To this end, the availability of a double laser (CO2 and diodes) allows treatment of a wide range of patients with different personalized anesthesiology techniques according to age, LM degree, and anatomic conditions of the laryngeal district. In addition, the possibility of an endoscopy-based classification of LM severity to be associated with the clinical classification was evaluated. The aim was to reach a more accurate staging of LM, based on endoscopy and symptoms, allowing an identification that is as objective as possible of the cases to be treated surgically.

Publications year 2012

1) Avanzini Stefano, Pio L., Buffa Piero, Panigada Serena, Sacco Oliviero, Pini Prato Alessio, Mattioli Girolamo, Bisio Giovanni Maria, Garaventa Alberto, Rossi Giovanni A, Jasonni Vincenzo.
   Intraoperative bronchoscopy for bronchial carcinoid parenchymal-sparing resection: a pediatric case report.
   PEDIATR SURG INT 2012; 28: 75-78.
   IF: 1.253 Norm. IF: 2.

2) Bondanza Sara, Derchi Maria Elena, Marasini Maurizio Francesco.
   Selective pulmonary artery embolization in two patients with single ventricle and acquired pulmonary vein occlusion.
   CATHETER CARDIO INTE 2012; 80: 101-106.
   IF: 2.29 Norm. IF: 4.

3) Buratti S., Lampugnani E., Tuo Pietro, Moscatelli A.
   Congenital diaphragmatic hernia repair during whole body hypothermia for neonatal hypoxic ischemic encephalopathy.
   J PERINATOL 2012; 32: 981-984.
   IF: 1.801 Norm. IF: 2.

4) Carinci S., Tumini S., Consilvio NP., Cipriano P., Di Stefano A., Vercellino Nadia, Dalmonte Pietro, Chiarelli F.
   A case of congenital hypothyroidism in PHACE syndrome.
   J PEDIATR ENDOCR MET 2012; 25: 603-605.
   IF: 0.875 Norm. IF: 0.5.

5) Catena Nunzio, Divizia Maria Teresa, Calevo Maria Grazia, Baban A., Torre Michele, Ravazzolo Roberto, Lerone Margherita, Senes Filippo.
   Hand and upper limb anomalies in poland syndrome: a new proposal of classification.
   J PEDIATR ORTHOPED 2012; 32: 727-731.
   IF: 1.156 Norm. IF: 2.

6) Dalmonte Pietro, Granata Claudio, Fulcheri E., Vercellino Nadia, Gregorio Sandro, Magnano Gian Michele.
   Intra-articular venous malformations of the Knee.
   J PEDIATR ORTHOPED 2012; 32(4): 394-398.
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7) De Corti F., Avanzini Stefano, Cecchetto G., Buffa Piero, Guida E., Zanon GF., Jasonni Vincenzo.

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IF: 1.45 Norm. IF: 4.

8) Lanza C., Raimondo S., Vergani L., Catena Nunzio, Senes Filippo, Tos P., Geuna S.
Expression of antioxidant molecules after peripheral nerve injury and regeneration.
J NEUROSCI RES 2012; 90: 842-848.
IF: 2.738 Norm. IF: 2.

9) Lerzo Franco, Peri G., Doni A., Bocca Paola, Morandi Fabio, Pistorio Angela, Carleo Anna Maria, Mantovani A., Pistoia Vito, Prigione Ignazia.
Dexamethasone prophylaxis in pediatric open heart surgery is associated with increased blood pentraxin PTX3: potential clinical implications.
CLIN DEV IMMUNOL 2011; ID 730828: 6 pages.
IF: 1.838 Norm. IF: 1.

10) Mattioli Girolamo, Guida E., Montobbio Giovanni, Pini Prato Alessio, Carlucci M., Cama Armando, Boero Silvio, Michelis MB., Castagnola Elio, Rosati Ubaldo, Jasonni Vincenzo.
Near-miss events are really missed! Reflections on incident reporting in a department of pediatric surgery.
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IF: 1.253 Norm. IF: 2.

11) Mattioli Girolamo, Guida E., Pini-Prato A., Avanzini S., Rossi V., Barabino Arrigo, Coran AG., Jasonni Vincenzo.
Technical considerations in children undergoing laparoscopic ileal-J-pouch anorectal anastomosis for ulcerative colitis.
PEDIATR SURG INT 2012; 28: 351-356.
IF: 1.253 Norm. IF: 2.

12) Mattioli Girolamo, Guida E., Rossi V., Podestà E., Jasonni Vincenzo, Ghiggeri Gian Marco.
Intraureteral injection of NASHA/Dx gel under direct ureteroscopic visualization for the treatment of primary high-grade vesicoureteral reflux.
J LAPAROENDOSC ADV S 2012; 22(8): 844-847.
IF: 1.4 Norm. IF: 4.

13) Montobbio Giovanni, Pini Prato Alessio, Guida E., Disma Nicola, Mameli Leila, Avanzini Stefano, Scali R., Tuo Pietro, Jasonni Vincenzo, Mattioli Girolamo.
Provisional unicentric experience with an electronic incident reporting form in pediatric anesthesia.
PEDIATR ANESTH 2012; 22: 1080-1086.
IF: 2.1 Norm. IF: 4.

14) Pini Prato Alessio, Castagnola Elio, Micalizzi Concetta, Dufour Carlo, Avanzini Stefano, Pio L., Guida El, Mattioli Girolamo, Jasonni Vincenzo, Disma Nicola, Mameli Leila, Montobbio Giovanni, Buffa Piero.
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J PEDIATR SURG 2012; 47: E23-E27.
IF: 1.45 Norm. IF: 4.

15) Romeo E., Jasonni Vincenzo, Caldaro T., Barabino Arrigo, Mattioli Girolamo, Vignola Silvia, Federici di Abriola G., 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; 47: 944-948.
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Correction of forearm deformities in congenital ulnar club ahnd: one-bone forearm.
J HAND SURG-AM 2012; 37A: 159-164.
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J PEDIATR ORTHOP B 2012; 21: 300-304.
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18) Speggiorin S., Torre Michele, Roebuck DJ., MRCPCH, McLaren CA., Elliott MJ.
A new morphologic classification of congenital tracheobronchial stenosis.
ANN THORAC SURG 2012; 93: 958-961.
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19) Torre Michele, Carlucci M., Speggiorin S., Elliott MJ.
Aortopexy for the treatment of tracheomalacia in children: a review of the literature.
ITAL J PEDIATR 2012; 38: 62.
IF: 0.791 Norm. IF: 1.

20) Torre Michele, Rapuzzi M., Carlucci M., Pio L., Jasonni Vincenzo.
Phenotypic spectrum and management of sternal cleft: literature review and presentation of a new series.
EUR J CARDIO-THORAC 2012; 41: 4-9.
IF: 2.55 Norm. IF: 6.

21) Tuo Giulia, Volpe P., Bondanza Sara, Volpe N., Serafino Margherita, De Robertis V., Zannini Lucio Valerio, Pongiglione G., Calevo Maria Grazia, Marasini Maurizio Francesco.
Impact of prenatal diagnosis on outcome of pulmonary atresia and intact ventricular septum.
J MATERN-FETAL NEO M 2012; 25(6): 669-674.
IF: 1.495 Norm. IF: 2.

STUDIES AND CLINICAL TRIALS YEAR 2012

Unit	Title	Year of approval
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 polyarticular or polyarticular course juvenile idiopathic arthritis (JIA)- STRIVE.	2010
Pediatric Gastroenterology with Digestive Endoscopy	A multicentre, prospective, long-term registry of pediatric patients with Crohn's disease.	2010
ICU/NICU	A multi-site RCT comparing regional and general anaesthesia for effects on neurodevelopmental outcome and apnoea in infants.	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
Oncology/Hematology and BMT	A randomised fase III study on the treatment of children and adolescent with refractory or relapsed acute myeloid leukemia.	2004
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
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
Cardiology	A randomized, open label study comparing safety and efficacy parameters for a high and a low dose of ambrisentan (aduste for body weight) for treatment of pulmonary arterial hypertension in paediatric patients aged 8 years up to 18 years.	2011
Oncology/Hematology and BMT	A retrospective data collection (RDC) study regarding patients enrolled in Italian sites during the previous international trial: "Prospective study of the incidence and outcome of veno-occlusive disease (VOD) with the prophylactic use of defibrotide (DF, Gentium, Italy) in Pediatric Stem Cell Transplantation.	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
Oncology/Hematology and BMT	A SIOPEN Study - Phase I-II study for dose and schedule of monoclonal antibody anti GD2 ch14.18/CHO in continuous infusion associated with Aldesleukin (IL2) in patients with refractory or relapsed neuroblastoma. Study of the International European Oncologic Pediatric Neuroblastoma Society (SIOPEN).	2011

Pediatric Rheumatology	Cross-cultural adaptation and validation of the version of parent and patient of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR).	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
Nephrology, Dialysis and Transplantation	An open-label extension study of Candesartan Cilexetil in hypertensive pediatric subjects aged 1 to <11 years: a long term study.	2007
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
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
Nephrology, Dialysis and Transplantation	Proteomic analysis of peritoneal effluents in patients treated with continuous cyclic peritoneal dialysis (CCPD).	2007
Oncology/Hematology and BMT	Anti-TNF monoclonal antibody (Etanercept) for the treatment of acute GvHD not responding to first line steroid therapy.	2009
Pediatric Pneumology and Allergology	Applicability of the "Visual Analogic Scale" in an asthmatic and/or rhinitic pediatric population as a screening tool for the evaluation of respiratory function.	2010
Pediatric Clinic	Anti-adrenal autoimmunity in pediatric subjects with type 1 diabetes mellitus and/or celiac disease.	2009
ICU/NICU	Comparison between stereofundin (and glucose 1%) and physiologic solution (and glucose 1%) for intraoperative fluid maintenance therapy in patients undergoing major and medium surgery aged below 36 years	2010
Oncology/Hematology and BMT	Cooperative multi center study for children and adolescents with low grade gliomas.	2005
Pediatric Clinic	Database of the European forum on growth increlex® (injection of mecasermin [origin rdna]): European registry to monitor long-term safety and efficacy of increlex®.	2011
Pediatric Clinic	Bone mass density, body composition, glucide homeostasis in preterms.	2009
Pediatric Clinic	Diagnosis of growth hormone deficiency in the transition period	2009
Oncology/Hematology and BMT	Active design of a phase II, multicentre, randomized open study on the association of bevacizumab with conventional chemotherapy in underage patients with rhabdmyosarcoma, soft tissue sarcoma, nonrhabdomyosarcoma or Ewing's sarcoma/primitive neuroectodermal metastatic soft tissue tumors.	2008
Pediatric Clinic	Easypod adherence in children with growth disorders treated with r-GH.	2010

Cardiovascular Surgery	Efficacy of fenoldopam mesylate in the control of splancnic ischemia during extracorporeal circulation in pediatric patients.	2009
Nephrology, Dialysis and BMT	Efficacy of anti-CD20 monoclonal antibodies in patients with nephrotic syndrome resistant to combined therapy with steroids and calcineurin inhibitors.	2008
Child Neuropsychiatry	Efficacy and safety of Eslicarbazepine Acetate (BIA 2-093) as adjunctive therapy of refractory partial epileptic seizures in children: double blind, randomized, placebo-controlled, parallel group multicentre clinical study	2010
Pediatric Clinic	Efficacy and tolerability of two substitution therapies in cases of amenorrhea following antiblastic treatment in pediatric age.	2007
Oncology/Hematology and BMT	EsPhALL: post-induction treatment of Ph+ Acute Lymphoblastic Leukemia in pediatric patients.	2006
Oncology/Hematology and BMT	Expression of ABCB1/P-glycoprotein as factor for biological stratification of non-metastatic osteosarcoma of extremities: prospective study.	2011
Pediatric Rheumatology	EUROFEVER. EULAR/PReS European network for the creation of a registry related to the classification of autoinflammatory diseases in pediatric age.	2009
Oncology/Hematology and BMT	European low and intermediate risk neuroblastoma - SIOPEN study.	2012
ICU/NICU	European network for central hypoventilation syndromes: optimizing health care to patients.	2010
Pediatric Rheumatology	Pharmacovigilance in patients with juvenile idiopathic arthritis (Pharmachild). PRINTO (Paediatric Rheumatology International Trials Organisation) and PRES (Pediatric Rheumatology European Society) registry.	2011
Pediatric Neurology and Muscular Diseases	Open label extension phase of double blind, placebo-controlled, dose-escalation, parallel group studies to evaluate the efficacy and safety of E2007 (perampanel) administered as adjunctive therapy in subjects with partial refractory epilepsy.	2010
Oncology/Hematology and BMT	Follow-up of patients at risk for bronchiolitis obliterans after allogenic stem cell transplantation	2011
Pediatric Clinic	Modifying genes in patients with cystic fibrosis and related hepatosis.	2007
Pediatric Clinic	Glycemic control and quality of life in children, adolescents and young adults with type-1 diabetes mellitus described 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
Laboratory of Molecular Genetics and Cytogenetics	Identification of the genetic basis of Poland disease.	2012
Pediatric Pneumology and Allergology	Acid and non-acid gastroesofageal reflux and respiratory disorders in pediatric age.	2009
Pediatric Pneumology and Allergology	Immunodiagnosis on serum and cells for evidence-based immunotherapy of the allergic child (science based pediatric allergy).	2005
Pathologic Anatomy/Laboratory of Molecular Biology	Use of material from BIT – Tissue-genomic Integrated Biobank of G. Gaslini Institute for diagnosis and research.	2008

Pediatric Pneumology and Allergology	Use of cellular material from human airway tissue for the study of the different biological activities of airway cells.	2005
Pediatric Clinic	Influence of aerobic training vs interval training on the activity of antioxidative enzymes and on glyco-metabolic parameters in children and adolescents with diabetes mellitus type 1.	2011
Surgery	Inoculation of botulin toxin for the treatment of achalasia of internal anal sphincter.	2005
Oncology/Hematology and BMT	Interfant 2006 for the treatment of children aged < 1 year with acute lymphoblastic leukemia.	2008
Nephrology, Dialysis and Transplantation	International Pediatric Peritoneal Biopsy Study in Children.	2012
Pediatric Clinic	Male hypogonadotropic hypogonadism with neonatal onset.	2009
Pediatric Pneumology and Allergology	Creation of a Biobank for patients with rheumatic diseases in pediatric age.	2004
Pediatric Clinic	Kuvan® Adult Maternal Paediatric European Registry.	2010
Pediatric Emergency/Urgency	Management of headache in pediatric emergency.	2011
Scientific Direction	Clinical trial: awareness of the minor.	2008
Pediatric Neurology and Muscular Diseases/Orthopedics	Botulin Toxin A (BT-A) in the treatment of spasticity during developmental age	2010
Pediatric Pneumology and Allergy	Ipratropium bromide-salbutamole association vs inhaled salbutamole in patients with bronchial asthma associated with gastroesophageal reflux.	2008
Oncology/Hematologia and BMT	LCH III: therapeutic protocol for the 3rd international study on Langerhans cell histiocytosis.	2001
Oncology/Hematology and BMT	Long-term psychosocial consequences and analysis of off-therapy patients' needs: assessment and psychological intervention. A pilot study.	2011
Oncology/Hematology and BMT	Guidelines for the treatment of children with operable localized neuroblastoma	2006
Pediatric Pneumology and Allergy	Vitamin D blood levels and respiratory infections in preschool children.	2011
Child Neuropsychiatry	Metallothionein in Rett syndrome.	2011
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
Oncology/Hematology and BMT	High-risk neuroblastoma refractory to therapy or relapsed after autotransplantation: pilot study on toxicity and antitumoral activity of allogenic transplantation from compatible or haploidentical family donor.	2004
Pediatric Clinic	Nordinet® - International Outcome Study (Nordinet®IOS).	2010
Oncology/Hematology and BMT	Rules for the management of biological material and for its use for diagnostic and research purposes in neuroblastoma.	2008

Pediatric Clinic	Participation of the Cystic Fibrosis Centre of Genova in the Cystic Fibrosis Italian Registry at the Istituto Superiore di Sanità.	2011
Nephrology, Dialysis and Transplantation	Pediatric chronic kidney disease and cardiovascular complications.	2009
Pediatric Pneumology and Allergology	Prevalence of resistence to macrolides in Mycoplasma pneumoniae in a pediatric population with lower airway infections.	2012
Pediatric Clinic	Prevalence of metabolic syndrome and other endocrine disorders in children conceived with ICSI.	2009
Pediatric Clinic	Prevalence of metabolic syndrome in off-therapy patients after pediatric tumor. Analysis of risk factors and biochemical markers of the syndrome.	2011
Oncology/Hematology and BMT	First European cooperative study for high-risk neuroblastoma	2001
Epidemiology and Biostatistics	“Pensiero” project: histological centralization and activation of the national Registry of CNS tumors.	2008
Neonatal Pathology	Educational program for mothers of preterms in NICU: evaluation of the effects on the ability to manage maternal stress, on the perception of newborn behaviour, and on maternal safety during care	2010
Pediatric Rheumatology	International observational, non interventional, volunteer study on lisosomal storage disease.	2011
Oncology/Hematology and BMT	International cooperative protocol for the treatment of children and adolescents with acute lymphoblastic leukemia	2011
Oncology/Hematology and BMT	Salvage protocol with associated Clofarabine, Vepeside and Cyclophosphamide (CLOVE) for the treatment of acute resistant or second relapse leukemias of pediatric age	2008
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
Oncology/Hematology and BMT	AIEOPLH 2004 therapeutic protocol.	2006
Oncology/Hematology and BMT	Collection of clinical data in comprehensive diagnosis of Fanconi’s anemia: creation of a clinical-biological database	2010
Oncology/Hematology and BMT	European Registry of Evoltra (Clofarabine).	2010
Oncology/Hematology and BMT	International Registry of chronic severe neutropenia	2003
Oncology/Hematology and BMT	Pediatric multicentre registry of essential thrombocythemia (ET).	2011
Pediatric Rheumatology	Registry for patients with Niemann-Pick Type C Disease.	2012
Pediatric Rheumatology	Relationship between body mass index and asthma in Ligurian children and adolescents.	2010
Oncology/Hematology and BMT	Innate "signalling" networks in the production of antibodies by B cells: new targets for the development of vaccines	2012
Oncology/Hematology and BMT	Search for glucan in CSF in a population of subjects treated for acute lymphoblastic leukemia/non Hodgkin lymphoma.	2011

Child Neuropsychiatry	Proinflammatory role of CC chemokines in the physiopathology of West syndrome and other epileptic encephalopathies	2010
Child Neuropsychiatry	Second protocol for diagnosis and treatment of ependymomas in pediatric age.	2003
Pediatric Clinic	Small intestine bacterial colonization syndrome in cystic fibrosis: epidemiology, clinical impact, and experimentation of a therapeutic protocol	2012
Oncology/Hematology and BMT	Single-dose pilot study of oral rivaroxaban in pediatric subjects with venous thromboembolism.	2010
Neonatal Pathology	Sli study: respiratory assistence in the delivery room with sustained lung inflation in extremely preterm newborns at risk for rds. Controlled randomized study	2012
Pediatric Rheumatology	Abdominal imaging substudy, substrate analysis and collection of laboratory samples from participants enrolled in LAL-2-NH01 study.	2012
Oncology/Hematology and BMT	Phase II, multicentre, historical data-controlled clinical study with Dasatinib added to standard chemotherapy in children and adolescents with new diagnosis of Philadelphia-positive (Ph+ ALL) acute lymphoblastic leukemia	2012
Pediatric Clinic	Phase III, multicentre, randomized, double-blind, placebo- and metformin-controlled clinical study to evaluate safety and efficacy of sitagliptin in children with poorly compensated diabetes mellitus type II	2012
Oncology/Hematology and BMT	Randomized, multicentre, prospective, clinical study on the use of two different doses of rabbit anti-lymphocyte serum in the prophylaxis of Graft-vs-Host Disease (GVHD) in children with malignant hematologic diseases undergoing allogeneic hemopoietic stem cell transplantation from unrelated donor	2008
Child Neuropsychiatry	Randomized, multicentre, double-blind, placebo-controlled, parallel group clinical study on the effects of eslicarbazepine acetate (BIA 2-093) as adjunctive therapy on cognitive function in children with partial refractory epilepsy	2010
Oncology/Hematology and BMT	Dose-definition, comparative, randomized open phase 1-2 study for the evaluation of efficacy and safety of plerixafor in addition to standard therapeutic regimens for the mobilization of hematopoietic stem cells in peripheral blood and subsequent collection by apheresis compared to simple standard mobilization therapeutic regimens in pediatric patients aged 2 to 18 years with solid tumors and suitable for autologous transplantation	2010
Laboratoriy of Molecular Genetics and Cytogenetics	Study of ion transport systems in human bronchial epithelium	2010
Child Neuropsychiatry	Study of brain blood flow with Transuranic Doppler sonography in alternating hemiplegia	2006
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

Laboratory of Oncology	Study of the expression of IL-12, IL-23, IL-27 and their receptors in pediatric leukemias and lymphomas.	2005
Pediatric Pneumology and Allergology	Phase III B study for the evaluation of efficacy, safety, and tolerability of Grazax in children aged 5 to 18 years with rhinoconjunctivitis induced by grass pollen with or without controlled or partially controlled asthma	2010
Pediatric Rheumatology	Phase III study in juvenile dermatomyositis at onset: prednisone vs prednisone plus cyclosporine vs prednisone plus methotrexate.	2006
Oncology/Hematology and BMT	Comparative drug-controlled randomized, double blind, double dummy phase III study to evaluate the efficacy and safety of Aprepitant in the prevention of nausea and vomiting induced by chemotherapy (CINV) in pediatric patients.	2011
Nephrology, Dialysis and Transplantation	Multicentre, intrapatient controlled (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 children with chronic renal insufficiency on dialysis, with extension to further 6 months of observation.	2009
Pediatric Clinic	Anti-pseudomonas, post-vaccination surveillance study in subjects with cystic fibrosis (CF) who received vaccination at least once; it includes a control arm.	2008
Pediatric Clinic	PKU-Q0L questionnaire validation study	2011
Pediatric Rheumatology	Randomized, double blind, placebo-controlled, 24-week withdrawal study preceded by an initial 16-week open phase and followed by a 64-week open follow-up to evaluate the efficacy and safety of tocilizumab in patients with active juvenile idiopathic arthritis with poliarticular course.	2009
Pediatric Rheumatology	Randomized, double blind, placebo-controlled, parallel group, two arm, 12-week study to evaluate the efficacy and safety of tocilizumab in patients with active systemic juvenile idiopathic arthritis (sJIA), with an extension period of 92 weeks for an open, single arm study of long-term use of tocilizumab.	2008
Pediatric Clinic	Descriptive epidemiologic study on the identification of the methylation state of the genome in children with idiopathic short stature	2011
Pediatric Clinic	European study on modifying genes in cystic fibrosis. Italian network	2012
Oncology/Hematology and BMT	European prospective observational study for the evaluation of the quality of life as related to the health status and for the identification of situations and events that impact on the quality of life of patients with moderate or severe hemophilia A treated with Helixate NexGen.	2010
Oncology/Hematology and BMT	Pharmacokinetic, multicentre, open study on oral nilotinib in pediatric patients with chronic phase (CF) or accelerated phase (AP) LMC Ph+ resistant/intolerant to Gleevec (imatinib) or with refractory/relapsing LLA Ph+	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 Clinic	Phase IV open study for the validation of genetic markers associated with response in terms of growth during the first year of treatment in prepuberal age children with growth hormone deficit or Turner syndrome: PREDICT pharmacogenetic validation study.	2011
Neurosurgery	Multicentre, expanded access, open study with RAD001 in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TSC).	2011
Child Neuropsychiatry	Open study to evaluate long-term safety and tolerability of AFQ056 in adolescent patients with X-fragile syndrome.	2012
Child Neuropsychiatry	Open study to evaluate the long-term safety, tolerability, and efficacy of AFQ056 in adult patients with X-fragile syndrome.	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
Infectious Diseases	International observational study on fungal infections in pediatric age ("International Pediatric Fungal Network").	2009
Oncology/Hematology and BMT	Italian ADVATE (rAHF-PFM) post-registration surveillance study on treatment of hemophilia A in order to evaluate its efficacy, safety, and immunogenicity	2008
Laboratory of Molecular Genetics and Cytogenetics	Molecular study of genetic disorders associated with RET gene alterations.	2011
Neurosurgery	Multicentre study of genes of Planar Cell Polarity (PCP) signal pathway in NTD pathogenesis	2007
Oncology/Hematology and BMT	Multicentre phase II study to evaluate the activity and toxicity of liposomal cytarabine in the treatment of children and adolescents with acute lymphoblastic leukemia and resistant or relapsed meningeal localization after systemic and intrarachidian treatment.	2012
Nephrology, Dialysis and Transplantation	Multicentre, randomized, controlled, 12-month, open study to evaluate the efficacy, tolerability, and safety of early administration of everolimus in association with lower-dose calcineurin inhibitor (CNI) and early steroid elimination compared to therapy with standard dose CNI, mycophenolate mofetil, and steroid in pediatric patients undergoing renal transplantation, with further 24-month safety follow-up	2011
Oncology, Hematology and BMT	Multicentre, open study on the safety and pharmacokinetics of progressive doses of recombinant coagulation factor IX albumin fusion protein (rIX-FP) in subjects with Hemophilia B.	2010
Pediatric Clinic	Multicentre, randomized, active control, open study to evaluate the efficacy, safety, and tolerability of Arikace in patients with cystic fibrosis associated with chronic infection due to Pseudomonas aeruginosa.	2012

ICU/NICU	Regional multicentre study on the risk of hospitalization for lower airway infections due to respiratory syncytial virus (RSV) in preterms: incidence and risk factors.	2011
Pediatric Rheumatology	Multicentre, long-term, observational study on Hunter syndrome (mucopolysaccharidosis type II) - HOS - Hunter Outcome Survey.	2007
Pediatric Clinic	National, multicentre, observational study to evaluate adherence to and long-term outcome of therapy in pediatric subjects using EasypodTM, an electromechanical device for the administration of growth hormone.	2011
Pediatric Rheumatology	Observational study on clinical characteristics and disease progression in patients with lisosomal acid lipase deficiency/cholesterol ester storage disease phenotype and agreement proposal	2011
Pediatric Clinic	Radiological study of anomalies of the male reproductive system in cystic fibrosis	2011
Pediatric Rheumatology	Randomized and controlled study to evaluate the efficacy and tolerability of intra-articular injections of corticosteroids in monotherapy or in association with methotrexate in juvenile idiopathic arthritis.	2009
Pediatric Neurology and Muscular Diseases	Randomized, double blind, placebo-controlled study for the evaluation of the safety and efficacy of intranasal Midazolam (USL261) in the treatment of cluster epileptic seizures in outpatients-ARTEMIS1.	2011
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 Clinic	Study on the natural history of the development of diabetes type 1	2007
Pediatric Pneumology and Allergology	Cross-sectional and longitudinal study of bronchial reactivity in asthmatic children and adolescents practicing or starting to practice swimming	2005
Pediatric Rheumatology	Development of diagnostic criteria for macrophage activation syndrome (MAS) in systemic juvenile idiopathic arthritis (SJIA).	2010
Nephrology, Dialysis and Transplantation	Therapy of post-Rituximab nephrotic syndrome relapse in Short-Mid and Lasting Remittent patients. Comparison of different therapeutic schemes	2012
Oncology, Hematology and BMT	Immunosuppressive therapy with anti-lymphocyte anti-TNFalpha serum and cyclosporine for Acquired Aplastic Anemia (AAA).	2009
Nephrology, Dialysis and Transplantation	Treatment of children with history of acute pyelonephritis or recurrent UTI and prevention of renal damage: randomized, prospective clinical study .	2009
Oncology, Hematology and BMT	Treatment Protocol for Lymphoblastic Lymphoma of the European Inter-groupfor Childhood Non-Hodgkin-Lymphoma (EICNHL).	2007
Oncology, Hematology and BMT	Treatment study for children and adolescents with acute Promyelocytic Leukemia.	2009
Oncology, Hematology and BMT	Wilms Tumor 2003-11-13. Diagnostic-therapeutic protocol.	2004

Oncology, Hematology and BMT	Use of pegylated filgrastim in severe chronic neutropenias	2006
Pediatric Clinic	Use of metformin in obese pediatric patients.	2011
Oncology, Hematology and BMT	Validation, characterization, and selective targeting of new tumor markers in patients with neuroblastoma	2011
Nephrology, Dialysis and Transplantation	Validation of assay of circulating antibodies against glomerular neo-autoantigens (SOD2, AR, PLA2r) as surrogate biomarker of the evolution of membranous glomerulonephritis	2011
Neonatal Pathology	Validation of "champs" instrument for the evaluation of the risk of fall of underage children hospitalized in a children's hospital	2011
Pediatric Rheumatology	Validation of a new multidimensional evaluation questionnaire in juvenile idiopathic arthritis in systemic juvenile lupus erythematosus, in juvenile dermatomyositis	2008
Cardiovascular Surgery/Laboratory of Molecular Biology	Evaluation of gene expression changes and identification of possible metabolic alterations in the cardiac tissue during extracorporeal circulation and aortic clamping in a population of patients with congenital cardiopathies	2007
Oncology, Hematology and BMT	Evaluation of metabolic profile in serum and urine of patients with Fanconi's anemia.	2011
Pediatric Clinic	Evaluation of long-term risk-benefit profile of therapy with levothyroxine in children with congenital hypothyroidism: influence of initial dose of levothyroxine on neurological development, growth, cardiovascular and skeletal systems.	2011
Pediatric Rheumatology	Evaluation of achievement of clinical remission (CR), of minimal disease activity (MDA), and of a disease status considered acceptable by the parent or the patient (pass) in children with juvenile idiopathic arthritis (JIA) treated with etanercept (ETN).	2009
Pediatric Neurology and Muscular Diseases	Evaluation of the function of upper limbs in non-walking patients with Duchenne muscular dystrophy.	2012
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 for neonatal screening on mother-child communication relationship and possible consequences on nutritional behaviour and/or growth in the first five years of life.	2011
Oncology, Hematology and BMT	Pharmacokinetic evaluation of the formulation of recombinant IX factor (Benefix) recently registered in Italy, in the Italian population of previously treated patients with severe and moderate hemophilia B	2009
Pediatric Rheumatology	NMR evaluation of early damage of articular cartilage in patients with juvenile idiopathic arthritis	2010
Oncology, Hematology and BMT	Preclinical evaluation of small molecules as potential therapeutic agents in Fanconi's anemia.	2009
Pediatric Rheumatology	Ultrastructural evaluation of articular cartilage by MR in subjects with joints not affected by pathogenic damage and comparison with subjects with juvenile idiopathic arthritis.	2009

SEMINARS

DATE	PROPOSING UNIT(S)	SPEAKER	TITLE
19/01/12	Nephrology, Dialysis and Transplantation	Alessia Fornoni	RITUXIMAB in recurrence FSGS: immunomodulation or direct podocytes repair?
30/01/12	Scientific Direction - Library	Angela Basile Angela Carbonaro Maria Valeria Corrias Enza Di Perna Marianna Napolitano Federica Sabatini	From bibliographic search to scientific publication: library resources – Basic course - II session
20/01/12	Neonatal Pathology	Eugenio Mercuri, Daniela Ricci	1) Neonatal neurologic examination, from research to routine: instructions for use. 2) What does my child see? Assessment of neonatal visual function
26/01/12	ICU/NICU	David Laffar	DITTO: interactive device. A clinically proven, non-pharmacological, advance in reducing paediatric anxiety, stress and pain
30/01/12	Scientific Direction	Claudia Alicata	Human telomeric chromatin: interactions between TRF proteins and telomeric nucleosomes
02/02/12	Scientific Direction	Roberto Accolla	The MHC Class II Transactivator CIITA: A Restriction Factor for Human Retroviruses
08/02/12	Hematology/Oncology and BMT	Mimmo Ripaldi	Hemorrhagic cystitis during bone marrow transplantation
15/02/12	Scientific Direction	Roberto Cingolani	Nanotechnologies for humanoids and humans
20/02/12	Neonatal Pathology	Stefano Martinelli	Retinopathy of prematurity: from theory to practice. Is it truly like that?
22/02/12	Scientific Direction	Christian Münz	Natural killer cell responses to a human tumorvirus in vivo
23/02/12	Scientific Direction	Claudio Ortolani	Tricks and traps of cytometric analysis
24/02/12	Pediatric Neurology and Muscular Diseases	Alberto Magi	Bioinformatics for second generation sequencing analysis
06/03/12	Epidemiology and Biostatistics	Lorenzo Moja	Role of systematic reviews and meta-analysis in the scientific literature and impact on the clinical practice
21/03/12	Scientific Direction	Daniela Cilloni	New molecular targets for hematologic tumors: examples of how new technologies allow research advances

29/03/12	Scientific Direction - Library	Davide Navone	UpToDate: a peer reviewed information resource
30/03/12	Scientific Direction - Library	Guido Forni	Vaccines for tumor prevention: where are we now and where are we leading to
04/04/12	Scientific Direction - Library	Angela Basile Angela Carbonaro Maria Valeria Corrias Enza Di Perna Marianna Napolitano Federica Sabatini	From bibliographic search to scientific publication: library resources – Basic course - III session
05/04/12	Scientific Direction	Fabio Malavasi	The ectoenzyme connection: an emerging regulator of cell homing and immune functions
16/04/12	Scientific Direction	Alberto Mantovani	From fruit fly to global health
02/05/12	Scientific Direction	Herman Favoreel	Antibody-resistant herpesvirus spread via modulations of the host cell cytoskeleton
07/05/12	Pediatric Neurology and Muscular Diseases	Ian D. Duncan	Remyelination of the CNS: is it functionally significant and how can it be achieved?
16/05/12	Neonatal Pathology	Liliana Gabrielli, Lazzaroto Tiziana	News on CMV congenital infections
23/05/12	Hematology/Oncology and BMT	Rosanna Parasole	New CILI protocol – Liposomal Cytarabine in acute lymphoblastic leukemias in CNS relapse
24/05/12	Scientific Direction	Sergio Romagnani	Main features of human Th17 cells
07/06/12	Laboratory of Molecular Genetics and Service of Cytogenetics	Cristina Lo Nigro	Methylation profiling in human cancers identifies novel candidate suppressors
19/06/12	Scientific Direction	Chiara Romagnani	Requirements of NK cell activation during differentiation
21/06/12	Pediatric Clinical Trial Office (PCTO)	Arthur J. Atkinson Jr	Conduct of pharmacokinetics (PK) studies in hemodialysis patients
22/06/12	Pediatric Clinical Trial Office (PCTO)	Arthur J. Atkinson Jr	Getting the dose right - Lessons from clinical practice and the medical literature
25/06/12	Pediatric Clinical Trial Office (PCTO)	Arthur J. Atkinson Jr	Models of physiology and physiologically based pharmacokinetics (PBPK) models
26/06/12	Nephrology Radiology	Pier Hugues Vivier, Michaela Dolores	Technique, application and analysis of URO, functional magnetic resonance in pediatric urology
27/06/12	Surgery	Carmen Gloria Morovic	1) Plastic surgery in pediatrics and adolescence; 2) Craniofacial anomalies: state of the art

05/07/12	Laboratory of Molecular Genetics and Service of Cytogenetics	Marie E. Egan	CFTR and the immune response
18/07/12	Genetic Diagnostics and Biochemistry of Metabolic Diseases	Enrico Moro	Zebrafish as molecular and imaging plataform for the study of pathogenetic mechanisms
19/09/12	ICU/NICU	Andrew Davidson	The GAS Study; the challenges in doing a clinical trial in seven countries
19/09/12	Pediatric Rheumatology	Dietmar Fuchs	Immune response-associated neopterin production and tryptophan breakdown
05/10/12	Laboratory of Oncology	Yves DeClerck	The bone marrow microenvironment in neuroblastoma progression
12/10/12	Pediatric Neurology and Muscular Diseases	Carlo Nobile	Genetic focal epilepsies of pediatric interest: new research directions
16/10/12	Laboratoriy of Oncology	John Anderson	Development of cell and gene therapies for childhood solid tumours
17/10/12	Lab. of Postnatal Stem Cells and Cell Therapies	Francesco Saglio	Generation of CMV-Adeno and EBV-specific CTL from cord blood
29/10/12	Surgery	Philippe Monnier	Airway stenosis: state of the art
14/11/12	Scientific Direction	Nadir Askenasy	Depletion of naïve lymphocytes with Fas-ligand ex vivo prevents GvHD without impairing T cell support of engraftment or GVT activity
14/11/12	Scientific Direction	Franco Locatelli	Depletion of alphaa/beta+ T lymphocytes: does future lie in transplantation?
14/12/12	Neonatal Intensive Care	Paolo Gancia e Giulia Pomero	Presentation of new SIN guidelines for the treatment of post-anoxic newborn
19/12/12	Scientific Direction	Umberto Dianzani	Updating of ALPS history

FUNDED RESEARCH PROJECTS IN 2012

EU-funded research projects

"**European Translational training for Autoimmunity & Immune manipulation Network" – EUTRAIN**
Principal investigator: Prof. Alberto Martini, Pediatric Rheumatology
Grant: € 504,972.60

"Anti-Biopharmaceutical Immunization: prediction and analysis of clinical relevance to minimize the risk" - ABIRISK
Principal investigator: Prof. Alberto Martini, Dr. Nicola Ruperto, Pediatric Rheumatology
Grant: € 348,525.00

"Single Hub and Access Point for Paediatric Reumatology in Europe" - SHARE
Principal investigators: Prof. Alberto Martini, Dr. Nicola Ruperto, Pediatric Rheumatology
Grant: € 171,175.00

"New approach to treatment of the blinding disease Retinopathy of Prematurity" - PREVENTROP
Principal investigator: Dr. Luca Antonio Ramenghi, Neonatal Pathology
Finanziamento: € 421,454.40

Epilepsy Pharmacogenomics: delivering biomarkers for clinical use" – EpiPGX
Principal investigator: Dr. Federico Zara, Pediatric Neurology and Muscular Diseases
Grant: 252,864.00

Research projects funded by public institutions

MINISTRY OF HEALTH

"Multisite RCT comparing regional and general anaesthesia for effects on neurodevelopmental outcome in infants – The GAS study"
Principal investigator: Dr. Nicola M. Disma, ICU/NICU
Grant : € 103,462.50

"Clinical history and long-term cost-effectiveness of Enzyme Replacement Therapy (ERT) for Gaucher Disease in Italy"
Principal investigator: Dr. Mirella Filocamo, Centre of Genetic and Biochemical Diagnostics of Metabolic Diseases
Grant: € 30,000.00

"Primary Ciliary Dyskinesia (PCD): diagnosis clinical phenotypes and prevalence in an italian pediatric population"
Principal investigator: Prof. Giovanni A. Rossi, Pediatric Pneumology and Allergology
Grant: € 40,000.00

"Modelling and treatment of Cystic Fibrosis through an integrated Systems Biology approach"
Principal investigator: Dr. Luis Galietta, Laboratory of Molecular Genetics and Service of Cytogenetics
Grant: € 254,500.00

"Genetic and functional analysis of copy number variations (CNVs) affecting ion channel genes in familial idiopathic generalized epilepsy"
Principal investigator: Dr. Pasquale Striano, Pediatric Neurology and Muscular Diseases
Grant: € 275,108.00

"The trafficking of hematopoietic stem cells and their bone marrow homing as the prerequisites to improve the out come of transplant"
Principal investigator: Prof. Francesco Frassoni, Laboratory of Postnatal Stem Cells and Cell Therapies
Grant: € 63,000.00

"Analysis of genome and transcriptome for the identification and functional evaluation of genetic diseases and, in general, of rare diseases in pediatrics. Applications of state-of-the-art technologies (Next Generation Sequencing – NGS and High Speed Chromosome and Cell Sorting – HSCCS) to research and diagnostics of pediatric diseases"
Principal investigator: Prof. Lorenzo Moretta, Scientific Director
Grant: € 800,000.00

"Analysis of lymphoid cells with effector or regulatory function in pediatric patients with solid tumors or high-risk leukemias"
Principal investigator: Prof. Lorenzo Moretta, Scientific Director
Grant: € 540,000.00

"Acquisition and implementation of a 3 Tesla MRI scan"
Principal investigator: Dr. Andrea Rossi, Neuroradiology
Grant: € 1,360,000.00

ITALIAN MEDICINES AGENCY (AGENZIA ITALIANA DEL FARMACO - AIFA)

"Evaluation of long-term risk-benefit profile of therapy with levothyroxine in children with congenital hypothyroidism: impact of initial dose of levothyroxine on neurological development, growth, cardiovascular and skeletal systems" (FARM8A8FHP)
In collaboration with the University of Naples "Federico II", Italy
Principal investigator: Dr. Roberto Gastaldi, Pediatric Clinic
Grant: € 11,000.00

Research projects funded by private institutions or companies

"UMBERTO VERONESI" FOUNDATION

"Tissue-penetrating peptides-coated nanoparticles as a personalized strategy for the targeted delivery of anticancer agents to Neuroblastoma tumors"
Principal investigator: Dr. Fabio Pastorino, Laboratory of Oncology
Grant: € 90,000.00

"Development of novel bisphosphonate-entrapping liposomes to target macrophages: application in cancer prevention and therapy"
Principal investigator: Dr. Chiara Brignole, Laboratory of Oncology
Grant: € 90,000.00

"Gene expression profile at the onset of severe cardiac failure: identification and validation of new biomarkers"
Principal investigator: Dr. Luigi Varesio, Laboratory of Molecular Biology
Grant: € 90,000.00

ITALIAN ASSOCIATION FOR CANCER RESEARCH (ASSOCIAZIONE ITALIANA PER LA RICERCA SUL CANCRO - A.I.R.C.)

"Biology-driven integrated approach for risk factor discovery in Neuroblastoma" – 3rd year
Principal investigator: Dr. Luigi Varesio, Laboratory of Molecular Biology
Grant: € 62,000.00

"PH0X2B overexpression and pathogenetic interactions as targets for a pharmacological approach to Neuroblastoma" - II annualità
Principal investigator: Dr. Tiziana Bachetti, Laboratory of Molecular Genetics and Service of Cytogenetics
Grant: € 50,000.00

"Interleukin-27 in the control of pediatric acute leukemia cell growth in humanized mice" – 1st year
Principal investigator: Dr. Irma Airoldi, Laboratory of Oncology
Grant: € 140,000.00

"Post-trascriptional control of RET gene expression: implication in thyroid cancer" – 1st year
Principal investigator: Dr. Isabella Ceccherini, Laboratory of Molecular Genetics and Service of Cytogenetics
Grant: € 65,000.00

"Micro-RNA replacement and RNAi-mediated silncing of ALK as combined targeted therapies for Neuroblastoma" - I annualità
Principal investigator: Dr. Patrizia Perri, Laboratory of Oncology
Grant: € 55,000.00

"NK cell subsets in germinal center B cell lymphoma microenvironment: cellular and molecular characterization" – 1st year
Principal investigator: Dr. Vito Pistoia, Laboratory of Oncology
Grant: € 90,000.00

ITALIAN FOUNDATION FOR CANCER RESEARCH (FONDAZIONE ITALIANA PER LA RICERCA SUL CANCRO - F.I.R.C.)

Three-year fellowship (2013-2015)
Dr. Alessia Zorzoli, Laboratory of Oncology
Grant: € 60,000.00

CYSTIC FIBROSIS FOUNDATION THERAPEUTICS INC.

"Functional evaluation of CFTR pharmacological modulators"
Principal investigator: Dr. Luis Galietta, Laboratory of Molecular Genetics and Service of Cytogenetics
Grant: € 74,545.90

NYCOMED GMBH

"Effects of roflumilast-N-oxide, the active metabolie of PD4 inhibitor roflumilast currently in development for COPD, on the regulation of the height of periciliary lining fluid in polarized primary human bronchial epithelial cells in vitro"
Principal investigator: Dr. Luis Galietta, Laboratory of Molecular Genetics and Service of Cytogenetics
Grant: € 20,000.00

COMPAGNIA DI SAN PAOLO

"Sensitizing brain tumors to radio- and chemotherapy with cell cycle checkpoint inhibitors"
Principal investigator: Dr. Valeria Capra, Neurosurgery
Grant: € 12,000.00

UNIVERSITY OF SOUTHERN CALIFORNIA

"Dietary Restriction, GH/IGF-I & Mechanisms of Differential Cellular Protection" – 1st year
Principal investigators: Dr. Vito Pistoia, Dr. Lizzia Raffaghello, Laboratory of Oncology
Grant: € 49,301.79

ITALIAN ASSOCIATION FOR THE STUDY OF MALFORMATIONS (ASSOCIAZIONE ITALIANA STUDIO MALFORMAZIONI - ASM ONLUS)

“New generation sequencing (NGS) of the whole exome in familial cases of Neural Tube Defects”
Principal investigator: Dr. Elisa Merello
Grant: € 20,000.00

VALEAS S.p.A.

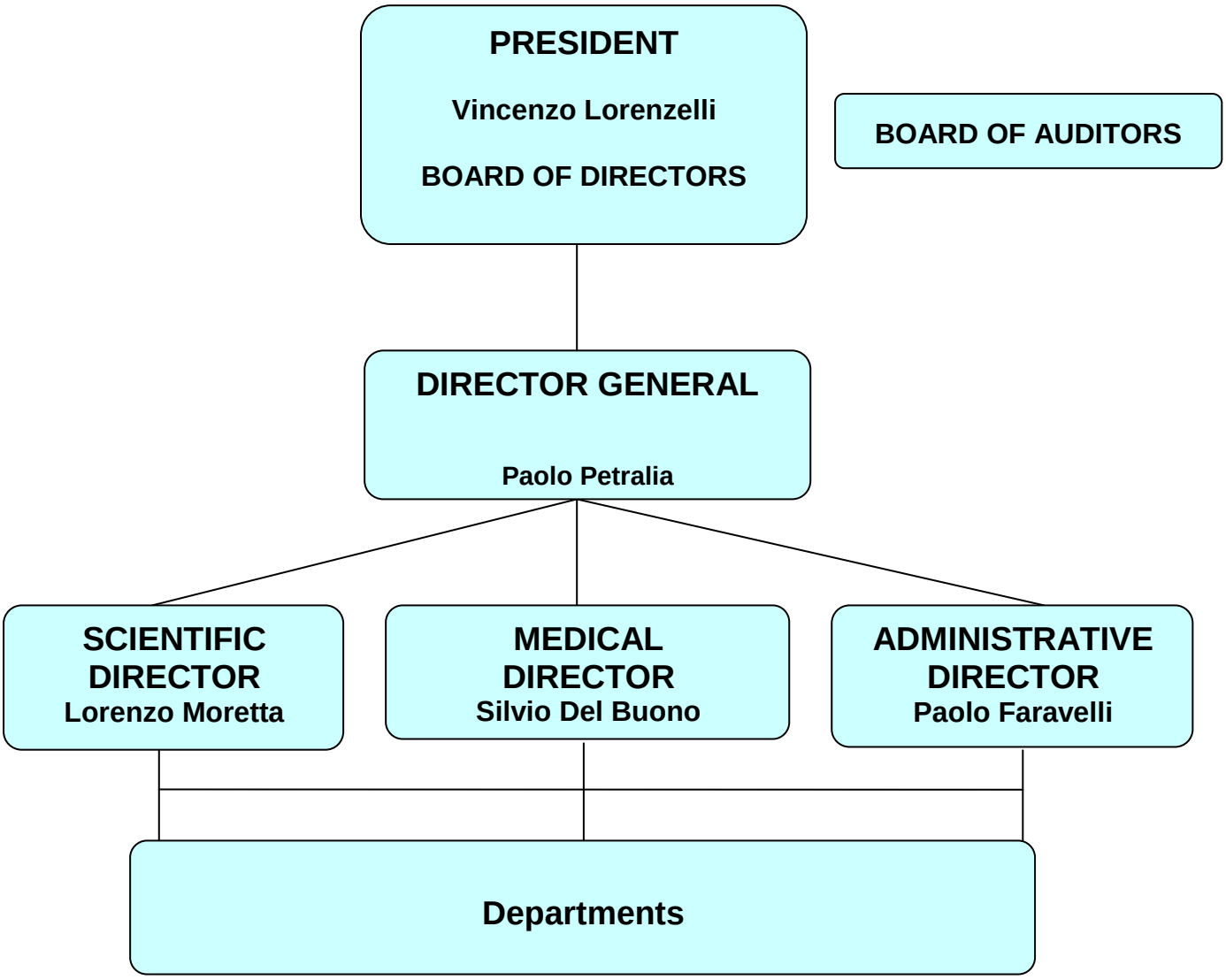
“Evaluation of Pidotimod on bronchial epithelial cells exposed in vitro to induced by LPS (lipopolysaccharide) of tumor necrosi factor (TNF)”
Principal investigator: Prof. Giovanni Rossi, Pediatric Pneumology and Allergology
Grant: € 35,000.00

GENZYME S.p.A.

Funding of research activity in the field of lisosomal diseases (Gaucher disease)
Principal investigator: Dr. Mirella Filocamo, Centre of Genetic and Biochemical Diagnostics of Metabolic Diseases
Grant: € 15,000.00

ITALIAN ASSOCIATION CONGENITAL CENTRAL HYPOVENTILATION SYNDROME (ASSOCIAZIONE ITALIANA SINDROME IPOVENTILAZIONE CENTRALE CONGENITA - A.I.S.I.C.C.)

“Genetic-molecular study of PHOX2B mutations in CCHS”
Principal investigator: Dr. Isabella Cecchetini, Laboratory of Molecular Genetics and Service of Cytogenetics
Grant: € 20,000.00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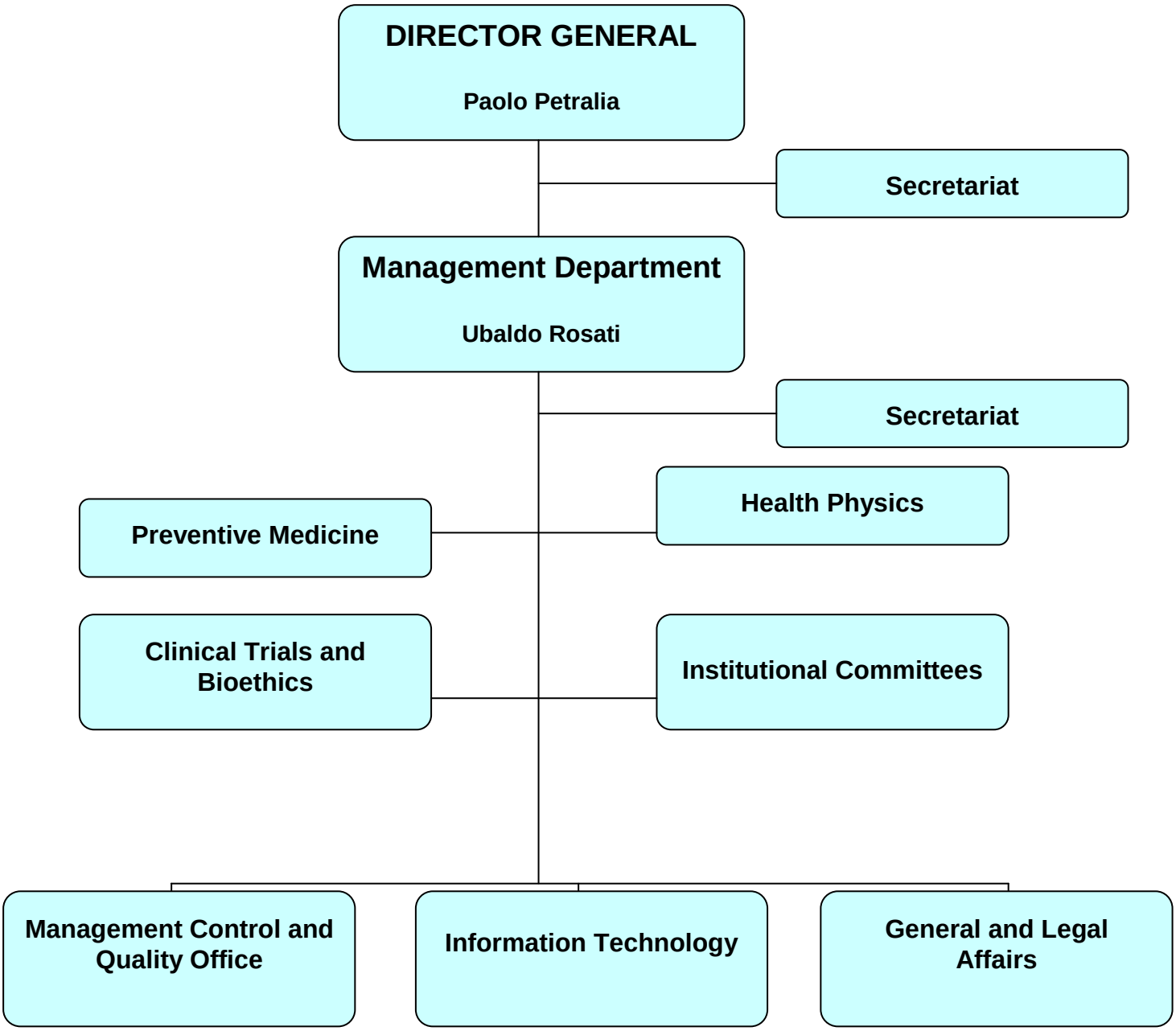
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Activity year 2012

Improvement pathway for the safety of patients in a tertiary hospital
Objectives:
- development of a methodological model to be adopted for the improvement of safety of pediatric patients in the following areas: medications, operating room, internal transport;
- definition and testing of a methodology for the evaluation of the activities undertaken for clincal risk reduction in pediatric age;
- implementation of a handbook on the safety of pediatric patients in hospital that can be used in any organizational context.

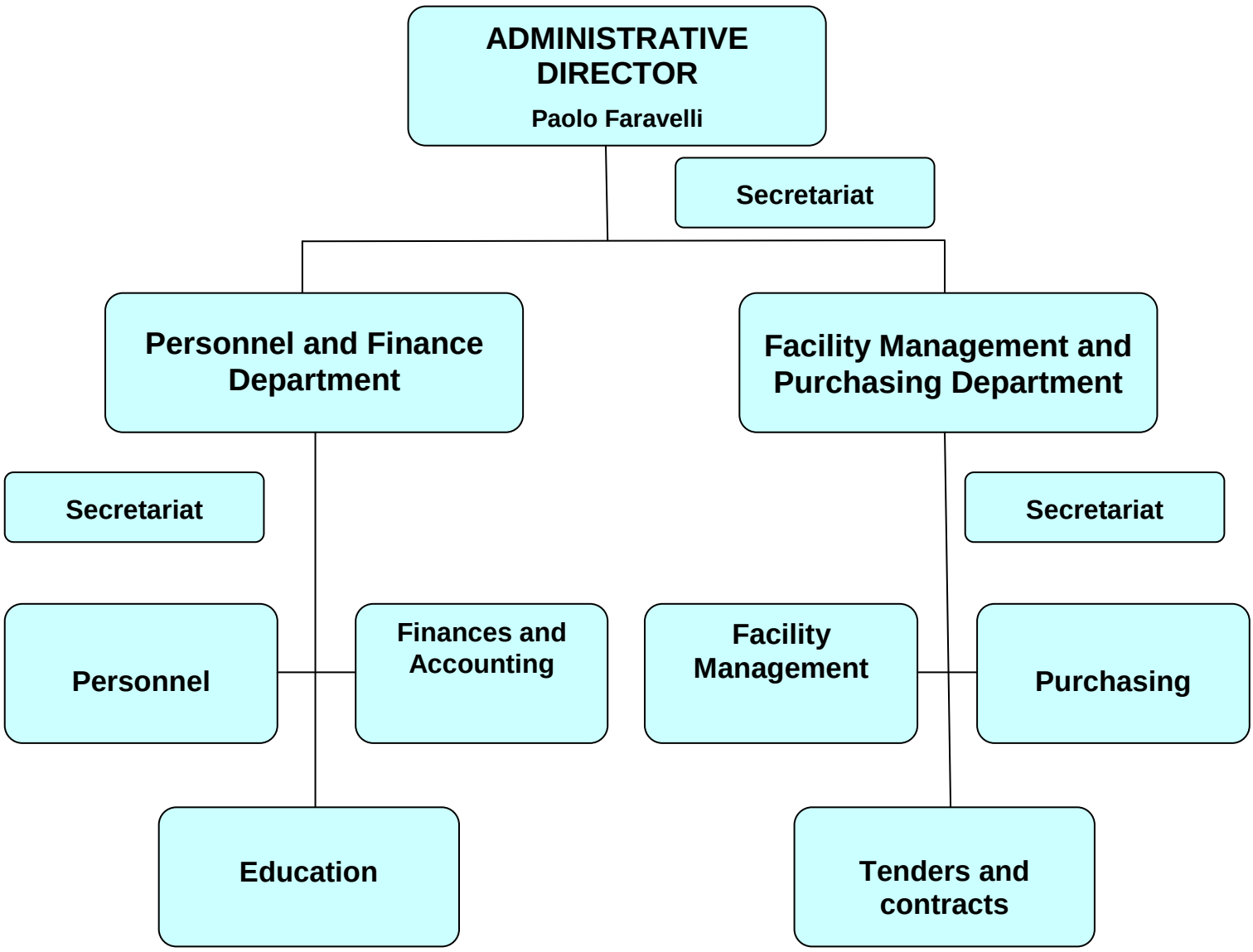
Progress report:
A questionnaire was developed on the procedures of prevention and management of clinical risk implemented in a group of pediatric units representative of Italian pediatric hospital units and a bibliographic search was performed.
Standards were grouped into three levels according to an incremental approach with specific reference to the type of requisites necessary for patient safety.
This three-level approach was adopted for schematic purposes, taking into account (i) the procedures, related to the topic areas of the project, implemented in hospitals participating in the programme, (i) the results of the survey conducted through the administration of questionnaires in hospitals that accepted to participate, and (iii) the data obtained from the bibliographic search. All this was aimed at defining an improvement pathway able to guarantee higher levels of safety.
Level 1: minimum threshold of acceptability.
The standards must always be observed in any organizational context where care is delivered to pediatric patients. This level guarantees the presence of the main policies and procedures.
Level 2: The basic requisites are met and the main policies and procedures are present. This level guarantees that improvement pathways to reach high levels of safety have been implemented.
Level 3: it represents the reference gold standard expressed on the basis of the good clinical practices reported in the international literature.

Research programme for 2013

Multicentre project for clinical risk management in pediatrics
Objective:
1) Benchmarking analysis comparing Gaslini with UK National Health Service hospitals
2) Analysis of risk problems related to the urgency/emergency area
3) Identification of instruments
4) Staff training

Description:
A. Development of a methodological model to be adopted for the improvement of safety of pediatric patients and proposal of actions to be undertaken according to their efficacy, on the basis of evidence available in the literature and of the results of administered questionnaires, respecting the ethical principles established by national and international bodies;
B. Definition and testing of a methodology for the evaluation of the activities undertaken to reduce clinical risk in pediatric age.

Ongoing main collaborations
- Unit for clinical risk management (Regione Toscana)
- Meyer Hospital, Firenze
- Bambino Gesù Children's Hospital, Roma
- Burlo Garofolo Hospital, Trieste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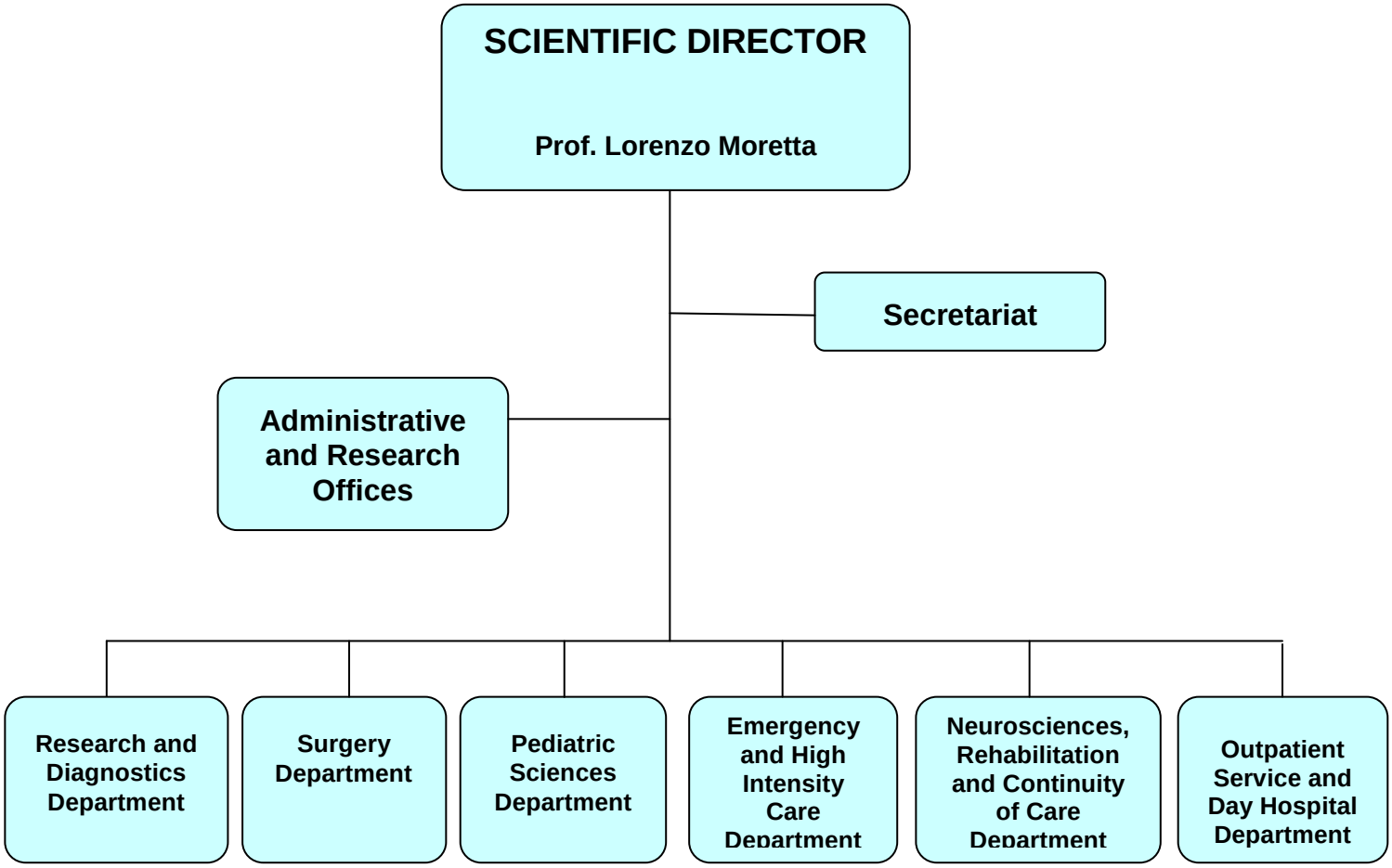
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Howard Hughes Medical Institute Research Laboratories, University of Alabama at Birmingham, Birmingham, Alabama, USA

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

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

ETHICS COMMITTEE FOR SCIENTIFIC AND BIOMEDICAL RESEARCH AND FOR CLINICAL EXPERIMENTATION

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SCIENTIFIC DIRECTOR

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Building no. 10

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)

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	**576**
Total Impact factor	**Over 3,300**
Total number of citations	**Over 38,000 among the "Highly Cited Scientists" of ISI**
Total h-index	***110 (Via Academy, Top Italian Scientists) – 108 (ISI web of knowledge)***

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 1,500 times. Professor Moretta is author of 576 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 38,000. Professor Moretta is in the ISI list of Highly Cited Scientists, that includes only a limited number of Italian researchers. His h-index is 110 (www.isiknowledge.com). In addition, in a recent analysis by Via Academy, Professor Moretta has been identified among the 188 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

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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.

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Administrative management of research funding by the Ministry of Health and by public and private institutions.

Computer Graphics Service
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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.

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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
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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
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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: tomwiley@ospedale-gaslini.ge.it
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: ornelladellacasa@ospedale-gaslini.ge.it
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 and Biostatistics

Director: Dr. Riccardo Haupt

Staff

Francesca Bagnasco, Luisella Bertoluzzo, Maria Grazia Calevo, Silvia Caruso, Giovanni Erminio, Anna Rita Gigliotti, Angela Pistorio

Activity year 2012

1) Methodological-statistical collaboration for the analysis of data from clinical trials or observational studies in the field of infectious diseases, hematology/oncology, endocrinology, metabolic diseases, and neonatology.
2) Management of the Italian Neuroblastoma Registry (RINB). Clinical and anatomic pathology data concerning children and adolescents with diagnosis of neuroblastoma from AIEOP centres (Italian Association Pediatric Hematology/Oncology) are collected and processed. Over 3,000 cases/year were included in the Registry and about 120 new cases are added every year.
3) Management of the Off-therapy Registry (OTR). Data are collected on children treated for tumor in AIEOP centres who have completed their therapeutic programme. Over 14,000 cases were included in the Registry.
4) Management of the International Registry on the association between Langerhans cell histiocytosis (LCH) and malignant tumor.
5) Design of the regional registry of congenital hearing loss
6) Collaboration with the Rheumatology unit a) for the analysis of data from experimental studies (RCT) on the evaluation of new treatments in the field of rheumatology (juvenile dermatomyositis, juvenile idiopathic arthritis, and systemic lupus erythematosus); b) for the validation of clinical and/or radiological/echographic standardized diagnostic instruments for the evaluation of articular/muscular activity and damage; c) for the development of new diagnosis classification systems and of new standardized criteria for the evaluation of outcome.

Research projects

- Application of bi- and multivariate biostatistical methods in clinical epidemiology of rheumatic or oncologic diseases in the child.
- EC projects: ENCCA and PanCareSurFup
- Neuroblastoma Italian Foundation : NB clinical project and Pensiero project

Research programme for 2013

Application of statistical-epidemiologiical methods for the analysis of clinical and laboratory data

Objective: Application of statistical-epidemiological methods for the analysis of clinical and laboratory data from i) disease registries; ii) pharmacovigilance; iii) clinical trials; iv) validation of standardized tools for diagnostics and classification criteria; v) design and development of systematic reviews of the literature and meta-analysis

Description: Methods will be applied to national or international institutional case series, prevalently in the field of rheumatology, oncology, neonatology, infectious diseases, and endocrine and metabolic diseases.

Systematic reviews will be focused on the neonatal and oncologic areas.

Main collaborations

- Pediatric Clinic, Milano-Bicocca University
- CINECA (Inter-University Centre for Automatic Calculation)

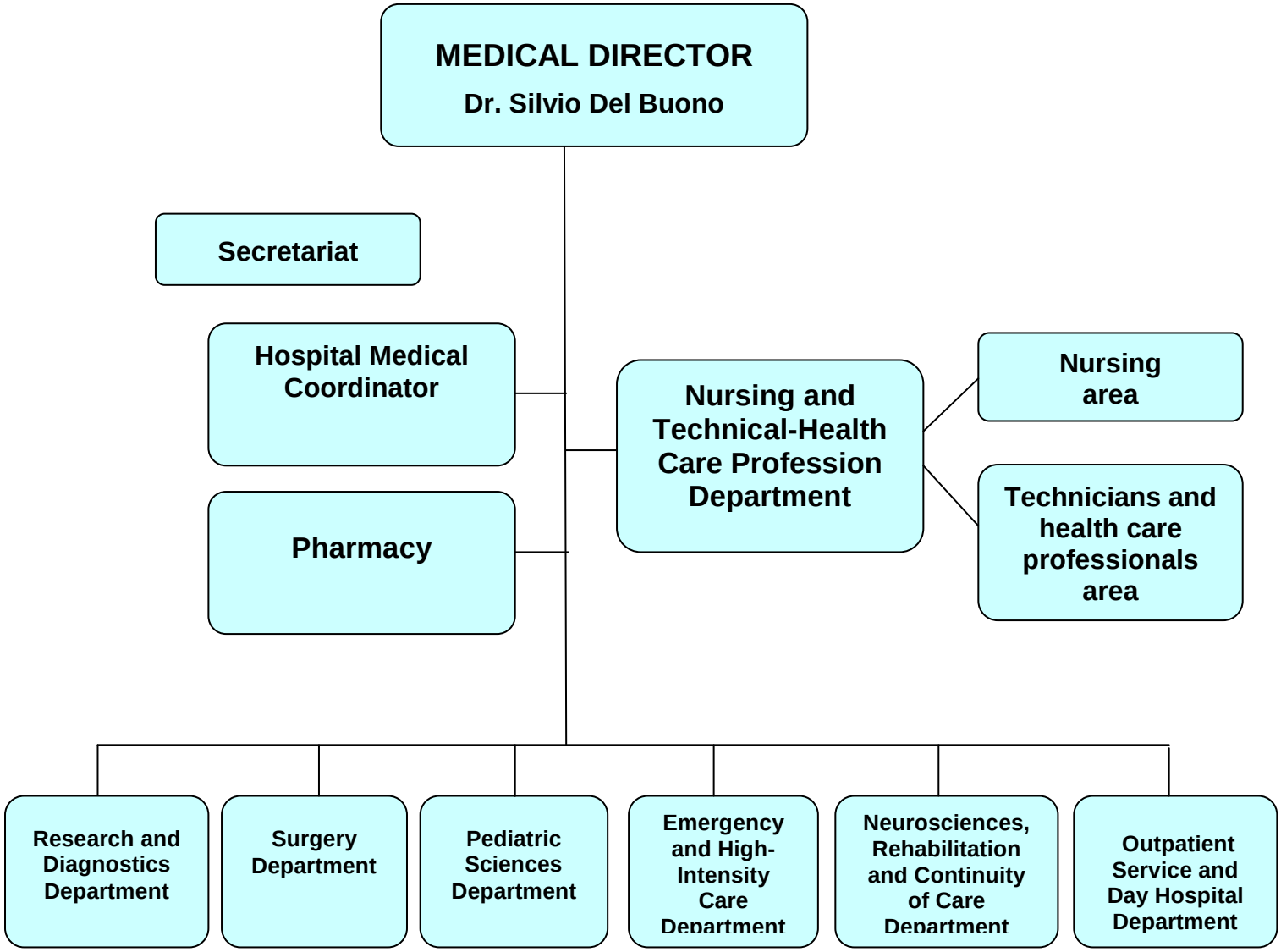
- PRINTO (Paediatric Rheumatology International Trials Organization)
- University of Lund (Sweden)
- Cochrane Italy (Bologna)
- National Institute of Enviromental Health Sciences - National Institutes of Health (NIEHS-NIH)

Major publications (2007-2012)

1. De Bernardi B, Gambini C, Haupt R, Granata C, Rizzo A, Conte M, Tonini GP, Bianchi M, Giuliano M, Luksch R, Prete A, Viscardi E, Garaventa A, Sementa AR, Bruzzi P, Angelini P. Retrospective study of childhood ganglioneuroma. J Clin Oncol 2008;26(10):1710-6.
2. Dufour C, Ferretti E, Bagnasco F, Burlando O, Lanciotti M, Ramenghi U, Saracco P, Van Lint MT, Longoni D, Torelli GF, Pillon M, Locasciulli A, Misuraca A, La Spina M, Bacigalupo A, Pistoia V, Corcione A, Svahn J; Marrow Failure Study Group of the AIEOP. Changes in cytokine profile pre- and post-immunosuppression in acquired aplastic anemia. Haematologica 2009;94(12):1743-7.
3. Saad-Magalhães C, Pistorio A, Ravelli A, Filocamo G, Viola S, Brik R, Mihaylova D, Cate RT, Andersson-Gare B, Ferriani V, Minden K, Hashkes P, Rygg M, Sauvain MJ, Venning H, Martini A, Ruperto N; Pediatric Rheumatology International Trials Organisation (PRINTO). Does removal of aids/devices and help make a difference in the Childhood Health Assessment Questionnaire disability index? Ann Rheum Dis 2010;69(1):82-7.
4. Foell D, Wulffraat N, Wedderburn LR, Wittkowski H, Frosch M, Gerss J, Stanevicha V, Mihaylova D, Ferriani V, Tsakalidou FK, Foeldvari I, Cuttica R, Gonzalez B, Ravelli A, Khubchandani R, Oliveira S, Armbrust W, Garay S, Vojinovic J, Norambuena X, Gamir ML, García-Consuegra J, Lepore L, Susic G, Corona F, Dolezalova P, Pistorio A, Martini A, Ruperto N, Roth J; Paediatric Rheumatology International Trials Organization (PRINTO). Methotrexate withdrawal at 6 vs 12 months in juvenile idiopathic arthritis in remission: a randomized clinical trial. JAMA. 2010;303(13):1266-73.
5. Haupt R, Garaventa A, Gambini C, Parodi S, Cangemi G, Casale F, Viscardi E, Bianchi M, Prete A, Jenkner A, Luksch R, Di Cataldo A, Favre C, D'Angelo P, Zanazzo GA, Arcamone G, Izzi GC, Gigliotti AR, Pastore G, De Bernardi B. Improved survival of children with neuroblastoma between 1979 and 2005: a report of the Italian Neuroblastoma Registry. J Clin Oncol. 2010;28(14):2331-8.
6. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, Buoncompagni A, Lazar C, Bilge I, Uziel Y, Rigante D, Cantarini L, Hilario MO, Silva CA, Alegria M, Norambuena X, Belot A, Berkun Y, Estrella AI, Olivieri AN, Alpigiani MG, Rumba I, Sztajnbok F, Tambic-Bukovac L, Breda L, Al-Mayouf S, Mihaylova D, Chasnyk V, Sengler C, Klein-Gitelman M, Djeddi D, Nuno L, Pruunsild C, Brunner J, Kondi A, Pagava K, Pederzoli S, Martini A, Ruperto N; Paediatric Rheumatology International Trials Organisation (PRINTO). EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis 2010;69(5):798-806.
7. Ghiotto F, Marcatili P, Tenca C, Calevo MG, Yan XJ, Albesiano E, Bagnara D, Colombo M, Cutrona G, Chu CC, Morabito F, Bruno S, Ferrarini M, Tramontano A, Fais F, Chiorazzi N. Mutation pattern of paired immunoglobulin heavy and light variable domains in chronic lymphocytic leukemia B cells. Mol Med 2011;17(11-12):1188-95.
8. 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.

9. 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.

10. 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.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Hospital Medical Coordinator
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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: Rossella Rossi

Staff

Tullia Emanueli Chiara Francesca Ines Lorenzi
Eleonora Panetta

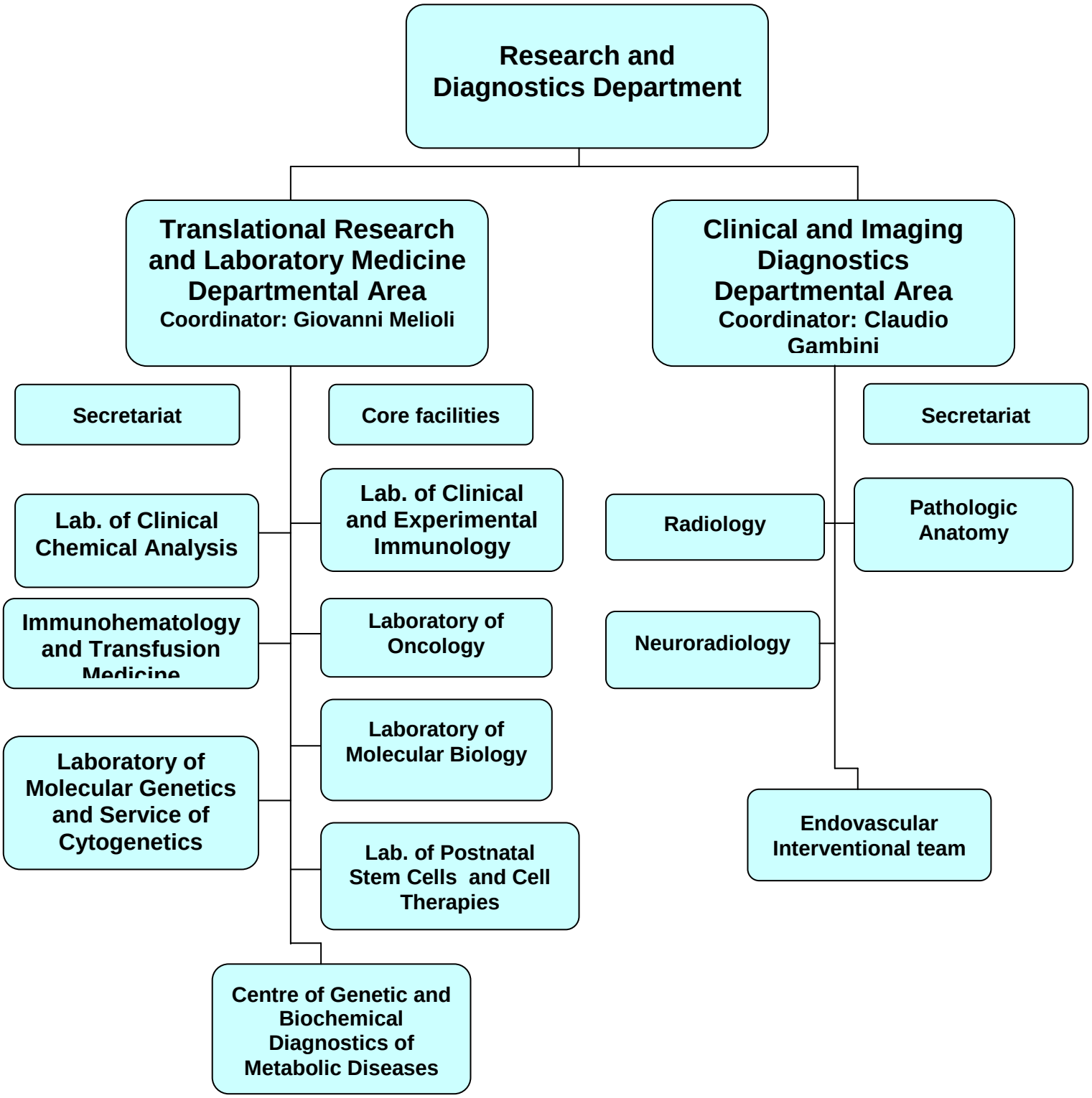
Activity year 2012

Applied research projects:

- Weekly high doses of liposomal amfotericin B for secondary prophylaxis of invasive fungal infection in immunocompromised children: experience in a pediatric case series.
- Treatment 3. Etanercept in Fanconi's anemia; US and Italian experience.
- Response to rituximab in 3 children with opsoclonus-myoclonus syndrome resistant to conventional treatment.

Research programme for 2013

Improvement of new procedures for preparation and supplying of drugs, galenics, magistral and officinal medicines, disinfectant solutions, laboratory reagents, orphan pediatric preparations not available on the market, unit dose preparations for children and newborns. Identification/improvement of new procedures for the centralized preparation of antiblastic chemotherapeutic drugs, mutagenic antiviral drugs, monoclonal antibodies. Identification/improvement of new procedures for the management of off-label prescriptions.


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

CLINICAL AND EXPERIMENTAL IMMUNOLOGY

Director: Cristina Bottino

Staff

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Claudia Cantoni
Michela Falco
Francesco Marras
Martina Serra
Francesca Bisio
Laura Chiossone
Martyna Kolosowska
Simona Minghelli
Francesca Canegallo
Marzia Dolcino
Fabrizio Loiacono
Antonio Puccetti

Activity year 2012

- Study of KIR repertoire in donors of hemopoietic stem cells (HSC) and statistical correlation with post-transplant clinical data of leukemic patients (survival, relapse).
- Analysis of the role of cytomegalovirus (HCMV) infection in the function/maturation of natural killer (NK) cells after HSC transplantation from umbilical cord blood.
- Characterization of interaction between NK cells and macrophages of healthy subjects or neoplastic patients (tumor-associated macrophages - TAM).
- Analysis of the capability of soluble factors produced by tumor cells to modulate function and phenotype of NK cells.
- Characterization of new serum markers of autoimmune diseases.

Research programme for 2013

Research project
miRNA profile in human NK cells
Objective: We have recently demonstrated that soluble factors (such as TGF beta) produced by tumor cells can modify the expression by NK cells of receptors for tumor ligands and chemokines. microRNAs (miRNA) are small non-coding RNA fragments that regulate gene expression by acting at post-transcriptional level. Our aim is to analyze the change of miRNA profile in NK cells after treatment with TGF beta and/or contact with tumor cells.
Description: miRNA expression profile in NK cells treated with TGF beta will be analyzed using PCR arrays. Single miRNA with expression levels resulting altered by treatment will be further considered for the identification of specifically regulated target genes. To this end, we will use data from software predicting miRNA-target interaction and from the analysis of TGF beta-correlated gene expression. Experimental validation of miRNA-target interaction will be performed using vectors with reporter genes. Through transfection with lentiviruses, NK cells overexpressing or not expressing specific miRNA will be produced to evaluate the expression profile of receptors for tumor ligands and chemokines. The interested miRNA expression will be evaluated also in NK cells co-cultured with tumor cells.

Main collaborations:

- A.Moretta, S.Sivori, R.Castriconi, F.Bellora (Di.Me.S), A.De Maria (DISSAL), E.Fulcheri (DISC), University of Genova
- M.C. Mingari, D. Pende, M.Vitale, P.Vacca, F.Frassoni, A.Pessino, S.Martino Hospital-Cancer Research Institute and University of Genova
- A. Mantovani, Humanitas Clinical Institute and Department of Transfusion Medicine, University of Milan
- F. Locatelli, Dept. of Pediatric Oncology-Hematology, Bambino Gesù Hospital, Rome
- C. Lunardi (Dept. of Medicine), L. Frulloni (Gastroenterology section),University of Verona
- L. Zitvogel, Institut Gustave Roussy and Université Paris Sud-XI, Villejuif, France
- Miguel Lopéz-Botet, Universitat Pompeu Fabra, Barcelona, Spain

Major publications (2007-2012)

1. Della Chiesa, M., Falco, M., Podesta, M., Locatelli, F., Moretta, L., Frassoni, F. and Moretta, A., Phenotypic and functional heterogeneity of human NK cells developing after umbilical cord blood transplantation: a role for human cytomegalovirus? *Blood* 2012. 119: 399-410.
2. Sivori, S., Carlomagno, S., Falco, M., Romeo, E., Moretta, L. and Moretta, A., Natural killer cells expressing the KIR2DS1-activating receptor efficiently kill T-cell blasts and dendritic cells: implications in haploidentical HSCT. *Blood* 2011. 117: 4284-4292.
3. Delahaye, N. F., Rusakiewicz, S., Martins, I., Menard, C., Roux, S., Lyonnet, L., Paul, P., Sarabi, M., Chaput, N., Semeraro, M., Minard-Colin, V., Poirier-Colame, V., Chaba, K., Flament, C., Baud, V., Authier, H., Kerdine-Romer, S., Pallardy, M., Cremer, I., Peaudecerf, L., Rocha, B., Valteau-Couanet, D., Gutierrez, J. C., Nunes, J. A., Commo, F., Bonvalot, S., Ibrahim, N., Terrier, P., Opolon, P., Bottino, C., Moretta, A., Tavernier, J., Rihet, P., Coindre, J. M., Blay, J. Y., Isambert, N., Emile, J. F., Vivier, E., Lecesne, A., Kroemer, G. and Zitvogel, L., Alternatively spliced NKp30 isoforms affect the prognosis of gastrointestinal stromal tumors. *Nat Med* 2011. 17: 700-707.
4. Bellora, F., Castriconi, R., Dondero, A., Reggiardo, G., Moretta, L., Mantovani, A., Moretta, A. and Bottino, C., The interaction of human natural killer cells with either unpolarized or polarized macrophages results in different functional outcomes. *Proc Natl Acad Sci U S A* 2010. 107: 21659-21664.
5. Falco, M., Romeo, E., Marcenaro, S., Martini, S., Vitale, M., Bottino, C., Mingari, M. C., Moretta, L., Moretta, A. and Pende, D., Combined genotypic and phenotypic killer cell Ig-like receptor analyses reveal KIR2DL3 alleles displaying unexpected monoclonal antibody reactivity: identification of the amino acid residues critical for staining. *J Immunol* 2010. 185: 433-441.
6. Vacca, P., Cantoni, C., Vitale, M., Prato, C., Canegallo, F., Fenoglio, D., Ragni, N., Moretta, L. and Mingari, M. C., Crosstalk between decidual NK and CD14+ myelomonocytic cells results in induction of Tregs and immunosuppression. *Proc Natl Acad Sci U S A* 2010. 107: 11918-11923.
7. Pende, D., Marcenaro, S., Falco, M., Martini, S., Bernardo, M. E., Montagna, D., Romeo, E., Cognet, C., Martinetti, M., Maccario, R., Mingari, M. C., Vivier, E., Moretta, L., Locatelli, F. and Moretta, A., Anti-leukemia activity of alloreactive NK cells in KIR ligand-mismatched haploidentical HSCT for pediatric patients: evaluation of the functional role of activating KIR and redefinition of inhibitory KIR specificity. *Blood* 2009. 113: 3119-3129.
8. Frulloni, L., Lunardi, C., Simone, R., Dolcino, M., Scattolini, C., Falconi, M., Benini, L., Vantini, I., Corrocher, R. and Puccetti, A., Identification of a novel antibody associated with autoimmune pancreatitis. *N Engl J Med* 2009. 361: 2135-2142.
9. Pende, D., Marcenaro, S., Falco, M., Martini, S., Bernardo, M. E., Montagna, D., Romeo, E., Cognet, C., Martinetti, M., Maccario, R., Mingari, M. C., Vivier, E., Moretta, L., Locatelli, F. and Moretta, A., Anti-leukemia activity of alloreactive NK cells in KIR ligand-mismatched haploidentical HSCT for pediatric patients: evaluation of the functional role of activating KIR and redefinition of inhibitory KIR specificity. *Blood* 2009. 113: 3119-3129.
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LABORATORY OF ONCOLOGY

Director: Vito Pistoia

Staff

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Activity year 2012

Research projects

HLA-Ib molecules in inflammation and tumors

The family of HLA classe Ib molecules includes HLA-G, HLA-E, HLA-F, and HLA-H. These molecules that, differently from HLA class Ia, have a low degree of polymorphism, are expressed not only on the surface of different cell types, but are also present in soluble form in biological fluids. The physiological role of HLA-G is to create a tolerogenic environment at the mother-fetus interface by inhibiting immune response against fetal tissues. HLA-G exerts different immunoregulatory functions: 1) inhibition of cytotoxicity mediated by cytotoxic T lymphocytes and NK cells; 2) induction of apoptosis of $CD8^+$ T lymphocytes and NK cells; 3) downregulation of the expression of some chemokine receptors on the surface of T lymphocytes and inhibition of chemotaxis at the corresponding ligands; 4) modulation of the release of cytokines and pro-angiogenic factors by $CD56^{bright}$ NK cells. HLA-G molecules carry out these functions by interacting with at least four different inhibiting receptors: immunoglobulin-like transcript (ILT)2 (expressed by T, B, NK cells and monocytes), ILT4 (on monocytes), KIR2DL4 (on NK cells), and CD160 (on T, NK, and endothelial cells).

The main function of HLA-E is the presentation of peptides deriving from the leader sequence of HLA class Ia molecules to NK cells through the interaction with the CD94/NKG2A complex, allowing NK cells to monitor the expression levels of HLA class I molecule. The interaction between HLA-E/peptide complex and CD94/NKG2A inhibits NK cytotoxicity.

Little information is available on HLA-F and HLA-H. The intracellular expression of HLA-F was demonstrated in resting lymphocytes, while surface expression was identified after cellular activation, suggesting that HLA-F is a potential immunological activation marker. In addition, HLA-F is expressed irrespective of the association with peptides and HLA-F heavy chain interacts with HLA-Ia molecule heavy chains, suggesting a role of HLA-F in the control of HLA-Ia molecule expression and function.

Objective of this project is to characterize the expression and function of HLA-Ib molecules in patients with autoimmune and inflammatory diseases or tumors. The role of HLA-G in tumor mechanisms has been largely characterized. HLA-G surface expression is upregulated in different human tumors and molecule concentration is serum of tumor patients is higher than in normal subjects. Conversely, soluble (s) HLA-G concentration in the serum of patients with various autoimmune diseases (as rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus) is lower than that detected in normal subjects, suggesting that low sHLA-G levels can cause a persistent activation of the immune system predisposing to these diseases.

Information is lacking, however, on HLA-G function, HLA-G-modulated intracellular signalling pathways, and possible regulation of microRNA (miRNA) expression induced by HLA-G. In addition, the role of HLA-E and HLA-F in tumors and chronic infllammatory diseases with autoimmune pathogenesis is still little known. This project is aimed at filling these gaps by focusing on neuroblastoma as tumor model and on multiple sclerosis as prototype of inflammatory autoimmune diseases.

Last year, a study was carried out on the role of miRNA in the regulation of gene expression induced by HLA-G in CD4+ activated human lymphocytes. The specifically analyzed function was the modulation induced by sHLAG of CXCR3 chemokine receptor. We demonstrated that miR 451 is downregulated, while miR 210 is upregulated in CD4+ cells incubated with sHLA-G; none of the two miRNA is involved in the regulation of CXCR3 expression. Analysis of miR210 and miR451 target genes showed an increased expression of OSR-1 (odd-skipped related 1) and HBP-1 (HMG-box transcription factor 1) and a decreased expression of CXCL16 (chemokine C-X-C motif ligand 16) and C11 or f30 (chromosome 11 open reading frame 30) in CD4+ lymphocytes treated with sHLA-G.

Immunotherapy with combined γδ T lymphocytes and zoledronate in a pre-clinical model of neuroblastoma

Neuroblastoma (NB) is a pediatric tumor that, in about half cases, appears as metastatic disease at diagnosis; two thirds of these patients do not survive at 5 years in spite of the use of the most advanced therapies. Immunotherapy of NB with non HLA-restricted lymphocytes is an interesting perspective since this tumor expresses very low or absent levels of HLA class I molecules. Circulating γδ T lymphocytes belong prevalently to Vδ2γ9 subset that lyse tumor cells through mechanisms depending on T cell receptor (TCR) or on the moecule stimulating NKG2D cytotoxicity. In both cases, the recognition of tumor cells does not depend on HLA restriction. Biphosphonates are inhibitors of bone reabsorption used for therapy of osteoporosis and bone metastases. A particular aminobiphosphonate, zoledronate (ZOL), causes an accumulation in target cells of IPP metabolite that is recognized by TCR of Vδ2γ9 T lymphocytes. These latter are activated to proliferate and expand from zoledronate itself. We have therefore developed a preclinical model of immunotherapy of NB based on the combination of Vδ2γ9 T lymphocytes and ZOL. First, we demonstrated the feasibility of in vitro expansion of Vδ2γ9 T lymphocytes from peripheral blood of normal donors and patients with metastatic NB through stimulation with ZOL. Secondly, we developed an orthotopic model of human NB and implanted the NB line HTLA-230 in the adrenal gland of immunodeficient mice subsequentyl treated with Vδ2γ9 T lymphocytes expanded in vitro, ZOL, Vδ2γ9 T lymphocytes together with ZOL and diluent, administered systemically. The results obtained showed a significant beneficial effect in terms of survival only for the combination Vδ2γ9 T lymphocytes + ZOL. Histological and immunohistochemical analyses showed in animals treated with the latter combination an inhibition of the proliferation and apoptosis induction of tumor cells associated with inhibition of angiogenesis. Tumors were infiltrated with Vδ2γ9 T lymphocytes that i) were cytotoxic since they were positive for the antigen associated with Tia-1 cytotoxic granules and ii) expressed IFN-γ, which in turn induced an intense diffused expression in neoplastic cells of CXCL10 antiangiogenic chemokine, but not of CXCL9. On the other hand, inoculated Vδ2γ9 T lymphocytes expressed CXCR3, CXCL10 receptor, suggesting that CXCL10 can be involved in their recruitment in the tumor mass.
These studies, that should be further continued to optimize timing and schedule of the association Vδ2γ9 T lymphocytes + ZOL, lay the foundations for the design of a phase I study on NB.

NB metastatic niche

Vascular mimicry (VM) is a phenomenon in which tumor cells can function as endothelial cells coating the vessels of tumor microenvironment. Years ago, we first demonstrated that VM occurs also in NB and consists of true transdifferentiation of tumor elements in mature endothelial cells that line fully functional vessels. We also identified the progenitor tumors of tumor-derived endothelial cells (TEC) as neuroblasts expressing Oct-4 and tenascin-C surface marker. TEC are implicated in tumor progression and drug resistance, and are also present in the metastatic niche. We asked ourselves whether the elimination of these cells can improve NB prognosis using the same previously described NB preclinical model. We therefore treated tumor-carrying animals with a human anti-CD31 monoclonal antibody or with an isotope-correlated control antibody in order to eliminate selectively CD31+ endothelial-like cells produced with VM. The results obtained demonstrated that anti-CD31 antibody causes TEC apoptosis followed by vascular remodeling with appearance of proliferating TEC and increase in tenascin C^+ progenitors. In terms of survival, treatment of tumor-carrying mice with anti-CD31 did not have any beneficial effect.

Similar results were obtained by therapy with an antibody directed against a PSMA epitope expressed selectively on human and murine endothelial cells.
Today, studies are being carried out to elucidate the mechanisms inderlying TEC resistance to immunotherapy with anti-endothelium monoclonal antibodies.

AIRC project

Cytokine receptors as potential targets for epigenetic silencing in hematopoietic malignancies

In 2012, the last year of this project, we studied the expression and function of IL-17A and of the corresponding receptor (IL-17AR) in the germinative centre (GC) of secondary lymphoid organs (in particular in the tonsil) and in lymph nodes invaded by GC tumors, i.e. follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL) and Burkitt lymphoma. The main subpopulations of normal B lymphocytes (naive, memory, and GC) express the two chains of IL-17AR, i.e. IL-17RA and IL-17RC. Similarly, tumor cells of the three types of lymphoma express the same receptor chains. Subsequently, we studied IL-17A expression in normal and lymphomatous GC microenvironment. Using immunohistochemistry and immunofluorescence on tissue sections, we observed that cells producing IL-17A were T lymphocytes and mastocytes, with particular concentration of the first in the paracortical area of the normal lymph node. Finally, we studied in vitro and in vivo the function of IL-17A on B lymphocytes of normal GC and on their neoplastic counterparts. In vitro IL-17A did not show any effect on the proliferation and survival of normal GC B lymphocytes; however, the cytokine proved to able to make the same competent cells migrate in reponse to CXCL12 and CXCL13 chemokines through a mechanism determining downregulation of RGS16 mediated by phosphorylation of NFkBp65 protein. IL-17A stimulated in vitro the proliferation of lymphomatous cells and in vivo it increased the growth of a line of DLBCL lymphoma through the following mechanisms: increased proliferation of tumor cells and of angiogenesis.
These results outline new scenarios concerning the role of IL-17A in normal GC and in deriving B cell neoplasias.

AIRC NUSUG Project

IL-23 receptor and WSWSX1 as potential tumor suppressor genes in human B cell malignancies

In 2012, the last year of this project, we studied the effects of some cytokines of IL-12 superfamily (IL-27, IL-23, IL-12) on acute myeloid leukemia (AML) of pediatric age and on FL and DLBCL lymphomas. It was demonstrated that AML cells express IL-27 receptors and cytokyne strongly inhibits the growth of in vivo primary leukemic cells in NOD/SCID/Il2rg(-/-) mice. The mechanism underlying this inhibition is the reduced expression of pro-angiogenic and pro-metastatic genes. In the case of IL-12, we demonstrated that primary AML cells express the two β1 and β2 chains of IL-12 receptor; this is true for both CD45+ and CD33+ leukemic blast cells and for different fractions containing leukemia initiating cells (CD34+, CD38-; CD33+, CD38+; e CD44+, CD38-). In vivo experiments using the same model described above showed that, in the first month of treatment, IL-12 was able to eradicate almost completely AML, with the exception of a population of CD33+ and CD38+ cells not expressing IL-12Rβ2. Between 30 and 60 days after the initial inoculation of primary leukemic cells in immunodeficient mice, these cells not responsive to IL-12 expanded and metastasized both in control mice and in mice treated with IL-12. These data show that the absence of IL-12Rβ2 on AML cells favours disease progression in the animal model that we adopted.
Finally, it was demonstrated that combined IL-23 and IL-27 exert anti-tumoral activity against human FL and DLBCL lines implanted in the same above mentioned immunodeficient mice. The action mechanisms of the two cytokines were complementary, i.e. IL-23 inhibited directly the proliferation of tumor cells, while IL-27 blocked the pro-angiogenic programme of the same cells.

MIUR/FIRB project

P2 purinergic receptors and ectonucleotidases: new targets for the development of innovative antitumoral drugs

In the first year of this project, we characterized myeloid-derived suppressor cells (MDSC) that expand in an NB immunocompetent murine model (A/J mice inoculated with Neuro-2 murine NB line). It was demonstrated that MDSC are present mainly in spleen and in peripheral blood of these tumor-carrying animals, and less present in primary tumor site. Granulocyte- and monocyte-derived MDSC are present, showing a good expression of P2X7 purinergic receptor. From the functional point of view, MDSC produce ROS, arginase and VEGF, but show only a minimal suppressing activity on the proliferation of lymphocytes induced by polyclonal stimulators.

Research programme for 2013

Research projects

Expression and function of ectoenzymes on cells with immunoregulating activity

Objective: Adenosine is a molecule with immunosuppressive activity produced abundantly as ATP metabolite. This production is particularly high in tumor microenvironment and is operated by ectoenzymes, among which the best characterized are CD39 and CD73, expressed for instance by regulatory T cells. The hypothesis is the existence of a new biochemical pathway of adenosine production involving CD203.

Description: The project is aimed at characterizing this hypothetical pathway in mesenchymal stem cells isolated from the bone marrow of normal donors CD56bright NK lymphocytes isolated from peripheral blood and tonsil. These two cell fractions will be characterized for the expression of a wide panel of ectoenzymes as CD38, CD26, CD157, CD39, CD73, and CD203. Subsequently they will be cultured in the short term in the absence or presence of stimuli and the supernatants will undergo biochemical analysis to assay the presence of various ATP metabolites. In correlated experiments, inhibitors specific for single ectoenzymes will be used to clarify the role of these latter in the generation of the above-mentioned metabolites.

Impact of caloric restriction on the immune system

Objective: We demonstrated that pre- and post-chemotherapy fasting in mice carrying different types of tumor, NB included, generates a phenomenon known as differential stress resistance, in which tumor cells are sensitized to cytotoxic drugs and normal host cells are protected against side effects of the same drugs. Aim of the project is to study the impact of fasting on the immune system and on antitumoral response.

Description: Immunocompetent control mice and mice carrying different types of transplantable solid tumors will undergo fasting cycles, receiving only fluids for standard periods (48-96 hrs), as already experimented in our previous studies. Subsequently, the animals will undergo sampling of peripheral blood and in-depth immunophenotypical analysis of circulating hemopoietic cells, and in particular of regulatory cell populations as MDSC, Treg and Breg lymphocyes, CD56bright NK cells. After sacrifice, spleen, bone marrow and primary tumor will be sampled and on these biological samples gene expression profiling experiments will be conducted. Finally, plasma will be used for the analysis of cytokynes and chemokines by multiplex technology.

Main collaborations:

- Prof. Fabio Malavasi, University of Torino
- Prof. Francesco Di Virgilio, University of Ferrara
- Prof. Emma Di Carlo, University of Chieti
- Dr. Maurilio Ponzoni, San Raffaele Hospital, Milano
- Dr. Francesco Bertoni, Cancer Research Institute, Bellinzona, Switzerland
- Prof. Gianmario Sambuceti, University of Genova

- Prof. Claudio Tripodo, University of Palermo
- Prof. Antonio Uccelli, University of Genova
- Prof. Alessio Nencioni, University of Genova
- Prof. Valter Longo, University of South California, Los Angeles

Major publications (2007-2012):

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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. Epub 2011 Oct 11.

LABORATORY OF MOLECULAR BIOLOGY

Director: Dr. Luigi Varesio

Staff

Massimo Acquaviva	Sara Barzaghi	Pamela Becherini
Fabiola Blengio	Maria Carla Bosco	Davide Cangelosi
Alessandra Eva	Massimiliano Izzo	Marzia Ognibene
Roberta Resaz	Daniela Segalerba	Cristina Vanni

Activity year 2012

In 2012, we focused on two research lines. The first studied tissue microenvironment and the impact of local signals, in particular hypoxia, on cells of the innate immune system (NK, DC, MN), and on endothelial and stromal tumor cells. From the data obtained, we defined molecular signatures specific of response to hypoxia of the different cell types that will be the structure on which the metabolic pathways involved in adaptation to tissue microenvironment will be mapped. These signatures were integrated with the hypoxic signature of neuroblastoma through bioinformatic analysis that attributes a weight to each signature in order to balance the contribution of each cell type in the tumor system.
The second research line was instead focused on the generation of a new murine model of glycogenosis type 1 in which the glucose-6-phosphatase gene is deleted only in liver at birth.
This model will allow the selective study of liver tissue alterations and the possible treatment of liver dysfunctions. We expect that mouse average lifetime is increased, allowing a better experimentation compared to total KO mice. This model will be extended to the selected deletion of the gene in kidney and/or intestine.

Research programme for 2013

Research project

New strategies for the treatment of Glycogenosis 1 a: from bench to bedside
Objective: This project is aimed at studying the use of stem cells to regenerate affected tissues and the identification of new pharmacological targets of altered metabolic pathways will make it possible to improve and prolong the life of patients with glycogenosis 1a.
Description: We will study the use of stem cells from adult tissue to regenerate the liver affected by GSD1a in a mouse model showing the same disease observed in man. We wil also be strongly committed to the study of the kidney. The collaboration among research units specialized in the use of these stem cells (Istituto G. Gaslini, Genova and MBC, Torino) guarantees the success of this phase of the project. In parallel, in collaboration with a clinical unit dealing with GSD1a at the Istituto Gaslini, we will establish the first GSDI Italian registry to define the range of clinical presentations and disease natural history. We will create a biobank of serum and tissues, in collaboration with BIT-Gaslini biobank, to conserve material collected in occasion of periodic patient visits and from liver transplantations performed in extreme cases. A new murine model of kidney disease obtained last year will be characterized and analysed.

Main collaborations

- Dr. Janice Chou (NIH, NICHD HDB, Bethesda, USA): glycogenosis type 1a, gene therapy
- Dr. Fiorella Altruda (Dept. Genetics, Medical Chemical Biology, Torino): knock-out and knock-in mice for Dbl gene
- Prof. Mara Torrisi (Dept. Experimental Medicine, Policlinico Umberto I, Roma): immunofluorescence, electronic microscopy
- Prof. Isabella Screpanti (Dept. Experimental Medicine and Pathology, La Sapienza University, Roma): immunology of tumors, T lymphocytes, animal models
- Dr. Bruno Bembi (Metabolic Disease unit, Burlo Garofolo Institute, Trieste): metabolic diseases, glycogenosis, diagnosis

Major publications (2007-2012)

1. Bosco, M. C., Delfino, S., Ferlito, F., Battaglia, F., Puppo, M., Gregorio, A., Gambini, C., Gattorno, M., Martini, A., and Varesio, L. (2008). Hypoxic synovial environment and expression of macrophage inflammatory protein 3gamma/CCL20 in juvenile idiopathic arthritis. Arthritis Rheum. 58, 1833-1838.

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7. Resaz, R., Emionite, L., Vanni, C., Astigiano, S., Puppo, M., Lavieri, R., Segalerba, D., Pezzolo, A., Bosco, M. C., Oberto, A., Eva, C., Chou, J. Y., Varesio, L., Barbieri, O., and Eva, A. (2011). Treatment of newborn G6pc(-/-) mice with bone marrow-derived myelomonocytes induces liver repair. J Hepatol. 55, 1263-1271.

8. Ognibene, M., Vanni, C., Segalerba, D., Mancini, P., Merello, E., Torrisi, M. R., Bosco, M. C., Varesio, L., and Eva, A. (2011). The tumor suppressor hamartin enhances Dbl transforming activity through interaction with ezrin. J Biol Chem. 89, 493-504.

9. Cattelani, S., Ferrari-Amorotti, G., Galavotti, S., Defferrari, R., Tanno, B., Cialfi, S., Vergalli, J., Fragliasso, V., Guerzoni, C., Manzotti, G., Soliera, A. R., Menin, C., Bertorelle, R., McDowell, H. P., Inserra, A., Belli, M. L., Varesio, L., Tweddle, D., Tonini, G. P., Altavista, P., Dominici, C., Raschella, G., and Calabretta, B. (2012). 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. 14, 634-643.

10. Molenaar, J. J., Domingo-Fernandez, R., Ebus, M. E., Lindner, S., Koster, J., Drabek, K., Mestdagh, P., van Sluis, P., Valentijn, L. J., van Nes, J., Broekmans, M., Haneveld, F., Volckmann, R., Bray, I., Heukamp, L., Sprussel, A., Thor, T., Kieckbusch, K., Klein-Hitpass, L., Fischer, M., Vandesompele, J., Schramm, A., van Noesel, M. M., Varesio, L., Speleman, F., Eggert, A., Stallings, R. L., Caron, H. N., Versteeg, R., and Schulte, J. H. (2012). LIN28B induces neuroblastoma and enhances MYCN levels via let-7 suppression. Nat Genet. 44, 1199-1206.

LABORATORY OF POSTNATAL STEM CELLS AND CELL THERAPIES

Director: Prof. Francesco Frassoni

Staff

Irma Azzari	Monica Ciarlo	Claudia Cossu
Antonella Linardi	Marina Podestà	Federica Sabatini

Activity year 2012

- Continuation of the study started in previous years at the San Martino hospital on the gene expression (Card analysis) of hemopoietic stem cells (CD34+) of cord and medullary blood before and after transplantation. In addition, the technique of expansion of mesenchymal stem cells (MSC) from the umbilical cord was developed and the protocol of MSC expansion from medullary blood was validated.
- In collaboration with the BMT section of the Hematology/Oncology unit, we prepared the protocol of pediatric intraosseous transplantation of cord blood that will be submitted to the Ethics Committee of Gaslini as soon as possible.
- Concerning the certification of the Clean Room, we prepared the operating procedures concerning the following: validation of disinfectants, methods of sanification of rooms and training of cleaning staff; preparation of Media-Fill procedures of productive processes; management of warehouse, products and suppliers of materials and services.

Research programme for 2013-2015

A) **Development of iPS (Induced Pluripotent Stem Cells)**
We decided to invest in the development of *induced Pluripotent Stem Cells* that represent the basis of any future cell therapy. We are sending fellowship holders to the Harvard Stem Cell Institute to establish a collaboration.

B) **Development of hematopoietic stem cell transplantation**
It is a new protocol for the launch of intraosseous umbilical cord blood transplantation in children. After approval by the Ethics Committee, the protocol will be adopted in the Hematology/Oncology unit

C) **Identification of genes conferring the characteristics of stem cells**
The project is aimed at identifying the genes that are hyperexpressed in hematopoietic stem cells during regeneration after transplantation. The objective is a) to identify self-renewal genes (also useful for expansion), b) to identify whether the behaviour of hematopoietic cells is influenced by their age and by microenvironment.

D) **Receptors and Molecular Targets of Neoplastic Cells**
We started a study on acute leukemias together with the Hematology/Oncology unit and in collaboration with the University of Torino and the Bambino Gesù hospital of Rome for the evaluation of new receptors and possible therapeutic targets. In this phase, we are evaluating EphA3r receptor that is expressed only on leukemic cells and on their normal counterparts.

E) **Bcl-xL and GATA-1**
In myeloproliferative diseases (Polycythemia, Thrombocytemia and Myelofibrosis), evidence is available of alternative molecular pathways and of a molecular background common to all these diseases. Bcl-xL and GATA-1 are genes that are very likely determinant in the pathogenesis of myeloproliferative diseases. In collaboration with the University of Torino, we developed new technological instruments (Peptide Nucleic Acid) to better define the role of these genes.

F) **Cellular Trafficking**
This study is carried out in collaboration with the Department of Nuclear Medicine of San Martino hospital and in particular with Prof GM Sambuceti.

The ambitious goal of this new research is the answer to many questions but, in particular, the evaluation of homing in BM as a pre-requisite for subsequent take and repopulation.

G) **Clean Room**
After outsourcing maintaining service to ADF Sistemi, we will proceed with requalification of facilities and equipment; we will organize microbiological quality controls of environment and products; we will prepare the Validation Master Plan for AIFA certification.

Main collaborations:

- Prof G Saglio and Dr. Daniela Cilloni
  Dept. Clinical and Biological Sciences, University of Torino
  S. Luigi Hospital
- Dr G Dini and Dr C Dufour
  Pediatric Hematology/Oncology unit, Istituto Gaslini
- Prof A Moretta
  Dept. of Experimental Medicine, Histology section
  University of Genova
- Prof GM Sambuceti
  Nuclear Medicine
  San Martino-IST Hospital
- Prof. Antonio Uccelli
  Chair of Neurology, University of Genova
- Prof F Locatelli
  Bambino Gesù Hospital, Roma
- Prof Massimilano Bonafè and Drssa F Bonifazi
  University of Bologna

Major publications (2007-2012)

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LABORATORY OF CLINICAL CHEMICAL ANALYSIS

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Activity year 2012

Research project

Pediatric reference ranges

The identification of reference ranges (RR) for the results of laboratory tests performed in pediatric patients becomes every day more important. In fact, we calculated that changes in about half RR in pediatrics is statistically correlated with age. In particular, some parameters change in a few days after birth, while others change over a much longer period. Actually, clinical use of non age-specific RR can cause gross diagnostic mistakes. Until a few years ago, the pediatric patient was evaluated on the basis of arbitrary age ranges. We could observe that RR can be calculated more accurately if age is considered a continuous variable. In that case, RR is much more usable. In addition, it is possible to modulate specificity and sensitivity of RR by using different percentiles: for instance, the 10th and 90th percentile improve sensitivity but lose specificity, whereas 2.5th and 97.5th percentiles worsen sensitivity but improve specificity.

Research programme for 2013

Research project

Pediatric reference ranges for lymphocyte populations and subpopulations.

Objective: Congenital immunodeficiencies become manifest after birth. Diagnostic protocols establish that phenotype defects are identified on immunocompetent effectors. It is therefore essential to have RR that change during a lifetime. Objective of this study os to calculate these RR using age as a continuous variable.
Description: Residues of whole blood samples undergoing routine tests in our laboratories will be used.

Age range between birth and 14 years will be considered, but with special focus on that between birth and 3 years.
Phenotype tests will be performed on whole blood and monoclonal antibody panels allowing a better characterization of T lymphocytes (in particular subpopulations) and B lymphocytes (in particular the different maturation stages in circulation) will be used. Absolute values and percentages willundergo statistical analysis to identify the 10^{th} and 90^{th} percentile of distribution..In addition, age-related vs independent RR will be identified. With these RR, it will be possible to analyze the phenotype of lymphoid cells in patients with suspected congenital immunodeficiency.

Main collaborations

- Istituto Giannina Gaslini, Genova, Italy
  - Pediatric Rheumatology, Prof. Martini and Dr. Gattorno (immunodeficiencies)
  - Infectious Diseases, Dr. Castagnola (opportunistic infections)
  - Laboratory of Cytofluorimetry and Cell Sorting, Core Facilities.
- Laboratory of Immunology, Novartis (Basilea, Switzerland)
- Dr. Elisabetta Traggiai and Dr. Alessandra Magnano

Major publications (2007-2012)

1. Administration of a polyvalent mechanical bacterial lysate to elderly patients with COPD: Effects on circulating T, B and NK cells. Lanzilli G, Traggiai E, Braido F, Garelli V, Folli C, Chiappori A, Riccio AM, Bazurro G, Agazzi A, Magnani A, Canonica GW, Melioli G. Immunol Lett. 2012 Dec 1. doi:pii: S0165-2478(12)00246-5. 10.1016/j.imlet.2012.11.009.
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8. Erythrocyte Galactose-1-phosphate measurement by GC-MS in the monitoring of classical galactosemia. Cangemi G, Barco S, Barbagallo L, Di Rocco M, Paci S, Giovannini M, Biasucci G, Lia R, Melioli G. Scand J Clin Lab Invest. 2012 Feb;72(1):29-33.

9. The ImmunoCAP ISAC molecular allergology approach in adult multi-sensitized Italian patients with respiratory symptoms. Melioli G, Bonifazi F, Bonini S, Maggi E, Mussap M, Passalacqua G, Rossi ER, Vacca A, Canonica GW; Italian Board for ISAC (IBI). Clin Biochem. 2011 Aug;44(12):1005-11.

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IMMUNOHEMATOLOGY AND TRANSFUSION MEDICINE

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Activity year 2012

Study design: we evaluated CD4+ and CD8+ lymphocytes, neutrophil granulocytes, and monocytes sampled before, immediately after, and at 7 and 14 days from the apheretic procedure for donation (in healthy subjects) or for therapy (in patients with autoimmune disease) for three successive procedures with 2 weeks' interval between each other. Evaluated parameters were absolute count, cell cycle and phenotype, intracellular concentration of $TGF\beta_1$ (protein and mRNA). Simultaneously, we evaluated plasma levels of $TGF\beta_1$, sHLA class I, and soluble FasL both in samples taken directly from donors and, subsequently, in plasma present in circuits at the end of apheretic procedures. **Results**: It was demonstrated that the significant increment (sustained over time) of $TGF\beta_1$ concentrations in neutrophil granulocytes, monocytes, and $CD8^+$ lymphocytes after the apheretic procedure results reproducible at each procedure in both groups. In the donor group, $TGF\beta_1$ and sHLA-I plasma levels result significantly increased up to 14 days after the apheretic procedure, but the degree of the increase results significantly higher in patients. FasL plasma values in donors do not show considerable changes while in patients there is a progressive and steady increase both after each single procedure and at repeated apheresis. **Conclusions**: Similarly to what has been demonstrated after transfusion, it is possible to hypothesize that, even during the apheretic procedure, there is an immunomodulating effect correlated with the ability to induce transcriptional and post-transcriptional modulation of $TGF\beta_1$ after interaction of leukocytes with the high concentrations of sHLA-I detectable in circuits. This effect seems much more significant in the patient group, in which FasL and $TGF\beta_1$ levels appear much higher and show a progressive increase correlated with the repetition of the apheretic procedure.

Research programme for 2013

Research project

Immunomodulation related to apheretic procedures and TRIM (Transfusion-Related ImmunoModulation): study of the role of conservation and of the effects of contact between blood and biocompatible plastic materials as related to the characteristics of donor/patient

Objective: Identification of the characteristics present in the patient or in the healthy subject (inflammation, activation of the immune system) able to influence the appearance of immunomodulating effects induced by the administration of therapeutic products derived from humans (plasma derivatives, conserved blood components, blood coming into contact with biocompatible plastic surfaces during apheretic procedures).

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 when these products are transfused/infused intravenously.

There are significant differences in the extent and typology of biological modifications between patients with autoimmune and/or inflammatory diseases and healthy subjects as donors of plasma and platelets. A study is proposed on a series of immunological/inflammatory parameters to evaluate their possible ability to influence the immunomodulation induced through sHLA-I.

Main collaborations

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

Major publications (2007-2012)

1. Tripodi G, Risso M, Tenerini L, Gandullia P, Castellano E, Rivabella L. Drug-resistant bullous pemphigoid and inflammatory bowel disease in a pediatric case successfully treated by plasma exchange and extracorporeal photochemotherapy. J Clin Apher. 2007 Feb;22(1):26-30.
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5. Motta M, Testa M, Tripodi G, Radicioni M. Changes in neonatal transfusion practice after dissemination of neonatal recommendations. Pediatrics. 2010 Apr;125(4):e810-7. Epub 2010 Mar 29.
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8. 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.
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10. 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

LABORATORY OF MOLECULAR GENETICS AND SERVICE OF CYTOGENETICS

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Activity year 2012

The research activity of the Laboratory of Molecular Genetics and Service of Cytogenetics was mainly focused on rare genetic diseases, in particular on the following research lines:

- Identification of genes responsible for monogenic hereditary diseases;
- Development of diagnostic methods for monogenic hereditary diseases;
- Development of new diagnostic instruments through Next Generation Sequencing ;
- Studies on pathogenetic mechanisms of monogenic hereditary diseases;
- studies on functional genomic approaches to identify interrelationships among disease genes;
- studies on innovative therapeutic approaches for rare genetic diseases;
- studies on cytogenetic diseases responsible for rare genetic diseases;
- studies on genomic imbalances through Comparative Genomic Hybridization.

Rcently obtained results concerned: Cystic Fibrosis, Congenital Central Hypoventilation Syndrome; Hirschsprung disease; Alexander disease; Progressive Ossifying Fibrodysplasia; Intestinal innervation defects; Congenital Anomaliees of Kidney and Urinary Tract (CAKUT); Genetic recurrent fevers; congenital limb anomalies; Poland syndrome; Animal model of cerebellar ataxia; Nail Patella syndrome.

Research programme for 2013

Research project

Genes, pathogenetic mechanisms and therapeutic approaches for rare genetic diseases
Objective: Genetic research, maily research on rare genetic diseases, is aimed at characterizing disease mechanisms starting from the mutated gene and the implicated biological processes in order to implement effective diagnostic methods useful for genetic counselling to patients and their families and to identify targets for possible therapeutic interventions.
Description: The research programme will be focused on the following: A) Search for new genes responsible for genetic diseases for which no causative gene is known through exome analysis using Next Generation Sequencing (NGS) in the case series with Poland syndrome; B) Development of a new diagnostic method for syndromes with recurrent fevers using NGS technology for sequencing of a panel of 11 candidate genes; C) Screening of chemical compounds or of siRNA for the identification of activators or inhibitors of gene expression or function: it will be carried out for molecular defects causing cystic fibrosis, Progressive Ossifying Fibrodysplasia, Alexander disease, Congenital Central Hypoventilation Syndrome, Neuroblastoma; D) Study of mechanisms of control of the production of mucus in the epithelium of airways related to inflammatory conditions.

Main collaborations

- Fred Kaplan and Eileen Shore, The University of Pennsylvania, School of Medicine: Pathogenetic mechanisms of Progressive Ossifying Fibrodysplasia.
- Maria Pia Rastaldi, Ospedale Maggiore Policlinico, D'Amico Foundation for Research on Renal Diseases, Milano: Studies on the role of mGlu1 receptor in renal function.
- International Consortium on Hirschsprung Disease: since 2004, it gathers gourps in Baltimora, Pargi, Groningen, Hong Kong, Siviglia and Genova (our laboratory)
- Pediatric Rheumatology unit, Istituto G. Gaslini: Genetic aspects and molecular diagnosis of autoinflammatory diseases.
- Pascale Fanen, INSERM 955 (equipe 11), Université Paris-Est: Study of action mechanisms of mutations causing cystic fibrosis

Major publications (2007-2012)

1. 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 Oct 22. [Epub ahead of print]
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. 2012 Oct 31. [Epub ahead of print]
3. Pedemonte N, Tomati V, Sondo E, Caci E, Millo E, Armirotti A, Damonte G, Zegarra-Moran O, Galietta LJ: Dual activity of aminoarylthiazoles on the trafficking and gating defects of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel caused by cystic fibrosis mutations. J Biol Chem. 2011 Apr 29;286(17):15215-26.
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7. Cuoco C, Ronchetto P, Gimelli S, Béna F, Divizia MT, Lerone M, Mirabelli-Badenier M, Mascaretti M, Gimelli G.: Microarray based analysis of an inherited terminal 3p26.3 deletion, containing only the CHL1 gene, from a normal father to his two affected children. Orphanet J Rare Dis. 2011 Apr 1;6:12.
8. Emison ES, Garcia-Barcelo M, Grice EA, Lantieri F, Amiel J, Burzynski G, Fernandez RM, Hao L, Kashuk C, West K, Miao X, Tam PK, Griseri P, Ceccherini I, Pelet A, Jannot AS, de Pontual L, Henrion-Caude A, Lyonnet S, Verheij JB, Hofstra RM, Antiñolo G, Borrego S, McCallion AS, Chakravarti A.: Differential contributions of rare and common, coding and noncoding ret mutations to multifactorial Hirschsprung disease liability. Am J Hum Genet. 2010 Jul 9;87(1):60-74.

9. Verkman AS, Galietta LJ. Chloride channels as drug targets. Nat Rev Drug Discov. 2009, 8:153-171.

10. Caputo A, Caci E, Ferrera L, Pedemonte N, Barsanti C, Sondo E, Pfeffer U, Ravazzolo R, Zegarra-Moran O, Galietta LJ. TMEM16A, a membrane protein associated with calcium-dependent chloride channel activity. Science. 2008, 322:590-594.

CENTRE OF GENETIC AND BIOCHEMICAL DIAGNOSTICS OF METABOLIC DISEASES

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Activity year 2012

The research interests of the Centre include the genetics of lisosomal diseases (LD) and of some white matter disorders. Another research line concerns the activities and regulations of genetic biobanks.
In the field of LD, Gaucher disease, due to glucocerebrosidase defect (GBA), is studied in various projects. In particular, studies are ongoing to clarify the molecular mechanisms underlying bone disease using zebrafish as animal model (Genzyme Generation Program) and to evaluate molecular mechanisms that can modulate response to substitution enzymatic therapy. Among possible factors, the role of LIMP-2 (receptor involved in trafficking of GBA endogenous enzyme) in *uptake* of recombinant-exogenous-GBA enzyme is being studied.
Among white matter disorders, hypomyelinating luekodystrophies are particularly interesting for the Centre (EU project, FP7-Health). Genotype-phenotype correlation studies were carried out, based on "*in silico"* functional characterization of protein sequences mutated in Pelizaeus-Merzbacher (PMD)-like. Within the same project, antisense oligonucleotides were used to correct "in vitro" a mutant allele causing an altered splicing pattern in a patient with the classic PMD form.
Concerning the second research line, the Centre and its genetic biobank supported internal and external research projects and continued its coordination activity 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 the specific competences acquired in the field of organizational, legal, and ethical aspects related to biobanking. Finally, it has continued the monitoring of specific indicators for Biobanks.

Research projects

Biobank of biological material from patients with genetic diseases: studies on biobabk-related best practices (SIGU) and their harmonisation with European guidelines

Molecular and functional analysis in neurometabolic genetic diseases

Analysis of the pathogenetic mechanism underlying lysosomal disorders using zebrafish biosensor

Clinical history and long term cost-effectiveness of Enzyme Replacement Therapy (ERT) for Gaucher Disease in Italy

Therapeutic challenge in Leukodystrophies: translational and ethical research towards clinical trials

Award of 2010 Gaucher Generation Program

Characterization of key pathogenetic pathways leading to bone abnormalities in Type 1 Gaucher patients through a biosensor fish model

Research programme for 2013

Research projects

Molecular and functional analysis in neurometabolic diseases
Objective: Aim of the project is to continue the molecular and functional characterization of mutant alleles selected among the cases sent to the centre for diagnosis and conserved, after informed consent, in the genetic biobank for further research.
Description: Research activity will be carried out using in silico systems (in collaboration with the School of Medicine, Cardiff University), “in vitro” expression systems in different cell types (COS7, NIH3T3, Oli-neu), and animal models, namely zebrafish in Gaucher disease (in collaboration with the University of Padova) and mice (Twitcher) in Krabbe leukodystrophy (in collaboration with NEST, Nanosciences Institute-CNR).

Biobank of biological material from patients with genetic diseases: testing of biobank-related best practices (SIGU)
Objective: Continuation of the study in biobank-related best practices (SIGU) and their harmonisation with national and European guidelines
Description: Constant monitoring of SIGU will be useful to highlight possible critical aspects that will allow necessary changes and improvements.

Training of staff involved in biobanking will be continued. In addition, thanks to know-how acquired in this field, the staff will continue to participate activelt in national (ERIC-BBMRI) and international (Bioresource Research Impact Factor-GEN2PHEN) working groups.

Main collaborations

- Department of biomedical sciences, University of Padova
- Regional Coordination Centre for Rare Diseases, University hospital “Santa Maria della Misericordia", Udine
- NEST, Nanosciences Institute-CNR, Pisa
- Institute of Medical Genetics, School of Medicine, Cardiff University, Cardiff, UK
- Institut National de la Sante 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
- Biopolimers and Proteomics, San Martino hospital- IST, Genova
- Dept. of Chemistry, Biochemistry and Biotechnologies for Medicine, University of Milano
- Institute of Genetic Medicine, Newcastle University, Newcastle, UK

Major publications (2007-2012)

1. Donnarumma M, Regis S, Tappino B, Rosano C, Assereto S, Corsolini F, Di Rocco M, Filocamo M. Molecular analysis and characterization of nine novel CTSK mutations in twelve patients affected by pycnodysostosis. Hum Mutat 2007;28:524.
2. Pittis M, Donnarumma M, Montalvo A, Dominissini S, Kroos M, Rosano C, Stroppiano M, Bianco M, Donati M, Parenti G, D'Amico A, Ciana G, Di Rocco M, Reuser A, Bembi B, Filocamo M. Molecular and functional characterization of eight novel GAA mutations in Italian infants with Pompe disease. Hum Mutat 2008;29:E27-36.
3. Grossi S, Regis S, Rosano C, Corsolini F, Uziel G, Sessa M, Di Rocco M, Parenti G, Deodato F, Lezzi V, Biancheri R, and Filocamo M. Molecular Analysis of ARSA and PSAP Genes in Twenty-one Italian Patients with Metachromatic Leukodystrophy. Identification and Functional Characterization of 11 Novel ARSA Alleles. Hum Mutat 2008;29:E220-230.

4. Tappino B, Chuzhanova NA, Regis S, Dardis A, Corsolini F, Stroppiano M, Tonoli E, Beccari T, Rosano C, Mucha J, Blanco M, Szlago M, Di Rocco M, Cooper DN, Filocamo M. Molecular characterization of 22 novel UDP-N-acetylglucosamine-1-phosphate transferase alpha- and beta-subunit (GNPTAB) gene mutations causing mucolipidosis types IIalpha/beta and IIIalpha/beta in 46 patients. Hum Mutat 2009;30:E956-73.

5. Lualdi S, Tappino B, Di Duca M, Dardis A, Anderson CJ, Biassoni R, Thompson PW, Corsolini F, Di Rocco M, Bembi B, Regis S, Cooper DN, Filocamo M, Enigmatic in vivo iduronate-2-sulfatase (IDS) mutant transcript correction to wild-type in Hunter syndrome. Hum Mutat 2010;31:E1261-85

6. Tappino B, Biancheri R, Mort M, Regis S, Corsolini F, Rossi A, Stroppiano M, Lualdi S, Fiumara A, Bembi B, Di Rocco M, Cooper DN, Filocamo M. Identification and characterization of 15 novel GALC gene mutations causing Krabbe disease. Hum Mutat 2010;31:E1894-914

7. 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;305:903-12.

8. 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.

9. 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:e41516.

10. Gali M, Filocamo M, Horowitz M. Itch Regulates Degradation of Mutant Glucocerebrosidase: Implications to Gaucher Disease. Hum Mol Genet. 2012 Dec 18. [Epub ahead of print]

PATHOLOGIC ANATOMY

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Activity year 2012

- Study of spontaneous abortion disease in the first trimester. Correlation between histomorphological aspects and chromosomal anomalies determined with FISH and cytofluorimetry;
- Study of an Italian case series derived from the NB registry of neuroblastomas at onset in adolescents and adults with biomolecular characterization;
- Study of an Italian case series derived from the NB registry of congenital neuroblastomas: morphological and biomolecular aspects;
- Study of atypical Spitz tumors;
- 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 aspirates, peripheral blood, and apheretic collections;
- Clinical-pathological immunohistochemical study and molecular characterization of mixed/myo-epitheliomas, bone juxtacortical;
- Study of glucide metabolism during pregnancy: screening, diagnosis, etiopathogenesis, maternal and fetal follow-up; newborn management;
- Study in oncologic and metabolic diseases of telomeres and telomerase activity.

Research programme for 2013

- Study of spontaneous abortion disease in the first trimester. Correlation between histomorphological aspects and chromosomal anomalies determined with FISH and cytofluorimetry;
- Study of an Italian case series derived from the NB registry of neuroblastomas at onset in adolescents and adults with biomolecular characterization;
- Study of an Italian case series derived from the NB registry of congenital neuroblastomas: morphological and biomolecular aspects;
- Study of atypical Spitz tumors; biomolecular characteristics and immunohistochemical aspects: national case series derived from the registry of rare pediatric tumors;
- 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 aspirates, peripheral blood, and apheretic collections;
- Study of glucide metabolism during pregnancy: screening, diagnosis, etiopatogenesis, maternal and fetal follow-up; newborn management;

- Study of IUGR;
- Study of the histological correlation between biopsies at onset and histological aspects of delayed surgery of peripheral neuroblastic tumors according to Unresectable Protocol (2001 - 2006).

Main collaborations

- SIOPEN-R-NET (European Society of Paediatric Oncology Neuroblastoma Research Network). Creation of a network for telematic sharing of main diagnostic aspects of cases characterized by higher complexity, rarity and/or therapeutic and scientific impact among participating centres:
- Univ. Clinic of Pathology, Wahringer Gurtel 18-20, A-1090 Vienna, Dott. Gabriele Amann. Dept. of Pathology Rikshospitalet, Sognsvannsveien 20, N-0027 Oslo, Dott. Klaus Beiske Histopathology Pathology Dept. St. James's University Hospital, Beckett Street UK, Leeds LS9 7TF, Dott. Catherine Culinane
- Departamento de patologìa, Facultad de medicina, Avda Blasco Ibanez 17, E-46010 Valencia, Dott. Samuel Navarro
- Service de Pathologie, Hopital Robert Debré, EA3102 Université Paris 7, 48 Boulevard
- Sérurier F – 75019 Paris, Prof. Michel Peuchmaur
- University of Padova and Anatomic Pathology Institute: soft tissue tumors and rare childhood tumors. Laboratory of Oncology: biological-molecular study of rhabdomyosarcoma and Ewing/PNET tumors
- Anatomic Pathology unit of Pini Orthopedic Institute of Milano: bone tumors
- King's College, University of London: liver disease.
- St. John's Hospital, University of London: skin disease.
- National Cancer Institute of Milan: pediatric renal tumors
- Anatomic Pathology, Dept. Experimental Medicine, Rome, Prof. F. Giangaspero: Oncologic neuropathology.
- Istitut fur Neuropathologie Sigmund-Freud-Strabe Bonn, Deutschland, Prof. T. Pietsch: Neuropathology.
- Childrens Hospital of Los Angeles, Dept. of Pathology, Prof. Hiro Shimada, Coordinator of INPC (International Neuroblastoma Pathology Committee).

Major publications (2007- 2012)

1. Garrè ML, Cama A, Bagnasco F, Morana G, Giangaspero F, Brisigotti M, Gambini, C, Forni M, Rossi A, Haupt R, Nozza P, Barra S, Piatelli G, Viglizzo G, Capra V, Bruno W, Pastorino L, Massimino M, Tumolo M, Fidani P, Dallorso S, Schumacher RF, Milanaccio C, Pietsch T. Medulloblastoma variants: age-dependent occurrence and relation to Gorlin syndrome--a new clinical perspective. Clin Cancer Res. 2009 Apr 1;15(7):2463-71.
2. Pezzolo A, Rossi E, Gimelli S, Parodi F, Negri F, Conte M, Pistorio A, Sementa A, Pistoia V, Zuffardi O, Gambini C. Presence of 1q gain and absence of 7p gain are new predictors of local or metastatic relapse in localized resectable neuroblastoma. Neuro Oncol. 2009 Apr;11(2):192-200. Epub 2008 Oct 15.
3. Alaggio R, Cecchetto G, Bisogno G, Gambini C, Calabrò ML, Inserra A, Boldrini R, Salvo GL, G d'Amore ES, Dall'igna P. Inflammatory myofibroblastic tumors in childhood: a report from the Italian Cooperative Group studies. Cancer. 2009 Oct 22.
4. Passoni L, Longo L, Collini P, Coluccia AM, Bozzi F, Podda M, Gregorio A, Gambini C, Garaventa A, Pistoia V, Del Grosso F, Tonini GP, Cheng M, Gambacorti-Passerini C, Anichini A, Fossati-Bellani F, Di Nicola M, Luksch R. Mutation-independent anaplastic lymphoma kinase overexpression in poor prognosis neuroblastoma patients. Cancer Res. 2009 Sep 15;69(18):7338-46.

5. Haupt R, Garaventa A, Gambini C, Parodi S, Cangemi G, casale F, Viscardi E, Bianchi M, Prete A, Jenkner A, Luksch R, Di Catlado A, Favre C, D'Angelo P, Zanazzo GA, Arcamone G, Izzi GC, Gigliotti AR, Pastore G, De Bernardi B. Improved survival of childhood neuroblastoma between 1979 and 2005: a report of the Italian Neuroblastoma Regristry. Journal of Clincial Oncology 2009.

6. Maria Valeria Corrias, Claudio Gambini, Andrea Gregorio, Michela Croce, Gaia Barisione, Claudia Cossu, Armando Rossello, Silvano Ferrini and Marina Fabbi. Different subcellular localization of ALCAM molecules in neuroblastoma: Association with relapse. Cellular Oncology 32 (2010) 77–86 77 DOI 10.3233/CLO-2009-0494 IOS Press.

7. Riccardo Haupt, Alberto Garaventa, Claudio Gambini, Stefano Parodi, Giuliana Cangemi, Fiorina Casale, Elisabetta Viscardi, Maurizio Bianchi, Arcangelo Prete, Alessandro Jenkner, Roberto Luksch, Andrea Di Cataldo, Claudio Favre, Paolo D'Angelo, Giulio Andrea Zanazzo, Giampaolo Arcamone, Gian Carlo Izzi, Anna Rita Gigliotti, Guido Pastore, and Bruno De Bernard. Improved Survival of Children With Neuroblastoma Between 1979 and 2005: A Report of the Italian Neuroblastoma Registry. Journal of clinical oncology.

8. Francesca Schena, Claudio Gambini, Andrea Gregorio, Manuela Mosconi, Daniele Reverberi, Marco Gattorno, Simona Casazza, Antonio Uccelli, Lorenzo Moretta, Alberto Martini and Elisabetta Traggia –Derived Interferon-_–Dependent Inhibition of B Cell Activation by Bone Marrow Mesenchymal Stem Cells in a Murine Model of Systemic Lupus Erythematosus. Arthritis & Rheumatism Vol. 62, No. 9, September 2010, pp 2776–2786. DOI 10.1002/art.27560 © 2010, American College of Rheumatology.

9. Peripheral neuroblastic tumors with genotype-phenotype discordance: A report from the Children's Oncology Group and the international neuroblastoma pathology committee. 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 ES, Gambini C, Jarzembowski JA, Joshi VV, Navarro S, Peuchmaur M, Shimada H., Pediatr Blood Cancer. 2012 Jun 28. doi: 10.1002/pbc.24238.

10. Pediatric adrenocortical tumors: morphological diagnostic criteria and immunohistochemical expression of matrix metalloproteinase type 2 and human leucocyte-associated antigen (HLA) class II antigens. Results from the Italian Pediatric Rare Tumor (TREP) Study project. Magro G, Esposito G, Cecchetto G, Dall'Igna P, Marcato R, Gambini C, Boldrini R, Collini P, D'Onofrio V, Salfi N, d'Amore E, Ferrari A, Bisogno G, Alaggio R., Hum Pathol. 2012 Jan;43(1):31-9. Epub 2011 Aug 4.

RADIOLOGY

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Activity year 2012

Research projects

New imaging techniques for evaluation of children with chronic rheumatic disease: MR in JIA

MR in juvenile idiopathic arthritis makes it possible to evaluate directly the inflammatory process and bone and cartilage joint damage. For the study of joint cartilages, we further implemented the sequences for T2 mapping and T1 mapping (dGEMRIC), which allow an in vivo quantitative analysis of collagen/proteoglycans, with the demonstration of early macromolecular alterations (i.e. without morphologic counterpart). In addition, we demonstrated that synovial CE can be quantified both by semiquantitative evaluation (synovitis scoring system) and calculation of synovial volume, and that it can be used for disease monitoring.

Whole body MR in rheumatic disease

Thanks to the simultaneous visualization of all body districs, Whole Body MR is a diagnostic instrument in systemic inflammatory disease and, in particular, in JDM follow-up, and the data obtained showed a good correlation between disease activity and muscular signal alteration, as well as new aspects related to the distribution of muscular involvement, not predictable on the basis of clinical/laboratory evaluation alone

Uro-MR with even functional evaluation of kidneys in nephrourologic disease

URO-MR with functional analysis is a non irradiating technique for renal morpho-functional evaluation that represents a diagnostic tool alternative to dynamic renal scintigraphy in the study of urologic disease. A multicentre comparative study fMRU-DRS is being conducted in collaboration with the group of the University of Rouen, directed by Prof. Dacher. About 150 FMRU examinations were performed in our institute; among them, we selected about 30 tests performed in our institute and 30 performed by the French group, all including functional evaluation (analyzed in postprocessing with MRU dedicated software version 5.0 of ImageJ), and we compared them with sequential dynamic scientigraphy. The results obtained, still beign processed, seems to show a good quantitative correlation between data of fRMU and DRS, this latter still considered as the gold standard.

Research programme for 2013

Research projects

New imaging techniques for the evaluation of children with chronic rheumatic disease (continuation)
Objective: validation of MR as gold standard for monitoring of JIA and JDM disease.
Description: comparison of imaging with clinical and laboratory data and with the gold standards presently recognized in patients with JIA and JDM for quantitative evaluation of osteocartilaginous damage in JIA and muscular damage in JDM.

Uro-MR with even functional evaluation of kidneys in nephrourologic disease (continuation)
Objective: validation of f-MRU (functional MR) as an alternative to SDS (Sequential Dynamic Scintigraphy).
Description: Multicentre comparative study between fMRI and SDS data in nephrourologic patients.

Prospective study on the role of DW-MRI in newborns and children with febrile UTI
Objective: identification of focuses of pyelonephritis in newborns and children with febrile UTI and their follow-up in comparison with DMSA static scintigraphy.
Description: all patients admitted to our hospital for febrile UTI will undergo, after previous informed consent, kidney echo color doppler examination and sequence DW-MR of kidneys within 48 hours from diagnosis, without sedation and with "feed and wrap" technique. The patients with suspected pyelonephritis focus at DWI-MR will undergo DWI-MR at 6 months. All the patients will also undergo static scintigraphy at 6 months, according to the protocol.
Comparative analysis of DW-MR and DMSA scintigraphy will be performed.

Main collaborations:

- 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
- Prof. Andrew Taylor (UCL, Professor in Cardiovascular Imaging), Cardiac-MRI unit of Great Ormond Street Hospital (GOSH) , London
- 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

Major publications (2007-2012)

1. 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 Maria Beatrice Damasio & Clara Malattia & Laura Tanturri de Horatio & Chiara Mattiuz & Angela Pistorio & Claudia Bracaglia & Domenico Barbuti & Peter Boavida. Pediatr Radiol (2012) 42:1047–1055.
2. Multi-detector CT in the paediatric urinary tract. Damasio MB, Darge K, Riccabona M. Eur J Radiol. 2012 Jul 2. [Epub ahead of print] PubMed PMID: 22762970.
3. 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 Michael Riccabona & Fred Efraim Avni & Maria Beatrice Damasio & Lil-Sofie Ording-Müller & Johan G.

Blickman & Kassa Darge & Maria Luisa Lobo & Frederica Papadopoulou & Pierre-Hugues Vivier & Ullrich Willi. Pediatr Radiol (2012) 42:1275–1283.

4. MRI assessment of bone marrow in children with juvenile idiopathic arthritis: intra- and inter-observer variabilità. Laura Tanturri de Horatio & Maria Beatrice Damasio & Domenico Barbuti & Claudia Bracaglia & Karen Lambot-Juhan & Peter Boavida & Lil-Sofie Ording Müller & Clara Malattia & Lucilla Ravà & Karen Rosendahl & Paolo Tomà Pediatr Radiol (2012) 42:714–720.
5. Development and preliminary validation of a paediatric-targeted MRI scoring system for the assessment of disease activity and damage in juvenile idiopathic arthritis. Clara Malattia, Maria Beatrice Damasio, Angela Pistorio, Maka Ioseliani, Iris Vilca, Maura Valle, Nicolino Ruperto, Stefania Viola, Antonella Buoncompagni, Gian Michele Magnano, Angelo Ravelli, Paolo Tomà, Alberto Martini. Ann Rheum Dis (2011);70:440–446.
6. Guidelines for Imaging and Staging of Neuroblastic Tumors: Consensus Report from the International Neuroblastoma Risk Group Project. Hervé J. Brisse, M. Beth McCarville, Claudio Granata, K. Barbara Krug. Radiology. (2011) Oct;261(1):243-57. Epub 2011 May 17.
7. The paediatric wrist revisited: redefining MR findings in healthy children. Lil-Sofi Ording Müller, D Avenarius, B Damasio, O P Eldevik, C Malattia, Ann Rheum Dis (2011);70:605–610.
8. Synovial and inflammatory diseases in childhood: role of new imaging modalities in the assessment of patients with juvenile idiopathic arthritis. Maria Beatrice Damasio & Clara Malattia. Pediatr Radiol (2010) 40:985–998.
9. Computerized tomography in pediatric oncology. Granata C, Magnano G. Eur J Radiol. (2011) Dec 29. [Epub ahead of print].
10. Ultrasound findings in dual kidney transplantation. Valutazione eco-color Doppler nel doppio trapianto di rene M.B. Damasio1 • G. Cittadini2 • D. Rolla3 • F. Massarino3 • N. Stagnaro1 • M. Gherzi3 • E. Paoletti3L.E. Derchi2. Radiol med DOI 10.1007/s11547-012-0791-9 Received: 31 May 2011 / Accepted: 14 July 2011.

NEURORADIOLOGY

Director: Dr. Andrea Rossi

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Activity year 2012

Research project

Validation of Magnetic Resonance as adjuvant method in the prenatal diagnosis of CNS disease

In 2012, 40 patients underwent fetal MR at 20 to 34 weeks of gestational age; 7 cases were followed up at 3-4 weeks for a total of 47 examinations. Main indications included ventriculomegaly and search for congenital malformations. In addition to traditional T2-dependent Ssh/TSE sequences, in 42 cases experimental sequences were performed, including: 42 diffusions (DWI), 2 tractographies (DTI), 8 dynamic studies of fetal movement (Dyn), and 7 spectroscopies (MRS). The examinations could be interpreted in all cases with the exception of tractographies, and provided additional information or confirmation of echographic data.

DWI study was validated and inserted in the protocol for the evaluation of the development of the cortical mantle at early phases (29-25 weeks) and for the recognition of disruptive lesions (ischemia/hemorrhagia) at late phases (26-35 weeks).

Research programme for 2013

Research project

Advanced MRI in pediatric brain tumors

Objective:

- Evaluation of pediatric brain tumors through the acquisition of an integrated group of morphofunctional data, obtained by non-invasive advanced MR (diffusion, tractography, perfusion, spectroscopy, fMRI).
- Translation of data into neurosurgical and neurooncologic management and evaluation of their overall diagnostic impact as well as the influence on therapeutic decisions.

Description:

All pediatric patients admitted to the Istituto Giannina Gaslini for brain tumors and treated with surgery and/or chemo-radiotherapeutic protocols will be eligible for inclusion in the study.

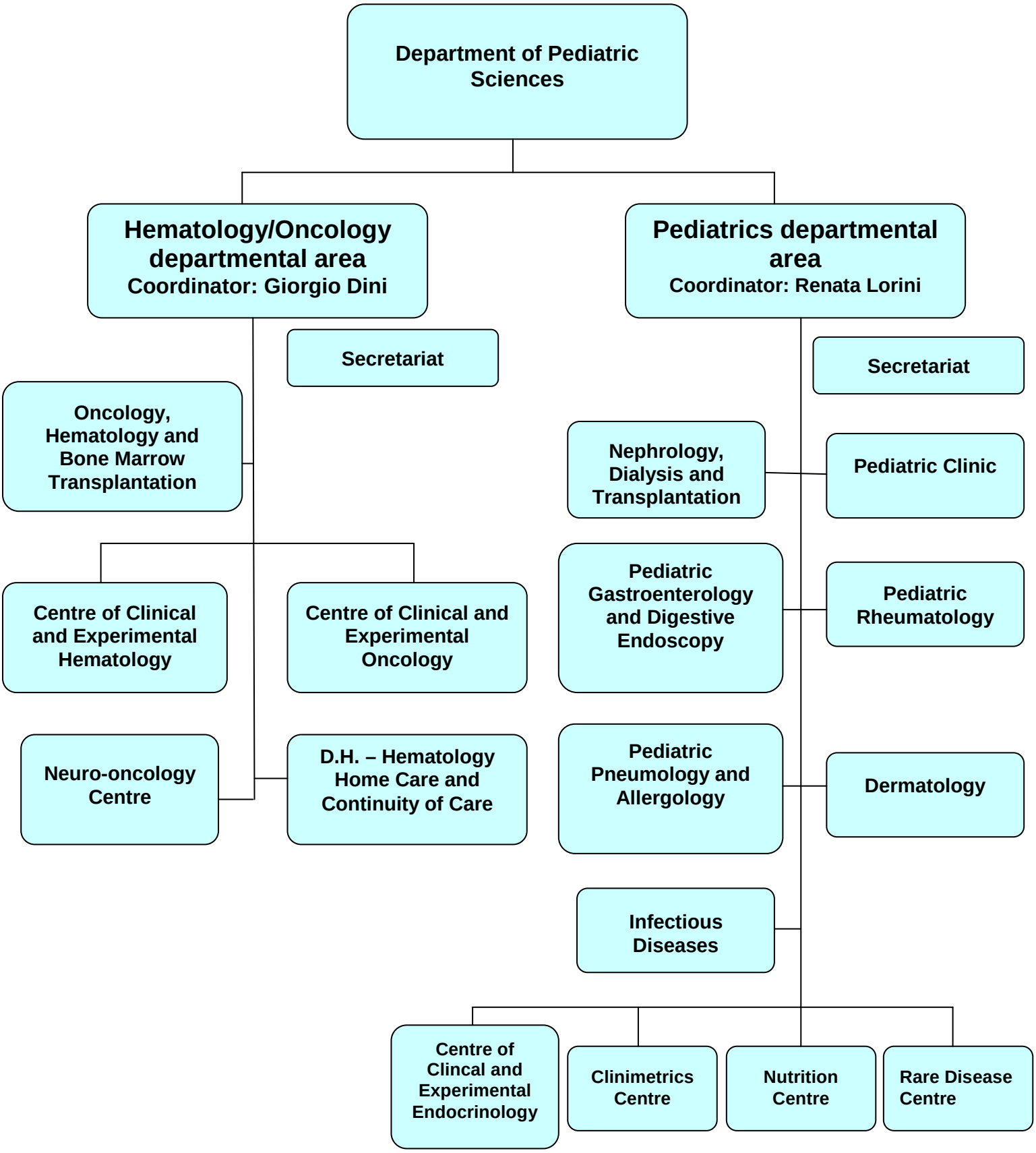
The patients will undergo MR examination with advanced sequences in diffusion, diffusion tensor/DTI, perfusion, and spectroscopy; according to clinical indication, collaborating patients will undergo fMRI for cortical activation. The data will be evaluated in the light of histopathological and surgical results to define their contribution to presurgical diagnosis, surgical planning, and monitoring during adjuvant therapy.

Main collaborations:

- DINOGMI University of Genova (Dr. Bonzano, Dr. Roccatagliata): bioengineering reprocessing of fMRI and DTI
- Starting Grant project, funded by the European Research Council, entitled "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, Mendel Institute, Roma)
- Children's Hospital of Philadelphia Department of Neuroradiology (Prof. R.A. Zimmerman): training in advanced neuroradiology

Major publications (2007-2012)

1. 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. 2012 Nov 19. [Epub ahead of print]
2. 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 Jun 21. [Epub ahead of print]
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. Cassandrini D, Biancheri R, Tessa A, Di Rocco M, Di Capua M, Bruno C, Denora PS, Sartori S, Rossi A, Nozza P, Emma F, Mezzano P, Politi MR, Laverda AM, Zara F, Pavone L, Simonati A, Leuzzi V, Santorelli FM, Bertini E. Pontocerebellar hypoplasia: Clinical, pathologic, and genetic studies. Neurology. 2010 Oct 19;75(16):1459-64.
6. Rossi A, Gandolfo C, Morana G, Severino M, Garrè ML, Cama A. New MR sequences (diffusion, perfusion, spectroscopy) in brain tumours. Pediatr Radiol. 2010 Jun;40(6):999-1009.
7. Severino M, Schwartz ES, Thurnher MM, Rydland J, Nikas I, Rossi A. Congenital tumors of the central nervous system. Neuroradiology. 2010 Jun;52(6):531-48.
8. De Grandis E, Di Rocco M, Pessagno A, Veneselli E, Rossi A. MR Imaging Findings in 2 Cases of Late Infantile GM1 Gangliosidosis. AJNR Am J Neuroradiol. 2009 Aug;30(7):1325-7.
9. Garrè ML, Cama A, Bagnasco F, Morana G, Giangaspero F, Brisigotti M, Gambini C, Forni M, Rossi A, Haupt R, Nozza P, Barra S, Piatelli G, Viglizzo G, Capra V, Bruno W, Pastorino L, Massimino M, Tumolo M, Fidani P, Dallorso S, Schumacher RF, Milanaccio C, Pietsch T. Medulloblastoma Variants: Age-Dependent Occurrence and Relation to Gorlin Syndrome-A New Clinical Perspective. Clin Cancer Res. 2009 Apr 1;15(7):2463-71.
10. Rossi A, Biancheri R, Zara F, Bruno C, Uziel G, van der Knaap MS, Minetti C, Tortori-Donati P. Hypomyelination and Congenital Cataract: Neuroimaging Features of a Novel Inherited White Matter Disorder. AJNR Am J Neuroradiol. 2008 Feb;29(2):301-5.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Pediatric Pneumology and Allergology
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Activity year 2012

Oncology, Hematology and HSCT: off-therapy project: management of medium- and long-term sequelae induced by treatment, monitoring for second tumor, in collaboration with the other units

Hematology: bone marrow failure: study of mechanisms underlying bone marrow damage; leukemias: study of genetic-metabolic factors favouring the development of disease and of negative prognostic factors

Hemostasis and Thrombosis: Characterization of antiphospholipid antibodies in pediatric age; identification and prevention of venous thrombotic risk; non invasive prenatal diagnosis; epidemiologic study of genetic and acquired risk factors related to thromboembolic diseases

Neuro-Oncology: study of malignant tumors in patients aged < 3 years; intracranial germ cell tumors and brain rhabdoid tumors.

Oncology: Neuroblastoma: prognostic factors and innovative therapeutic modalities; phase I and II studies on new antiblastic drugs in pediatrics

HSCT: prospective study on the incidence and evolution of hepatic venocclusive disease after HSCT: role of prophylaxis with defibrotide; phase II prospective study on the treatment of graft-versus-host disease (GVHD) refractory to cortisone treatment

Day Hospital and Home Care: evaluation of the possibility to create a new system of reimbursement of costs of delivered home care services.

Research programme for 2013

Research project

Continuation of the projects described above
Objectives:
Implementation of guidelines for the prevention of late effects in patients treated with chemotherapy;

Identification of new prognostic factors in severe aplasia, neuroblastoma, CNS tumors;
Prevention of venous thrombotic risk;
Improvement of GvHD treatment

Description:

Study of the incidence of side effects and statistical analysis of risk factors.
In collaboration with the Anatomic Pathology unit, the Laboratory of Molecular Biology and the Laboratory of Experimental Oncology of the Istituto Gaslini and the Italian centres of pediatric oncology, we will evaluate the prognostic weight of gene signatures and circulating disease in neuroblastoma.
Phase I-II studies in collaboration with Italian and European centres.
Study of genetic-metabolic markers favouring disease development and negative prognostic factors.

Main Italian collaborations

- Italian Association of Pediatric Hematology and Oncology (AIEOP)
- Chair of Medical Genetics, Clinics of the Insubria University
- Hemophilia and Thrombosis Centre, Ospedale Maggiore, Milano.
- Hemophilia Centre, Castelfranco Veneto Hospital
- University Thrombosis Centre USMI, Genova.
- Dept. Of Pediatric Hematology and Oncology Pausilipon – Napoli.
- Dept. of Pediatrics, DIMES, DOBIG, USMI, Genova.
- Dept. of Orthopedic Surgery, Careggi Hospital, Firenze.
- Laboratory Neuroblastoma Foundation USMI, Genova.
- Tissue Laboratory and Italian Registry Bone Marrow Donors (IBMDR)
- Dept. of Urology, Galliera Hospital, Genova
- Radiotherapy unit USMI, Genova.
- Laboratory of Physiopathology of orthopedic implants, Rizzoli Orthopedic Institute, Bologna.
- Laboratory of Genetics, S. Giovanni Rotondo (FG).
- Laboratory of Cell Differentiation, USMI, Genova.
- Cytogenetics and Genetics unit, Careggi Hospital, Firenze
- Thyroid Surgery unit, Galliera Hospital, Genova
- Nuclear Medicine unit, Galliera Hospital, Genova
- Pediatric Radiotherapy unit USMI, Genova.

Main international collaborations

- European Commission, Contract QLRT-2001-01768, SIOPEN-R-NET
- Department of Haematology Hospital's Center of Science and Innovation, Aalborg, Denmark.
- Pediatric Oncology Branch, National Cancer Institute NIH, Bethesda, Maryland
- European Group for Bone Marrow Transplantation (EBMT)
- Société Internationale D'Oncologie Pediatrique (S.I.O.P.): CNS Sub-Committee
- Euroepan Cooperative Group on Neuroblastoma (E.S.I.O.P.- NB)
- Kinderklinik University di Dusseldorf
- Neuropathology Department University of Oregon Cancer Center, Portland, Oregon (USA). Professor Grover Bagby
- Dept Pediatric Hematology and Oncology Fundeni Children's Hospital, Bucarest, Romania
- Dept Haematology Hospital's Center Science and Innovation. Aalborg, Denmark,
- Raissa Gorbaciova Foundation

Major publications (2007-2012)

1. Dini G, Zecca M, Balduzzi A, Messina C, Masetti R, Fagioli F, Biral E, Associazione Italiana Ematologia ed Oncologia Pediatrica–Hematopoietic Stem Cell Transplantation (AIEOP-HSCT)

Group. No difference in outcome between children and adolescents transplanted for acute lymphoblastic leukemia in second remission. Blood. 2011 Dec 15;118(25):6683-90

2. Corbacioglu S, Cesaro S, Faraci M, Valteau-Couanet D, Gruhn B, Rovelli A, Dini G. Defibrotide for prophylaxis of hepatic veno-occlusive desease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomized controlled trial. LANCET 2012; 379: 1301-1309.
3. Dufour C. in Appendix for the EBMT, Severe Aplastic Anaemia Working Party Rabbit ATG for aplastic anaemia treatment: a backward step? Lancet. 2011 Nov 26;378(9806):1831-3.
4. Marsh JC, Bacigalupo A, Schrezenmeier H, Tichelli A, Risitano AM, Passweg JR, Dufour C, et all 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
5. Puga I, Cols M, Barra CM, HE B, Cassis L, Gentile M, Calvillo M, Dufour C, et al B cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. NATURE IMMUNOLOGY 2012; 13(2): 170-180.
6. Rubie H, De Bernardi B, Gerrard M, Canete A, Ladenstein R, Couturier J, Garaventa A, et al 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;29(4):449-55.
7. P, Yates J, Garbati MR, Vanderwerf S, Keble W, Rathbun K, Hays LE, Cappelli E, Dufour C, Bagby GC. p38 MAPK inhibition suppresses the TLR-hypersensitive phenotype in FANCC- and FANCA-deficient mononuclear phagocytes. BLOOD 2012; 119(9): 1992-2002.
8. Mussolin L, Pillon M, d'Amore ESG, Conter V, Piglione M, Lo Nigro L, Garaventa A, et al. Minimal disseminated disease in high-risk Burkitt's lymphoma identifies patients with different prognosisJ CLIN ONCOL 2011;29(13):1779-84.
9. Taggart DR, London WB, Schmidt ML, Du Bois SG0, Monclair TF, Nakagawara A, De Bernardi B et al. Prognostic value of the stage 4S metastatic pattern and tumor biology in patients with metastatic neuroblastoma diagnosed between birth and 18 months af age. J CLIN ONCOL 2011;29(33):4358-64
10. Ladenstein R, Potschger, Siabalis D, Garaventa A, Bergeron C, Lewis IJ, et al. Dose finding study tor the use of subcutanous recombinant interleukin-2 to augment natural killer cell numbers in an outpatient setting for stage 4 neuroblastoma after megatherapt and autologous stem-cell reinfusion. J CLIN ONCOL 2011;29(4):441-8.

CLINICAL AND EXPERIMENTAL HEMATOLOGY

Staff

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Activity year 2012

1. Genotype-phenotype analysis (cellular, somatic and hematologic) of 90 Italian patients with Fanconi's anemia (data from the national database in our unit) (completed)
2. Analysis of immunological phenotype of 25 Italian patients with Fanconi's anemia (completed)
3. Molecular analysis of 5 Italian patients with congenital dyskeratosis (completed)
4. Molecular analysis of 5 Italian patients with genetic neutropenia (data from the Italian Registry of Neutropenias in our unit (completed)
5. Analysis of clinical infectious profile of 73 neutropenic patients (data from the Italian Registry of Neutropenias at our unit) (completed)
6. Analysis of the infectious profile of Italian aplastic patients (completed)
7. Clinical-hematological-immunological database of patients with immunologic cytopenias (started)
8. Analysis of pharmacologic inhibition of P38MAPK in bone marrow hematopoietic cells of subjects with Fanconi's anemia (implemented).

Overall, these activities have improved significantly the efficiency and quality of the diagnosis of rare diseases with indirect beneficial effect of treatment.
These activities were implemented with the contributìons of the Ministry of Health 2008 and of Pfizer and ERG.

Research programme for 2013

Research project

Epidemiology, advanced diagnostics and therapeutic impact of bone marrow failure in children.

Objectives:

1. to optimize survery and molecular diagnostics of genetic and non-genetic bone marrow failure diseases through the implementation of already existing disease registries at our unit and of new registries (congenital dyskeratosis registry). Screening of newborns with hematological malformations and/or anomalies in collaboration with ICU/NICU and the Neonatal Pathology unit of the Istituto G.Gaslini.
2. to define some cell mechanisms leading to functional exhaustion of Fanconi's anemia hematopoietic cells

Description: The activity will be based on already activated pathways and collaborations. This wide programme will need all the personnel already recruited in this unit.

Main collaborations

- Oregon Health & Science University, Professor Grover Bagby, Portland, Oregon USA.
- Cincinnati Children's Hospital. Dr Stella Davies, Dr Parinda Metha, Cinvcinnati, OH. USA.
- Severe Aplastic Anemia Working Party EBMT (European Society for Blood and Marrow Transplant)
- Granulocyte and Monocyte Scientific Working Group, EHA (European Haematology Association)
- AIEOP Centres (Associazione Italiana Emato-Oncologia Pediatrica).
- Istituto Giannina Gaslini: ICU/NICU, Neonatal Pathology.

Major publications (2007-2012)

1. Infectious Complications in Children with Severe Congenital, Autoimmune or Idiopathic Neutropenia: A Retrospective Study from the Italian Neutropenia Registry.Fioredda F, Cavillo 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. Pediatr Infect Dis J. 2012 Dec 17.

2. Etanercept treatment in Fanconi anaemia; combined US and Italian experience.Mehta PA, Svahn J, Davies SM, Pang Q, Harris R, Ghezzi P, Lanza T, Ferretti E, Barabino P, Mueller R, Dufour C.Br J Haematol. 2012 Sep;158(6):809-11.

3. Bone marrow versus peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups. Bacigalupo A, Socié G, Schrezenmeier H, Tichelli A, Locasciulli A, Fuehrer M, Risitano AM, Dufour C, Passweg JR, Oneto R, Aljurf M, Flynn C, Mialou V, Hamladji RM, Marsh JC; Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT).Haematologica. 2012 Aug;97(8):1142-8.

4. Prospective study of rabbit antithymocyte globulin and cyclosporine for aplastic anemia from the EBMT Severe Aplastic Anaemia Working Party.Marsh JC, Bacigalupo A, Schrezenmeier H, Tichelli A, Risitano AM, Passweg JR, Killick SB, Warren AJ, Foukaneli T, Aljurf M, Al-Zahrani HA, 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. Blood. 2012 Jun 7;119(23):5391-6.

5. p38 MAPK inhibition suppresses the TLR-hypersensitive phenotype in FANCC- and FANCA-deficient mononuclear phagocytes. Anur P, Yates J, Garbati MR, Vanderwerf S, Keeble W, Rathbun K, Hays LE, Tyner JW, Svahn J, Cappelli E, Dufour C, Bagby GC.Blood. 2012 Mar 1;119(9):1992-2002

6. Epidemiology of infections in children with acquired aplastic anaemia: a retrospective multicenter study in Italy. Quarello P, Saracco P, Giacchino M, Caselli D, Caviglia I, Longoni D, Varotto S, Rana I, Amendola A, Misuraca A, Licciardello M, Paolucci P, Ladogana S, Rivetti E, Dufour C, Castagnola E. Eur J Haematol. 2012 Jun;88(6):526-34.

7. Rabbit ATG for aplastic anaemia treatment: a backward step?European Blood and Marrow Transplant Group, Severe Aplastic Anaemia Working Party. Lancet. 2011 Nov 26;378(9806):1831-3. Review.

8. B cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen.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. Nat Immunol. 2011 Dec. 5;13(2):170-80

9. Fertility recovery and pregnancy after allogeneic hematopoietic stem cell transplantation in Fanconi anemia patients. Nabhan SK, Bitencourt MA, Duval M, Abecasis M, Dufour C, Boudjedir K, Rocha V, Socié G, Passweg J, Goi K, Sanders J, Snowden J, Yabe H, Pasquini R, Gluckman E; Aplastic Anaemia Working Party, EBMT. Haematologica. 2010 Oct;95(10):1783-7.

10. Changes in cytokine profile pre- and post-immunosuppression in acquired aplastic anemia. Dufour C, Ferretti E, Bagnasco F, Burlando O, Lanciotti M, Ramenghi U, Saracco P, Van Lint MT, Longoni D, Torelli GF, Pillon M, Locasciulli A, Misuraca A, La Spina M, Bacigalupo A, Pistoia V, Corcione A, Svahn J; Marrow Failure Study Group of the AIEOP.Haematologica. 2009 Dec;94(12):1743-7.

NEPHROLOGY, DIALYSIS AND TRANSPLANTATION
LABORATORY OF PHYSIOPATHOLOGY OF UREMIA

Director: Dr. Gian Marco Ghiggeri

Staff

Roberta Bertelli Armando Di Donato

Activity year 2012

We studied different cell populations potentially involved in the activation and regulation of mechanisms determining the onset of idiopathic nephrotic syndrome (iNS). On monocytes isolated from the peripheral blood of iNS patients, we evaluated the membrane expression of the Urokinase Plasminogen Activator (uPAR) receptor. The study was carried out also on normal controls and on patients with other renal diseases with different etiology in order to verify the specificity of this marker as iNS causative agent and to correlate its expression with disease severity, in particular with response to drugs and remission of proteinuria. We investigated the presence of the receptor in soluble form (sUPAR) in the serum of patients and we examined the possible mechanisms determining its release and remote action. We studied the role of regulatory T lymphocytes (Tregs) in patients with iNS and the possible induction of these cells in response to different therapeutic protocols. Tregs contribution is still being investigated, in terms of the potential ability of these cells to modulate iNS course, through the use of transgenic mice. In these animal models, the disease was induced by inoculation of LPS which presumably activates oxidative burst and therefore the actual responsibility of this mechanism was studied in parallel on a defective animal strain for expression of P2X7, i.e. the main receptor activated by ATP, which is known to trigger the inflammatory process. This animal model also allows an easy visualization of the presence of Tregs in peripheral blood and in the main lymphoid organs, and therefore their activation after various “in vivo” treatments. Experiments aimed at in vitro preactivation of autologous Tregs previously isolated through cell sorting are ongoing, aimed at potentiating their activity and ability to regulate “in vivo” in the animal model iNS pathogenetic mechanisms.

Research programme for 2013

Research project:

Cells involved in oxidative stress during the course of idiopathic Nephrotic Syndrome (iNS): their characterization and regulation

Objective: Identification of the main mechanisms responsible for iNS pathogenesis and cellular and/or soluble factors able to modulate their activity

Description: We will continue the study already started last year on the role of UPAR receptor and, in particular, we will study the correlation with its expression on the cell membrane and the presence in soluble form (sUPAR) in order to better understand the different activities of the two molecules as related to iNS progression. In vitro studies will be performed to highlight factors determining the release of the receptor from the cell surface as potential pathogenetic regulators. In the animal model, the role of P2X7 receptor will be studied in depth, in particular the possible involvement of oxidative burst during iNS, as well as regulatory T cells (Tregs) as main mediators of innate immunity, in order to evaluate their possible therapeutic use.

Main collaborations

- Dr. Fabio Grassi, Istituto di Ricerca Biomedica (IRB), Bellinzona (CH)
- Dr. Maria Pia Rastaldi, Ca' Granda Foundation, Osp. Maggiore Policlinico, Milano
- Dr. Emanuela Ognio, Animal Facility, San Martino hospital– IST, Genova
- Dr. Genny Del Zotto, Lab. Core Facilities, Istituto G.Gaslini, Genova

Major publications (2007-2012)

1. Bertelli R, et al Clin Exp Immunol. 2011 Oct;166(1):55-63
2. Bertelli R, et al Clin Exp Immunol. 2010 Jul 1;161(1):151-8
3. Magnasco A, Corselli M, Bertelli R, et al Cell Transplant. 2008;17(10-11):1157-67

PEDIATRIC CLINIC

Director: Prof. Renata Lorini

Staff

Concetta Aloi	Caridi Gianluca	Giuseppe D'Annunzio
Nicola Minuto	Alessandro Salina	

Activity year 2012

Research projects

Differential diagnosis of forms of diabetes mellitus not associated with autoimmune process

In the laboratory of diabetology of the Pediatric Clinic, in 2012 we performed molecular analysis by direct sequencing of genomic DNA of 67 subjects with occasional hyperglycemia, diabetes mellitus (DM) or glycosuria in the absence of antibodies against the beta cell, DM1 marker, autoimmune. Differential diagnosis on the basis of clinical and metabolic data included MODY (*GCK, HNF1a, HNF1b*), Wolfram 1 e Wolfram 2 syndromes (*WFS1, ZCD2*), neonatal diabetes (*GCK*, *KCNJ11*), and familial renal glycosuria (*SLC5A2*). Of the 67 requests of genetic analysis, 36 were from the Istituto Gaslini and 31 from other institutions. *GCK* gene analysis, performed in 37 subjects (17 from Gaslini), showed mutations in 16 patients. *HNF1a* gene analysis, performed in 7 subjects (6 from Gaslini), showed mutations in 2 patients. *HNF1b* gene sequencing performed in 5 subjects (4 from Gaslini) did not document any mutations. *KCNJ11* gene analysis performed in a patient with neonatal diabetes and in 1st and 2nd degree relatives showed mutations in the proband and in the mother. This allowed suspension of insulin therapy and replacement with sulphanyl-urea. *SLC5A2* gene analysis performed in 2 patients with glycosuria in the absence of hyperglycemia and in their relatives (4 subjects from Gaslini) showed a variant in the 2 siblings and in the father. *WFS1* gene analysis performed in 5 subjects from other institutions showed a mutation to homozygosis in 1 patient and mutations to heterozygosis in 3 parents. *ZCD2* gene analysis performed in 1 patient with Wolfram syndrome and peptic disease and in his relatives showed deletion in homozygosis in the proband and in heterozygosis in the relatives.

AIFA FARM8MR2J7

Validation of questionnaires by Varni et al on quality of life in Italian language according to MAPI Research Institute guidelines (Lyon, France) (http://www.mapiinstitute.com/; http://www.pedsql.org/translations.html) and statistical analysis of results were performed.

Research programme for 2013

Research projects

Differential diagnostics in the forms of diabetes mellitus not associated with autoimmune process

Objective: Extended knowledge of the etiopathogenesis of the various forms of non autoimmune diabetes mellitus from newborns to young adults

Secondary objectives: 1) identification of the most appropriate therapeutic choice on the basis of genetic data (e.g. sulphanyl-urea in neonatal diabetes); 2) extension of the range of known mutations 3) definition of genotype/phenotype relationship.

Description: The case series with the studied diseases will be increased, extending genetic analysis to patient relatives. In addition, the essential diagnostic criteria for the execution of the most specific genetic analysis will be established with higher accuracy. Another aspect concerns genotype/phenotype correlation, in families with specific gene variants associated with non frequent diseases.

AIFA FARM8MR2J7
Objective: Use of BIASP 70/30 premixed insulin in children and adolescents with diabetes mellitus type 1 aged between 6 and 18 years to obtain improved metabolic control and quality of life (QoL).

Main collaborations

- Nephrology and Laboratory of Uremia Physiopathology, Istituto Gaslini
- Ophthalmology unit, Istituto Gaslini
- Child Neuropsychiatry unit , Istituto Gaslini
- Laboratory of Molecular Genetics and Service of Cytogenetics, Istituto Gaslini
- Clinical Pharmacology service, Istituto Gaslini
- Epidemiology and Biostatistics unit, Istituto Gaslini
- Pneumology unit, Istituto Gaslini

Major publications (2007-2012)

1. 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
2. Ramondetti F, Sacco S, Comelli M, Bruno G, Falorni A, Iannilli A, d'Annunzio G, Iafusco D, Songini M, Toni S, Cherubini V, Carle F, RIDI Study Group. Type 1 diabetes and measles, mumps and rubella childhood infections within the Italian Insulin-dependent Diabetes Registry. Diabet Med 2012;9:9761-9766
3. Minuto N, Emmanuele V, Vannati M, Russo C, Rebora C, Panarello S, Pistorio A, Lorini R, d'Annunzio G. Retinopathy screening in patients with Type 1 diabetes diagnosed in young age using a Nonmydriatic Digital Stereoscopic Retinal Imaging. J Endocrinol Invest 2012; 35:389-394
4. 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;66:1612-1613
5. Bruno G, Maule M, Merletti F, Novelli G, Falorni A, Iannilli A, Iughetti L, Altobelli E, d'Annunzio G, Piffer S, Pozzilli P, Iafusco D, Songini M, Roncarolo F, Toni S, Carle F, Cherubini V; RIDI Study Group. Age-Period-Cohort Analysis of 1990-2003 Incidence Time Trends of Childhood Diabetes In Italy: The Ridi Study. Diabetes 2010;59:2281-2287
6. Lorini R, Klersy C, d'Annunzio G, Massa O, Minuto N, Iafusco D, Bellannè-Chantelot C, Frongia AP, Toni S, Meschi F, Cerutti F, Barbetti F; Italian Society of Pediatric Endocrinology and Diabetology (ISPED) Study Group. Maturity-onset diabetes of the young in children with incidental hyperglycemia: a multicenter Italian study of 172 families. Diabetes Care 2009;32:1864-1866
7. Marciano R, d'Annunzio G, Minuto N, Pasquali L, Santamaria A, Di Duca M, Ravazzolo R, Lorini R. Association of alleles at polymorphic sites in the Osteopontin encoding gene in young type 1 diabetic patients. Clin Immunol 2009;131:84-91
8. D'Annunzio G, Giannattasio A, Poggi E, Castellano E, Calvi A, Pistorio A, Barabino A, Lorini R. β-cell autoimmunity in pediatric celiac: the case for routine screening? Diabetes Care 2008;32:254-256
9. D'Annunzio G, Minuto N, D'Amato E, de Toni T, Lombardo F, Pasquali L, Lorini R. Wolfram syndrome (diabetes insipidus, diabetes, optic atrophy, and deafness): clinical and genetic study. Diabetes Care 2008;31:1743-1745
10. Orilieri E, Cappellano G, Clementi R, Cometa A, Ferretti M, Cerutti E, Cadario F, Martinetti M, Larizza D, Calcaterra V, D'Annunzio G, Lorini R, Cerutti F, Bruno G, Chiocchetti A, Dianzani U. Variations of the perforin gene in patients with type 1 diabetes. Diabetes 2008;57:1078-1083

METABOLIC DISEASES - LABSIEM

Staff

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Activity year 2012

Research projects

Development and validation of 2nd tier test applied to extended metabolic neonatal screening
2nd tier tests performed on the same screening bloodspot cards are able to assay analytes not detectable by 1st tests whose presence is strongly suggestive of a specific metabolic disease. This allows screening of positives at the first test, reducing recall threshold and especially guaranteeing the identification of all affected subjects and also reducing the number of recalled patients, with a reduced psychological impact on the families.

Kuvan Adult Maternal Paediatric European Registry-Kamper
Some forms of phenylketonuria can be responsive to BH4 cofactor of phenylalanine hydroxylase enzyme. Sapropterin (Kuvan) is the synthetic version of BH4 existing in nature. Primary objective of the study involving 9 European countries is the evaluation of long-term safety in treated subjects trying to obtain further information on growth indicators in subjects with phenylketonuria treated with the drug, on the degree of adherence to treatment, and on diet and long-term sensitivity to sapropterin therapy.

Psychometric validation of questionnaires assessing the impact of phenylketonuria on patients' and parents' quality of life.PKU-QOL
Diet therapy is the most important treatment of phenylketonuria. However, due to type of food used and, in particular, of phenylalanine-free aminoacid mixtures, it is often difficult to follow, especially in adolescents and adults.
Objective of the study was to evaluate the impact of phenylketonuria and the effects of treatment on the quality of life.

Research programme for 2013

Research projects

Kuvan Adult Maternal Paediatric European Registry-Kamper (continuation)

Extended neonatal screening: proposal of a national operational model to reduce disparities in the access to health care services in the different regions
Objective: Definition of a national strategy for the development and application of the extended national screening as a system of secondary prevention of proved efficacy, in agreement with European lines (including Health Technology Assessment) and in collaboration with the Ministry of Health, regions, AGENAS, and national scientific associations.
Description:
- Study of the organization of existing screening systems (from sampling to treatment of cases) aimed at the development of an informative tool for sharing of experiences and consequent improvement of current practices
- Definition of selection criteria of diseases to be submitted to screening and listing of a series of diseases to be included, according to priority, in the screening programme. Recommended analytical methods, quality management and control systems, periodic reporting of results, and evaluation of screening programmes.

- Criteria for optimization of sample flows according to different organizational needs and regional contexts, i.e. laboratory management costs, training of staff, easy and fair access to services, and participation in networks of centres with expertise in the specific diseases.
- Shared criteria for possible use of collateral information obtained through the screening that are not of interest for neonatal health but that can be used for genetic *counselling* to the patient's family.

Neonatal screening for ADA SCID defect
Objective: evaluation of the feasibility of the inclusion of ADA SCID defect in the panel of diseases submitted to extended neonatal screening. Severe combined immunodeficiencies (SCID) represent a very heterogeneous group of diseases that severely affect the immune system.
Description: The analytical method by tandem mass spectrometry on blood spots from newborns presently undergoing screening will be developed, with evaluation and interpretation of identified parameters. In addition, we will participate in a national project in this field.

Assay of serum acylcarnitine
Objective: evaluation of the inclusion of this assay among specific diagnostic tests for diagnostic confirmation of hereditary metabolic diseases
Description: using tandem mass spectrometry, we will develop the analytical method and identify age-related cut-offs in patients with known diagnosis of metabolic disease

Main collaborations

- Region4 Genetics collaborative MS-MS data project (Mayo Clinic, BGL Lab, Rochester, MN,USA) for sharing at international level of data related to extended neonatal screening programmes
- Istituto Superiore di Sanità: Congenital hypothyroidism registry
- Rare Disease Centre (Rome) for the development and application of guidelines and the diffusion of extended neonatal screening programmes at national level.
- Division of Medical Genetics,University of Utah, USA for the study and identification of patients with carnitine transport deficit

Major publications (2007-2012)

1. Homocysteine, reactive oxygen species and nitric oxide in type 2 diabetes mellitus. Signorello MG, Viviani GL, Armani U, Cerone R, Minniti G, Piana A, Leoncini G. Thromb Res 120(4):607-613, 2007.
2. Effect of carnitine supplementation on lipid profile and anemia in children on chronic dialysis. Verrina E, Caruso U, Calevo MG, Emma F, Sorino P, De Palo T, Lavoratti G, Turrini Dertenois L, Cassanello M, Cerone R, Perfumo F,: Italian Registry of Pediatric Chronic Dialysis. Pediatr Nephrol. 22(5):727-33, 2007.
3. Spectrum of MMA/HC mutations in Italian and Portuguese patients with combined methylmalonic aciduria and homocystinuria, cblC type. Nogueira C, Aiello C, Cerone R, Martins E, Caruso U, Moroni I, Rizzo C, Diogo L, Leao E,Kok F, Deodato F, Schiaffino MC, Bonzi S, Danhaive O, Barbot C, Sequeira S, Locatelli M, Santarelli FM, Uziel G, Vilarinho L, Dionisi-Vici C. Mol Genet Metab 93(4):475-80, 2008.
4. Phenotypic variability, neurological outcome and genetics background of 6-pyruvoyl-tetrahydropterin synthase deficiency. Leuzzi V, Carducci C, Carducci C, Pozzessere S, Burlina A, Cerone R, Concolino D, Donati MA, Fiori L, Meli C, Ponzone A, Porta F, Strisciuglio P, Antonozzi I, Blau N. Clin Genet. 2010 Jan 3.
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9. Enhanced interpretation of newborn screening results without analyte cutoff values. Marquardt G, Currier R, McHugh DM, Gavrilov D, Magera MJ, Matern D, Oglesbee D, Raymond K, Rinaldo P, Smith EH, Tortorelli S, Turgeon CT, Lorey F, Wilcken B, Wiley V, Greed LC, Lewis B, Boemer F, Schoos R, Marie S, Vincent MF, Sica YC, Domingos MT, Al-Thihli K, Sinclair G, Al-Dirbashi OY, Chakraborty P, Dymerski M, Porter C, Manning A, Seashore MR, Quesada J, Reuben A, Chrastina P, Hornik P, Atef Mandour I, Atty Sharaf SA, Bodamer O, Dy B, Torres J, Zori R, Cheillan D, Vianey-Saban C, Ludvigson D, Stembridge A, Bonham J, Downing M, Dotsikas Y, Loukas YL, Papakonstantinou V, Zacharioudakis GS, Baráth Á, Karg E, Franzson L, Jonsson JJ, Breen NN, Lesko BG, Berberich SL, Turner K, Ruoppolo M, Scolamiero E, Antonozzi I, Carducci C, Caruso U, Cassanello M, la Marca G, Pasquini E, Di Gangi IM et al Genet Med. 2012 Jul;14(7):648-55.

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PEDIATRIC GASTROENTEROLOGY AND DIGESTIVE ENDOSCOPY

Director: Dr. Arrigo Barabino

Staff

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Lia Giovannini

Activity year 2012

Research project

Retrospective clinical study on severe attacks of ulcerative colitis in the child
We retrospectively analyzed the clinical records of all children who, from May 1997 to March 2012, had a severe attack of ulcerative colitis, defined according to an international clinical score, refractory to first line treatment with i.v. steroid and therefore receiving rescue therapy with i.v. or oral cyclosporine. Objective of the study was to evaluate efficacy and safety of the drug, in order to avoid urgency or long-term colectomy. The study has been concluded and was presented in abstract form at the last national meeting of SIGENP. 42 children with 43 severe attacks were identified. Among them, in 27% of cases, treatment was ineffective and urgency colectomy was required after mean 6 days. In 73%, clinical recovery occurred in mean 6 days, with no need for surgery. Long-term course in this group of patients was the following: 32% underwent early colectomy (on average, within 1 year from the severe attack) while 68% maintain the colon at mean 3.5 years (range 2.8-9.8). Eight patients presented side effects (18%) whose severity required suspension of treatment in 5 cases (11%). Statistical analysis to search for outcome predictivity factors is still lacking.
The scope of the study is topical in pediatric gastroenterology since 1) it has been included in recent guidelines of international scientific associations; 2) cyclosporine use is in contrast with the use of biological Infliximab; 3) at present, only about 90 cases of children treated with this drug have been published. For these reasons, we decided to delay the publication of the study, pooling our case series with that of the **Gastroenterology Dept. of Meyer Hospital of Firenze** (prof Paolo Lionetti) including about 20 cases treated in the same way, thus increasing the clinical importance of the study itself. The collaboration was started about one month ago and will be concluded in about 2-3 months.

Research programme for 2013

Research project

Urine neopterins as markers of interstinal inflammation in pediatric IBD
Objective: To evaluate the predictive values of intestinal inflammation of urine neopterins in children with Crohn's disease and ulcerative colitis at onset and during follow-up.
Description: Urine neopterins, known markers of macrophage activation and therefore of ongoing inflammatory process, will be assayed in the laboratory of Prof Fuchs (expert biochemist) of Innsbruck and in all studied patients with the following parameters: clinical disease scores, inflammation biohumoral indices, fecal calprotectin, endoscopic and histological pictures. A protocol is being developed and the study is expected to produce a non-invasive diagnostic tool predicting the conditions of the intestinal mucosa and, as a consequence, to make it possible to improve theray in these children.

Main collaborations
- Meyer Children's Hospital -Firenze (prof Lionetti)
- Bambino Gesù Hospital -Roma (Dr Dall'Oglio)
- La Sapienza University -Roma (prof Cucchiara)
- Division of Biological Chemistry, Biocenter Innsbruck Medical University Austria (Prof Fuchs)

Major publications (2007-2012)

1. Tubular Esophageal Duplication In A Boy: Further Evidence of A Possible Endoscopic Treatment. Barabino A, Nardi F, Arrigo S, Gandullia P, Vignola S, Muraca M, Montobbio G, Pini-Prato A. J Pediatr Gastroenterol Nutr. 2012 Aug 7. [Epub ahead of print] No abstract available.
2. A validated HPLC method for the monitoring of thiopurine metabolites in whole blood in paediatric patients with inflammatory bowel disease. Cangemi G, Barabino A, Barco S, Parodi A, Arrigo S, Melioli G. Int J Immunopathol Pharmacol. 2012 Apr-Jun;25(2):435-44.
3. Strictureplasty and intestinal resection: different options in complicated pediatric-onset Crohn disease. 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. J Pediatr Surg. 2012 May;47(5):944-8.
4. Duodenal web: complications and failure of endoscopic treatment. Barabino A, Arrigo S, Gandullia P, Vignola S. Gastrointest Endosc. 2012 May;75(5):1123-4. No abstract available
5. Technical considerations in children undergoing laparoscopic ileal-J-pouch anorectal anastomosis for ulcerative colitis. Mattioli G, Guida E, Pini-Prato A, Avanzini S, Rossi V, Barabino A, Coran AG, Jasonni V. Pediatr Surg Int. 2012 Apr;28(4):351-6. doi: 10.1007/s00383-011-3030-1. Epub 2011 Nov 30
6. Complications of percutaneous endoscopic gastrostomy in children: results of an Italian multicenter observational study. Fascetti-Leon F, Gamba P, Dall'Oglio L, Pane A, dé Angelis GL, Bizzarri B, Fava G, Maestri L, Cheli M, Di Nardo G, La Riccia A, Marrello S, Gandullia P, Romano C, D'Antiga L, Betalli P. Dig Liver Dis. 2012 Aug;44(8):655-9. Epub 2012 Apr 25.
7. Long-term home parenteral nutrition in children with chronic intestinal failure: A 15-year experience at a single Italian centre. Gandullia P, Lugani F, Costabello L, Arrigo S, Calvi A, Castellano E, Vignola S, Pistorio A, Barabino AV. Dig Liver Dis. 2011 Jan;43(1):28-33. Epub 2010 May 31
8. Sudden blindness in a child with Crohn's disease. Barabino AV, Gandullia P, Calvi A, Vignola S, Arrigo S, Marco RD. World J Gastroenterol. 2011 Oct 14;17(38):4344-6.
9. Successful endoscopic treatment of a double duodenal web in an infant. Barabino A, Gandullia P, Arrigo S, Vignola S, Mattioli G, Grattarola C. Gastrointest Endosc. 2011 Feb;73(2):401-3. Epub 2010 Sep 24. No abstract availab
10. Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. Pironi L, Joly F, Forbes A, Colomb V, Lyszkowska M, Baxter J, Gabe S, Hébuterne X, Gambarara M, Gottrand F, Cuerda C, Thul P, Messing B, Goulet O, Staun M, Van Gossum A; Home Artificial Nutrition & Chronic Intestinal Failure Working Group of the European Society for Clinical Nutrition and Metabolism (ESPEN). Gut. 2011 Jan;60(1):17-25. Epub 2010 Nov 10.

PEDIATRIC RHEUMATOLOGY

Director: Prof. Alberto Martini

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Paolo Picco
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Research projects

Prof. Angelo Ravelli

Concluded research projects

1. Definition of disease state considered acceptable by the parent and by the patient with juvenile idiopathic arthritis
2. Survey of opinion of international pediatric rheumatologists for the identification of the most useful diagnostic parameters for the detection of macrophage activation syndrome
3. Development of cut-offs of Juvenile Arthritis Disease Activity Score (JADAS) that identify disease activity states in juvenile idiopathic arthritis.
4. Identification of factors associated with the achievement of remission in children with juvenile idiopathic arthritis treated with etanercept (study supported by Wyeth-Pfizer).
5. Evaluation of the efficacy of methotrexate in the prevention of the onset of uveitis in children with juvenile idiopathic arthritis.

New or ongoing projects

Multinational study on the epidemiology, treatment and long-term evolution of juvenile idiopathic arthritis

Objective: To make a survey of the frequency of the different clinical subtypes of juvenile idiopathic arthritis, of the present disease evolution, and of the most common therapeutic choices in international centres of pediatric rheumatology.

Description: The study was based on a multidimensional questionnaire, that is being translated into 38 languages, to be filled in by the parent and child, and on the evaluation of disease state by the physician in a sample of 100 consecutive patients with juvenile idiopathic arthritis followed at each participating centre. To date, pediatric rheumatology centres of 55 countries have decided to participate in the study.

Development of new diagnostic criteria of macrophage activation syndrome in juvenile idiopathic arthritis

Objective: To develop new diagnostic criteria of the macrophage activation syndrome through the combination of the analysis of data from real patients with expert consensus procedures .

Description: The study is based on the collection of data related to the main clinical, laboratory and histopathological parameters of children with macrophage activation syndrome and of 2 control groups observed in international pediatric rheumatology centres. The new diagnostic criteria will be developed through statistical analysis of collected data and the organization of an international consensus conference of experts in this field.

Comparative therapeutic study on the efficacy of intra-articular injections of steroids with or without methotrexate in juvenile idiopathic arthritis (study supported by AIFA)

Objective: To evaluate whether the association with methotrexate increases the duration and efficacy of intra-articular injections of steroids in children with juvenile idiopathic arthritis

Description: Children enrolled in clinical trials are randomized in 2 groups: one group dooes not receive any therapy and the other group starts treatment with methotrexate. In both cases, the study duration is 1 year. Primary outcome of the study is maintenance of the remission state of arthritis at the end of follow-up.

Development of new clinical measures for the evaluation of the disease state in children with juvenile dermatomyositis
Objectives: To develop a multidimensional questionnaire for recording of perception of the disease state by parent and patient, and new easier indices for evaluation by the physician of muscular strength and of global disease activity.
Description: The multidimensional questionnaire and the new measures of muscular strength and of global disease activity will be validated following the procedures of the OMERACT filter, including the detailed analysis of a wide range of metrologic properties such as user-friendliness, correlation with other consolidated measures, reliability of evaluations by different examiners, and ability to identify changes over time.

Evaluation of clinical evolution in children with juvenile idiopathic arthritis treated with etanercept (project funded by Pfizer)
Objective: To evaluate the percentage of Italian children with juvenile idiopathic arthritis and treated with the biological drug etanercept in Italian pediatric rheumatology centres who achieved clinical remission, the state of minimal disease activity or a disease condition acceptable for parent and child.
Description: The study is observational, multicentre, non randomized, retrospective, and cross-sectional. Patients receiving etanercept for at least 6 months will undergo a cross-sectional clinical evaluation and a retrospective analysis of clinical data will be performed, while patients in whom the drug was suspended will undergo only a retrospective analysis.

Main collaborations

- Histiocyte Society: development of new diagnostic criteria of macrophage activation syndrome
- Childhood Arthritis & ***Rheumatology*** Research Alliance (CARRA): study of future clinical applications of Juvenile Arthritis Disease Activity Score (JADAS)

Major publications

1. Filocamo G, Consolaro A, Schiappapietra B, Ruperto N, Pistorio A, Solari N, Pederzoli S, Verazza S, Martini A, Ravelli A. Parent and child acceptable symptom state in juvenile idiopathic arthritis. J Rheumatol. 2012 Apr;39(4):856-63.
2. Ravelli A, Grom AA, Behrens EM, Cron RQ. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. Genes Immun. 2012 Jun;13(4):289-98.
3. Consolaro A, Bracciolini G, Ruperto N, Pistorio A, Magni-Manzoni S, Malattia C, Pederzoli S, Davì S, Martini A, Ravelli A; Paediatric Rheumatology International Trials Organization. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score. Arthritis Rheum. 2012 Jul;64(7):2366-74.
4. Consolaro A, Ruperto N, Filocamo G, Lanni S, Bracciolini G, Garrone M, Scala S, Villa L, Silvestri G, Tani D, Zolesi A, Martini A, Ravelli A. Seeking insights into the EPidemiology, treatment and Outcome of Childhood Arthritis through a multinational collaborative effort: Introduction of the EPOCA study. Pediatr Rheumatol Online J. 2012 Nov 20;10(1):39. [Epub ahead of print]
5. 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. 2012 Dec 1. [Epub ahead of print]

Dr. Nicolino Ruperto

New or ongoing projects

Pharmacovigilance in juvenile idiopathic arthritis patients (pharmachild) treated with biologic agents and/or methotrexate (EU-funded within FP7, project 260353)
Objectives: to evaluate the long-term efficacy and tolerability of biological agents and medications used for the treatment of juvenile idiopathic arthritis
Description: It is an international registry managed by the Paediatric Rheumatology International Trials Organisation (PRINTO) at the Istituto G. Gaslini of Genova collecting data on the efficacy and tolerability of biological agents and medications used for the treatment of juvenile idiopathic arthritis.

Anti-Biopharmaceutical Immunization: Prediction and analysis of clinical relevance to minimize the risk (ABIRISK). (EU-funded, Innovative Medicine Initiative)
Objectives: to evaluate the immungenicity of new biopharmaceutical products for the treatment of Hemophilia A, multiple sclerosis, inflammatory diseases, and to develop standardized laboratory tests for the evalulation of the appearance of anti-drug antibodies and of neutralizing antibodies for each biopharmaceutical product.
Description: As project partner, the Paediatric Rheumatology International Trials Organisation (PRINTO), at the l'Istituto G. Gaslini of Genova, will collect biological samples and clinical information on children with juvenile idiopathic arthritis treated with infliximab and adalimumab. After test standardization for the evaluation of the appearance of anti-drug antibodies and of neutralizing antibodies, these will be tested also in the pediatric population.

Five-year single-blind, phase III effectiveness randomised actively controlled clinical trial in new onset juvenile dermatomyositis: prednisone versus prednisone plus cyclosporine and versus prednisone plus methotrexate (funded by AIFA FARM52EBT5)
Objectives: Evaluation of the efficacy and tolerability of 3 different therapeutic protocols for the treatment of children with juvenile dermatomyositis at onset: prednisone versus prednisone plus cyclosporine and versus prednisone plus methotrexate.
Description: It is a phase III study for off-patent drugs managed by Paediatric Rheumatology International Trials Organisation (PRINTO) at the Istituto G. Gaslini of Genova. Patient enrolment has been concluded (138 randomized patients) and analysis is ongoing

Single HUB and Access Point for Paediatric Rheumatology in Europe (SHARE) (EU-funded, project 201112 02)
Objectives: to improve the quality of care of children with pediatric rheumatic diseases
Description: The Paediatric Rheumatology International Trials Organisation (PRINTO) at the Istituto G. Gaslini of Genova, as project partner, will improve a website for families of children with pediatric rheumatic diseases containing information in over 50 languages on what pediatric rheumatic diseases are, which are the specific care centres and associations for helping familiies (www.pediatric-rheumatology.printo.it)

An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis (funded by Bristol-Myers Squibb)
Objective: to evaluate the long-term efficacy and tolerability of the biological drug abatacept for the treatment of juvenile idiopathic arthritis
Description: It is an international registry managed by the Paediatric Rheumatology International Trials Organisation (PRINTO) at the Istituto G. Gaslini of Genova that will collect data on the efficacy and tolerability of abatacept for the treatment of juvenile idiopatic arthritis

A Multicenter, Double Blind, Randomized-Withdrawal Trial of Subcutaneous Golimumab, a Human Anti-TNFa Antibody, in Pediatric Subjects with Active Polyarticular Juvenile Idiopathic Arthritis (JIA) Despite Methotrexate Therapy (funded by Centocor)
Objective: to evaluate the efficacy and tolerability of the biological drug golimumab for the treatment of juvenile idiopathic arthritis

Description: It is an international phase II study in which the Paediatric Rheumatology International Trials Organisation (PRINTO) at the Istituto G. Gaslini of Genova is evaluating response to golimumab for the treatment of juvenile idiopathic arthritis

An open-label extension study of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and active systemic manifestations (funded by Novartis)
Objectives: to evaluate the efficacy and tolerability of the biological drug canakinumab for the treatment of systemic juvenile idiopathic arthritis
Description: It is an international phase III study in which the Paediatric Rheumatology International Trials Organisation (PRINTO) at the Istituto G. Gaslini of Genova is evaluating response to canakinumab for the treatment of systemic juvenile idiopathic arthritis

A 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study to evaluate the efficacy and safety of tocilizumab in patients with active systemic juvenile idiopathic arthritis (sJIA); with a 92-week single arm open-label extension to examine the long term use of tocilizumab (funded by Roche)
Objectives: to evaluate the efficacy and tolerability of the biological drug tocilizumab for the treatment of systemic juvenile idiopathic arthritis
Description: It is an international phase III study in which the Paediatric Rheumatology International Trials Organisation (PRINTO) at the Istituto G. Gaslini of Genova is evaluating response to tocilizumab for the treatment of systemic juvenile idiopathic arthritis

A 24 week randomized double-blind, placebo controlled withdrawal trial with a 16 week open label lead-in phase, and 64 week open label follow-up, to evaluate the efficacy and safety of tocilizumab in patients with active polyarticular-course juvenile idiopathic arthritis (funded by Roche)
Objectives: to evaluate the efficacy and tolerability of the biological drug tocilizumab for the treatment of polyarticular course systemic juvenile idiopathic arthritis
Description: It is an international phase III study in which the Paediatric Rheumatology International Trials Organisation (PRINTO) at the Istituto G. Gaslini of Genova is evaluating response to tocilizumab for the treatment of polyarticular course juvenile idiopathic arthritis

Collaborations

Dr. Nicolino Ruperto, MPH is Senior Scientist of the Pediatric Rheumatology International Trials Organisation (PRINTO). Prof. Alberto Martini is Chairman. PRINTO is a no profit research network gathering about 60 countries all over the worlds with over 400 pediatric rheumatology centres.

Publications

1. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, Cuttica R, Ravelli A, Schneider R, Woo P, Wouters C, Xavier R, Zemel L, Baildam E, Burgos-Vargas R, Dolezalova P, Garay SM, Merino R, Joos R, Grom A, Wulffraat N, Zuber Z, Zulian F, Lovell DJ, Martini A, for the Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG). Randomized Trial of Tocilizumab in Systemic Juvenile Idiopathic Arthritis. N Engl J Med 2012;367:2385-2395.
2. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, Brik R, McCann L, Kasapcopur O, Rutkowska-Sak L, Schneider R, Berkun Y, Calvo I, Erguven M, Goffin L, Hofer M, Kallinich T, Oliveira SK, Uziel Y, Viola S, Nistala K, Wouters C, Cimaz R, Ferrandiz MA, Flato B, Gamir ML, Kone-Paut I, Grom A, Magnusson B, Ozen S, Sztajnbok F, Lheritier K, Abrams K, Kim D, Martini A, Lovell DJ for the Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG). Canakinumab in systemic juvenile idiopathic arthritis: 2 randomized trials. N Engl J Med 2012;367:2396-2406.

Dr. Clara Malattia

Concluded or ongoing projects

MR study of the main pathological data detectable in juvenile idiopathic arthritis (JIA) has been concluded with the standardization of the protocol for image acquisition and with the development and preliminary validation of a semiquantitative score for the evaluation of the importance of the inflammatory process and structural damage. In parallel, an intense activity aimed at the creation of software for automated quantitative evaluation of MR is ongoing. To date, software for quantitative analysis of enhancement curves after contrast medium administration and for automated evaluation of synovial volume has been developed and validated. Software for automated reading of erosive damage progression and for functional-ultrastructural evaluation of macromolecules constituing the cartilage matrix is being validated.

Finally, a score for the evaluation of disease activity through total body MR in patients with juvenile dermatomyositis has been developed and validated.

New projects

Standardization and quantification of disease activity and progression of structural damage by joint echography in patients with juvenile idiopathic arthritis (JIA)

Objectives: 1) Achievement of a standard method for image acquisition by echography 2) Score quantification for the semiquantitative evaluation of pathological data detected by joint echography 3) Validation of semiquantitative score for the quantification of disease activity and articular damage in patients with JIA

Description: it is a 2-year prospective observational cohort study enrolling patients with JIA.. The study will include the definition of acquisition projections for each joint, the development of a semiquantitative score for the evaluation of disease activity parameters (joint effusion, thickening of synovial membrane, presence of vascular signal within the hypertrophic synovia, tendon involvement) and of joint damage (cartilage morphostructural alterations, bone erosions); validation of the above-mentioned score according to criteria established by OMERACT. Number of patients that will be enrolled according to sample size: 80.

Study of the impact of biomechanical alterations at joint level on structural damage progression in JIA

Objective: to evaluate the impact of biochemical alterations at joint level secondary to disease on joint damage progression.

Description: Prospective cohort study enrolling patients with JIA and knee and/or tibiotarsal joint involvement. Biomechanical anomalies will be detected through the integration of information from rheumatologic evaluation, physiatric evaluation (including gait analysis) and imaging evaluation (radiography, dynamic echography, MR, DXA). Information deriving from these evaluations will be integrated in a multi-scale model of the musculoskeletal system able to predict the distribution of forces acting on joint surface during movement. Longitudinal data will be collected in order to evaluate the impact of biomechanical alterations on the progression of radiological joint damage.

Collaborations

- Dept. of Informatics, University of Genova: creation of software for automated quantitative evaluation of the main pathological observations in JIA by MR and echography of joint.
- Participation in research activity of the international group OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) focused on the use of MR in the evaluation of JIA patients.

Publications:

1. Malattia C, Damasio MB, Magnaguagno F, Pistorio A, Valle M, Martinoli C, Viola S, Buoncompagni A, Loy A, Ravelli A, Tomà P, Martini A. Magnetic resonance imaging, ultrasonography, and conventional radiography in the assessment of bone erosions in juvenile idiopathic arthritis. Arthritis Rheum. 2008 Dec 15;59(12):1764-72. PubMed PMID: 19035414.

2. 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 L, Magnano G, Ravelli A, Martini A. A novel automated system for MRI quantification of the inflamed synovial membrane volume in patients with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken); 2012 Nov;64(11):1657-64 3).
3. 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 Mar;70(3):440-6.

Dr. Marco Gattorno

Concluded or ongoing projects:

The following aspects of autoinflammatory diseases were studied:

1. Evaluation of the clinical impact of MEFV genotype in familial mediterranean fever
2. Long-term follow-up of CAPS patients treated with anti-IL-1 monoclonal antibody (Canakinumab)
3. Role of TH17 in CAPS syndrome (in collaboration with the Istituto di Ricerca in Biomedicina, Bellinzona)
4. Role of autophagy in the pathogenesis of TRAPS syndrome (in collaboration with the Lab, of Molecular Genetics)
5. Study of IL-1 production mechanisms in familial mediterranean fever

New projects

Efficiency of the different diagnostic criteria for FMF in pediatric age: follow-up study
Objective: to evaluate the sensitivity and specificity of the various diagnostic criteria for FMF in a cohort of FMF patients followed prospectively
Description: 3 different diagnostic criteria will be tested (Tel-Hashomer, Livneh, Yakalinkaya) on a population of 120 pediatric patients with FMF followed prospectively in 10 different Italian centres. Clinical manifestations at diagnosis, MEFV genotype, response to treatment (colchicine), and long-term follow-up will be evaluated.

Study of genotype-phenotype relationship and pathogenetic mechanisms of PAPA syndrome
Objective: description of phenotype variability of an Italian case series with PAPA syndrome
Description: at Gaslini, 18 patients were diagnosed with PAPA syndrome, including a large family living in the north-east of Sardinia. The clinical picture will be described as related to the genotype.

Clinical impact of Q703K mutation of NLRP3 gene
Objective: description of the clinical impact of the Q703K variant of NLRP3 gene in subjects with suspected cryopyrinopathy, commonly considered as a ploymorphism with little functional impact .
Description: Over the last 10 years, we screened 480 patients sent for suspected cryopyrinopathy. 42 of these patients presented the Q703K variant. This study will evaluate: i) the prevalence of the variant in the Italian population, ii) the clinical characteristics at onset, iii) long-term follow-up and response to treatment; iv) functional study on IL-1 secretion compared to other CAPS patients

Collaborations

- Laboratory of Immunology, San Martino Hospital- IST (A Rubartelli)
- Laboratory of Molecular Genetics – Istituto Gaslini
- Institute of Immunology – Istituto Gaslini (C. Bottino)
- Institute of Biomedicine, Bellinzona (F.Sallusto, A. Lanzavecchia)

- Italian study group on autoinflammatory diseases
- Eurofever project (www.printo.it/eurofever)

Publications

1) Clinical impact of MEFV mutations in children with periodic fever in a prevalent western European Caucasian population. Federici S, Calcagno G, Finetti M, Gallizzi R, Meini A, Vitale A, Caroli F, Cattalini M, Caorsi R, Zulian F, Tommasini A, Insalaco A, Sormani MP, Baldi M, Ceccherini I, Martini A, Gattorno M. Ann Rheum Dis. 2012 May 12. [Epub ahead of print]

2) Pathogen-induced human TH17 cells produce IFN-γ or IL-10 and are regulated by IL-1β., Zielinski CE, Mele F, Aschenbrenner D, Jarrossay D, Ronchi F, Gattorno M, Monticelli S, Lanzavecchia A, Sallusto F. Nature. 2012 Apr 26;484(7395):514-8.

3) Autophagy contributes to inflammation in patients with TNFR-associated periodic syndrome (TRAPS). 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*. Ann Rheum Dis. 2012 Oct 31 (*last co-authors)

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5) Increased nlrp3-dependent interleukin (il) 1β secretion in patients with familial mediterranean fever (fmf): correlation with mefv genotype. Omenetti A, Carta S., Delfino L, Martini A, Gattorno M*, Rubartelli A*. (submitted) (*last co-authors)

Pediatric Pneumology and Allergology

Director: Prof. Giovanni A. Rossi

Staff

Cristina Baschieri	Sonia Carta	Enrica Canepa
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Donata Girosi	Pietrina Giannarelli	Annunziata Langella
Silvia Leveratto	Roberta Olcese	Serena Panigada
Giovanna Ranzoni	Stefania Riccardi	Anna Sabatino
Oliviero Sacco	Piera Sale	Lorella Santato
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Edvige Turrato	Alessandra Ugoletti	Anna Vitali

Activity year 2012

A) We evaluated the *in vitro* effect of medications able to increment [cAMP]i levels on repair processes of bronchial epithelium exposed to cigarette smoke. Using human bronchial epithelial cell lines (BEAS-2B), we demonstrated that cell preincubation with a cAMP analogue, Salmeterol or Roflumilast N-oxide (a selective inhibitor of PDE4), induced a significant increase in BEAS-2B migration towards fibronectin. A significant reduction of the distance between "wound" margins was observed. Therefore, the medications normally used in the clinical practice as bronchodilators can favour *in vivo* tissue repair processes in respiratory tract diseases with an allergic or infectious basis.

B) In order to evaluate bronchial reactivity (BHR) in children/adolescents practising competitive sports, we enrolled 30 subjects playing tennis or soccer and 32 swimmers. BHR and asthma-like symptoms were more frequently observed in swimmers alone, FEV_1 and Tiffenau index correlated with the duration of competitive activity, suggesting that this practice can mainly improve lung volume. The higher frequency of BHR in swimmers could be due to a greater irritability of airways due to exposure to chloride.

C) In order to evaluate the reliability of the Visual Analogic Scale "VAS" in the screening of pediatric asthma, we recruited 703 children [mean age 10.3 years (range 8.3–12.6)]. Analyzing the whole population, we observed that the frequency of bronchial obstruction was limited to 6.5%. Therefore, to have a balanced sample of subjects with and without bronchial obstruction, we analyzed a sample including all subjects with bronchial obstruction (N=46) and only some subjects without bronchial obstruction (N=92) (1:2 ratio). VAS correlated with FEV_1 (r=0.47) and/or $FEF_{25–75}$ (r=0.42). VAS value equal to 6 resulted a reliable cut-off to discriminate children with bronchial obstruction [sens: 80.4, spec: 69.6, AUC: 0.8 (0.8–0.9), diagnostic OR: 9.4 (4.0–22.1)].

Research programme for 2013

Research projects

Vitamin D and respiratory infections in pediatric age

Objective: to evaluate the relationship between vitamin D levels and respiratory infections in the preschool child and in particular whether low blood levels a) are associated with a higher frequency or severity of the disease, b) reflect a poor nutritional intake or sun exposure; c) are the effect of an increased turnover, further lowering in the acute infection phase and then rising during convalescence.

Description: The study will continue to recruit children with acute lower airway infection to evaluate whether a) during infection, vitamin D serum levels are low (<30 ng/ml); b) there are significant correlations between vitamin D levels and gestational age, breast feeding, repeated

hospital admissions for wheezing, life and nutritional habits; c) there are significant differences in vitamin D levels during airway infection and in the subsequent recovery phase at one month from discharge; d) vitamin D levels during respiratory infection or in the recovery phase can be different in the various months of the year.

Mycoplasma pneumoniae resistance to macrolides
Objective: Through a cross-sectional observational study and using both cultural and molecular methods, we will a) evaluate the prevalence and the clinical impact of resistance to macrolides of M. pneumoniae in children hospitalized at Gaslini; b) identify new mutations correlated with resistance to macrolides; c) identify possible risk factors for the acquisition of resistance.
Description: We will study subjects with lower airway infections diagnosed on the basis of clinical and radiological evidence. The subjects will be evaluated both during hospital stay and day hospital admission. Enrolled patients will undergo nasopharyngeal swab performed by double sampling: one sample will be sent to the Laboratory of Clinical Chemical Analysis of Gaslini for routine cultures and molecular analyses, the other sample will be sent to the Laboratory of Microbiology of San Martino hospital–CRI – University of Genova (Prof. Anna Marchese) for further microbiological and molecular investigations. Expected beneficial effects include a better identification of antibiotic resistances and, in particular, resistances to macrolides in order to develop possible personalized therapeutic strategies for patients with diseases caused by resistant strains.

Main collaborations

- Fabio LM. Ricciardolo, Respiratory Disease Clinic, University ofi Torino
- Andrew A. Colin. Division of Pediatric Pulmonology, University of Miami, FL, USA.
- Andrew Bush. Dept. of Paediatric Respirology, Royal Brompton Hospital, London, UK.
- Giorgio Ciprandi, Dept. of Internal Medicine, University of Genova.
- Franca Rusconi, Epidemiology unit, Anna Meyer Children's Hospital (Firenze).
- Angelo Barbato. Dept. of Pediatrics, University of Padova (Padova).
- Anna Marchese. Microbiology section, University of Genova

Major publications (2007-2012)

1. Rossi GA, Cerasoli F, Cazzola M. Safety of inhaled corticosteroids: Room for improvement. Pulm Pharmacol Ther. 2007; 20: 23-35.
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6. Petecchia L, Sabatini F, Usai C, Carnevali S, Ognibene M, Vanni C, Eva A, Fabbri LM, Rossi GA, Ricciardolo FL. Mechanisms of bradykinin-induced contraction in human fetal lung fibroblasts. Eur Respir J. 2010 Sep;36(3):655-64.
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10. 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: 3061-85.

DERMATOLOGY

Director: Dr. Corrado Occella

Staff

Dario Bleidl Valentina Fausti Odette Nemelka
Gianmaria Viglizzo

Activity year 2012

In 2012, we studied neurocutaneous melanosis (NCM), a rare congenital, non familial neurocutaneous syndrome characterized by melanocytic nevi and excessive proliferation of melanocytes within the CNS. In particular, we examined the pathological surgical characteristics of a lesion in the right temporal lobe of a 3-year-old child with NCM and complex partial seizures. The study of this case confirms that NCM should be listed among the possible causes of chronic drug-resistant partial epilepsy. Surgical resection should be considered for the treatment of this type of lesion.

Research programme for 2013

Research projects

Study of cytokeratin 17 gene in patients with alopecia areata
Objective: Analysis of gene polymorphisms or mutations present in the KRT17 coding gene in patients with alopecia areata and evaluation of their functional impact on KRT 17 keratin expression.
Confirmation of the hypothesis according to which keratin is the target of the immune system in the complex pathogenesis of alopecia areata.
Description: In patients admitted to our outpatient service for alopecia areata, blood will be sampled for DNA analysis and search for polymorphisms will be performed in the Laboratory of Immunology of CEBR (University of Genova, San Martino hospital-IST, Genova). Some single nucleotide polymorphisms (SNPs) localized in the 3' UTR region of KRT17 gene can react with microRNAs (miRNAs). miRNAs are a class of small non-coding regulatory molecules controlling post-transcriptional gene expression. The altered function of miRNA affects a variety of biological processes involved in the etiopathogenesis of different mendelian and complex diseases (7,8). For this reason, it is predictive to hypothesize that the aberrant expression and function of some miRNA could contribute to the development of alopecia areata.

Main collaborations

Prof. Indiveri, Laboratory of Immunology, DIMI, San Martino hospital, Genova

Major publications (2007-2012)

1. 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.
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5. Viglizzo G, Cozzani E, Nozza P, Occella C, Parodi A. A case of linear IgA disease in a child with IgA and IgG circulating antibodies directed to BPAg2. Int J Dermatol. 2007 Dec;46(12):1302-4.

INFECTIOUS DISEASES

Director: Dr. Elio Castagnola

Staff

Anna Bazzani	Maura Maria Ernesta Bellando	Lorella Boggiani
Elisabetta Bondi	Maria Buccolieri	Daniela Bruzzone
Paola Capponi	Ilaria Caviglia	Emilio Cristina
Rosella Cuneo	Donatella Finocchi	Alma Gandini
Maria Rosaria Gentile	Francesca Ginocchio (up to April 2012)	Marina Icardi
Giuseppe Losurdo	Anna Loy	Cristina Moroni
Anna Nuzzolese	Laura Angela Quattrocchi	Federica Romagna
Cinzia Rossi	Monica Sale	Paola Spallarossa
Angela Tacchella	Marina Tonietto	

Activity year 2012

Monitoring activity of the epidemiology of infections in children undergoing antineoplastic chemotherapy or HSCT has been continued: bacteriemias and invasive fungal infections. Internal protocols of personalized therapy based on type of underlying disease and different disease phases were developed. In addition, this activity allowed the participation in national and international cooperative studies evaluating this type of infections and their management and in international study groups for the preparation of guidelines on therapy of febrile neutropenia in children (J Clin Oncol. 2012 Sep 17. [Epub ahead of print]) and the management of Candida infections (Clin Microbiol Infect 2012; 18, suppl. 7: 1-77).
Data were collected on the efficacy and toxicity of treatment protocols of particular infectious diseases such as indwelling CVC-related bacteremias and invasive fungal infections. These data are presently undergoing statistical analysis.
Data on the performance of diagnostic tests for invasive fungal infections in children were collected (search for 1-3-beta-D-glucan) and will undergo statistical analysis in the short term.

Research programme for 2013

Research project

Epidemiology of bacteremias and invasive fungal infections in children undergoing antineoplastic chemotherapy or HSCT and analysis of sensitivity of isolated bacteria to antibiotics
Objective: to analyse the etiology of bacteremias and invasive fungal infections; to evaluate the proportion of bacteria resistant to commonly used antibiotics; to analyse survival of patients with bacteremia and invasive fungal infection in the light of the present diagnostic techniques and of the medications available for therapy.
Description: the collection performed over the last few years will be continued, also participating in national (AIEOP) and international (PFN, PICNICC) multicentre studies. Concerning bacterial infections, we will analyse sensitivity patterns to antibiotics of bacteria isolated in different contexts (blood cultures in oncology, urine culture in nephrology, CSF culture in surgery) in order to evaluate the sensitivity to different drugs and to identify the best prophylactic or therapeutic treatments.
Concerning invasive fungal infections, factors related to a better survival will be analysed in patients undergoing antineoplastic chemotherapy or HSCT.
A programme for the evaluation of blood levels of some drugs in particular pediatric populations (e.g. low-weight newborns) will be started.
Main collaborations

- Pediatric Fungal Network (PFN): studies on pediatric fungal infections

- European Conference of Infections in Leukemia, (ECIL): preparation of therapy recommendations
- International Pediatric Fever and Neutropenia Guideline Panel: preparation of therapy recommendations
- PICNICC (Predicting Infectious Complications of Neutropenic sepsis in Children with Cancer) Collaboration: establishment of predictive-therapeutic regulations
- Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP): studies on infections in pediatric hematology/oncology and preparation of recommendations
- Gruppo Italiano Trapianto Midollo Osseo (GITMO): studies on infections during transplantation
- Società Italiana di Infettivologia Pediatrica: clinical and epidemiologic studies

Major publications (2007-2012)

1. 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; and the 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):1252-1257
2. Bagnasco F, Haupt R, Fontana V, Valsecchi MG, Rebora P, Caviglia I, Caruso S, Castagnola E. Risk of repeated febrile episodes during chemotherapy-induced granulocytopenia in children with cancer: a prospective single center study. J Chemother. 2012 Jun;24(3):155-60.
3. Quarello P, Saracco P, Giacchino M, Caselli D, Caviglia I, Longoni D, Varotto S, Rana I, Amendola A, Misuraca A, Licciardello M, Paolucci P, Ladogana S, Rivetti E, Dufour C, Castagnola E. Epidemiology of infections in children with acquired aplastic anaemia: a retrospective multicenter study in Italy. Eur J Haematol. 2012 Jun;88(6):526-34.
4. Livadiotti S, Milano GM, Serra A, Folgori L, Jenkner A, Castagnola E, Cesaro S, Rossi MR, Barone A, Zanazzo G, Nesi F, Licciardello M, De Santis R, Ziino O, Cellini M, Porta F, Caselli D, Pontrelli G; Infectious Diseases Working Group of the Associazione Italiana Ematologia Oncologia Pediatrica. A survey on hematology-oncology pediatric AIEOP centers: prophylaxis, empirical therapy and nursing prevention procedures of infectious complications. Haematologica. 2012 Jan;97(1):147-50.
5. Castagnola E, Garrè ML, Bertoluzzo L, Pignatelli S, Pavanello M, Caviglia I, Caruso S, Bagnasco F, Moroni C, Tacchella A, Haupt R. Epidemiology of febrile neutropenia in children with central nervous system tumor: results from a single center prospective study. J Pediatr Hematol Oncol. 2011 Oct;33(7):e310-5.
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7. 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.
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Pseudomonas aeruginosa infection in children undergoing chemotherapy and hematopoietic stem cell transplantation. Haematologica. 2010 Sep;95(9):1612-5.

9. Castagnola E, Furfaro E, Caviglia I, Licciardello M, Faraci M, Fioredda F, Tomà P, Bandettini R, Machetti M, Viscoli C. Performance of the galactomannan antigen detection test in the diagnosis of invasive aspergillosis in children with cancer or undergoing haemopoietic stem cell transplantation. Clin Microbiol Infect. 2010 Aug;16(8):1197-203.

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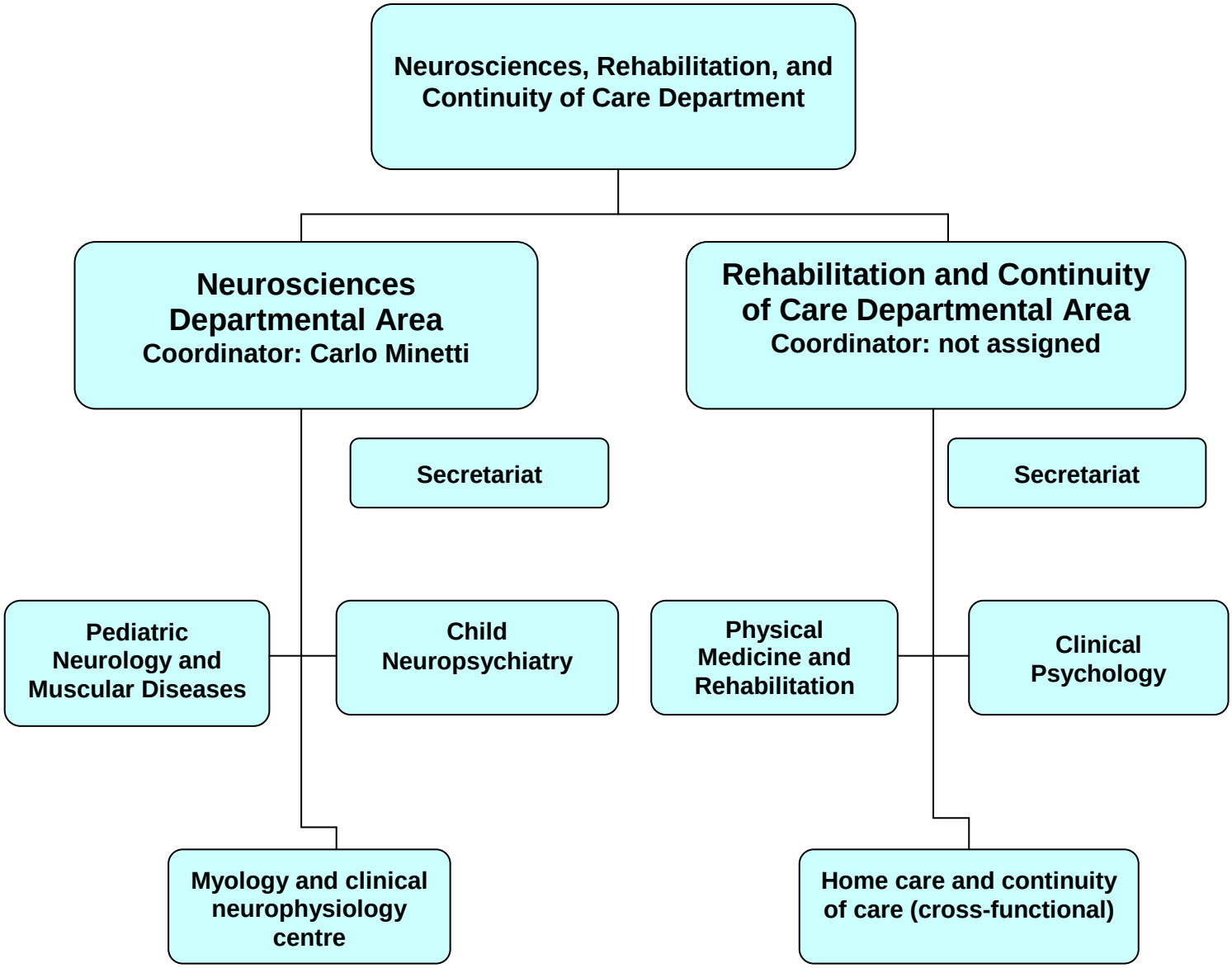
Neurosciences, Rehabilitation, and Continuity of Care Department
Neurosciences Departmental Area
Coordinator: Carlo Minetti
Rehabilitation and Continuity of Care Departmental Area
Coordinator: not assigned
Secretariat
Secretariat
Pediatric Neurology and Muscular Diseases
Child Neuropsychiatry
Physical Medicine and Rehabilitation
Clinical Psychology
Myology and clinical neurophysiology centre
Home care and continuity of care (cross-functional)

PEDIATRIC NEUROLOGY AND MUSCULAR DISEASES

Director: Prof. Carlo Minetti

Staff

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Elisabetta Gazzerro	Giovanna Giudizioso	Fabrizio Giusquiami
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Marina Pedemonte	Marianna Pezzella	Angela Robbiano
Pasquale Striano	Monica Traverso	Nicola Vanni
Federico Zara		

Activity year 2012

Research projects

Clinical and molecular characterization of a new leucoencephalopathy due to hyccin deficit
After the first identification of patients with hypomyelinization and congenital cataract, we described 6 new cases with new mutations. Data show that, in spite of a higher clinical variability compared to the first description, the neuroradiological picture at MR is constant in all patients and distinguishes this leucoencephalopathy from other hypomyelinating forms. In parallel, the laboratory generated knock-out hyccin mice and analyzed their neurological phenotype. In this model, hyccin gene deletion causes a delay of myelinization in CNS with a reduction of myelinated fibers and axonal caliber.

Genotype-phenotype correlation in Neurofibromatosis type 1
In order to identify gene factors modifying the clinical picture of neurofibromatosis, we identified 10 parent-child discordant couples, that will undergo exome sequencing for the identification of genetic factors specifically associated with mild or severe NF1 picture.

Study of functional molecular mechanisms in the pathogenesis of primary myopathies: perspectives of new therapeutic approaches
In order to identify which components of the proteasome system are specifically involved in the degradation of the dystrophin complex in Duchenne muscular dystrophy, we determined in a cohort of genetically confirmed DMD patients a specific up-regulation of E3 ligase TRIM32 protein. TRIM32 induction was confirmed in degenerating muscular fibers and it was demonstrated that its induction correlates with disease severity. TRIM32 increase is specific for DMD since it is not present in muscular dystrophies caused by other gene defects (merosin, dysferlin, sarcoglycans).

Identification of genome rearrangements involving neuronal ion channels in generalized idiopathic epilepsies
We performed a screening of about 400 genes coding for neuronal ion channels in 150 cases affected by idiopathic generalized epilepsy and 150 control subjects for the identification of genome rearrangements significantly associated with epilepsies. The study showed that cumulative incidence of rearrangements does not differ in the two groups. However, subjects with epilepsy show a higher number of rearrangements involving exone regions of candidate genes ($p< 0.003$) and with larger size ($p< 0.0001$).

Research programme for 2013

Identification of rare neurodevelopmental disease genes through new generation sequencing techniques
Objective: This project is aimed at identifying the genes causative for rare neurological development diseases using state-of-the-art genome technologies.

These diseases show heterogeneous transmission modalities and include recessive autosomal traits, sporadic conditions due to de novo mutations, and diseases characterized by a degree of familial aggregation and lacking a definite transmission modality.

Description:

- Identification of disease genes through mappijng for homozygosity and NGS sequencing
- Identification of de novo mutations involved in sporadic syndromes through exome sequencing in case-parent triads
- Identification of genes involved in complex diseases through the comparative analysis of the genome profile of variants in unrelated patients

Role of adenosine triphosphate (e-ATP) and of purinergic receptors in the pathogenesis of muscular dystrophy due to alpha-sarcoglycan deficit (LGMD2D)

Objective: Study of the pathogenetic mechanisms of a rare form of limb-girdle muscular dystrophy (due to alpha-sarcoglycan deficit, LGMD2D) and evaluation of the effect of a particular class of medications in the animal model of the disease itself.

Description:

- Study of content, release, function, and degradation of extracellular ATP in primary myoblasts isolated in muscular tissue of patients with alpha-sarcoglycan defect (alpha-SG) and in controls.
- Study of the effect of a purinergic antagonist on the dystrophic phenotype of Sgca-null murine model, hypothesizing that purinergic/eATP pathway could be altered in muscular cells with a-DG deficit and that signal inhibition, using an antagonist of the purinergic receptor, oATP, can improve muscular tissue.

Search for new medications for dystroglycanopathies through a screening based on the activation of LARGE gene promoter

Objective: To define a screening of compounds able to increment LARGE protein in muscular cells.

Description: LARGE is an enzyme involved in glycosylation of alpha-dystroglycan (akpha-DG), a transmembrane protein expressed in myoblastic and neuronal cells that, once appropriately glycosylated, binds proteins of the extracellular matrix. Dystroglycanopathies are congenital muscular dystrophies due to mutations in 8 different glycosyltransferases or accessory proteins and are associated with alpha-DG hypoglycosylation. Literature data showed that an increment of LARGE levels can bypass functionally alpha-DG hypoglycosylation caused by defects of other glycosyltransferases, thus improving the muscular phenotype. We propose to use a high-throughput screening system for small compounds or already existing medications able to activate LARGE transcription.

Main collaborations

- Dr. E. Bertini, Bambino Gesù hospital, Roma
- Dr. F. Santorelli, Stella Maris Institute, Calambrone (PI)
- Prof. F. Benfenati, University of GenovaItalian Institute of Technology, Genova
- Dr. T. Sander, Cologne Center for Genomics, Cologne (Germany)
- Prof. S. Sisodiya, University College London, London (UK).

Major publications (2007-2012)

1. Biancheri R, Zara F, Bruno C, Rossi A, Bordo L, Gazzerro E, Sotgia F, Pedemonte M, Scapolan S, Bado M, Uziel G, Bugiani M, Lamba LD, Costa V, Schenone A, Rozemuller AJ, Tortori-Donati P, Lisanti MP, van der Knaap MS, Minetti C. Phenotypic characterization of hypomyelination and congenital cataract. *Ann Neurol*. 2007, 62:121-7.
2. Striano P, Perruolo G, Errichiello L, Formisano P, Beguinot F, Zara F, Striano S. GAD-antibodies in idiopathic generalized epilepsy and type 1 diabetes. *Ann Neurol*. 2008, 63:127-8.

3. Striano P, Striano S, Minetti C, Zara F. Refractory, life-threatening status epilepticus in a 3-year-old girl. *Lancet Neurol*. 2008; 7:278-84.

4. Falace A, Filipello F, La Padula V, Vanni N, Madia F, De Pietri Tonelli D, de Falco FA, Striano P, Dagna Bricarelli F, Minetti C, Benfenati F, Fassio A, Zara F. TBC1D24, an ARF6-interacting protein, is mutated in familial infantile myoclonic epilepsy. *Am J Hum Genet*. 2010; 87:365-370.

5. Cassandrini D, Biancheri R, Tessa A, Di Rocco M, Di Capua M, Bruno C, Denora PS, Sartori S, Rossi A, Nozza P, Emma F, Mezzano P, Politi MR, Laverda AM, Zara F, Pavone L, Simonati A, Leuzzi V, Santorelli FM, Bertini E. Pontocerebellar hypoplasia: clinical, pathologic, and genetic studies. *Neurology*. 2010; 75:1459-1464.

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Child Neuropsychiatry

Director: Prof. Edvige Veneselli

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Activity year 2012

Research projects

Genetic neuropathies-CMT with infantile onset without known genetic marker: clinical-electrophysiological and genetic correlations (Dr. L Doria-Lamba)

Recruitment of patients with pediatric onset genetic neuropathy selected according to a clinical flow-chart and specific electrophysiology. Genetic definition:
for axonal forms with AR or de novo transmission modality: GDAP1, LMNA;
for axonal forms with AD transmission modality: MFN2, GDAP1, HSP22,27;
for demyelinating forms with AR or de novo transmission modality: GDAP1, EGR2, PRX, MTMR2 and 13 KIAA;
for demyelinating forms with AD transmission modality: PMP22, MPZ, EGR2.
In 2011: A) recruitment of 10 new cases; B) increased series of patients candidates for the study of mutations of the following genes: GDAP1, LMNA, MFN2, HSP22,27, KIAA, PMP22, MPZ: 8 new cases.
C) Selection of patients with very early onset neuropathy (congenital-first year of life), recruitment of 4 new patients: ongoing genetic-molecular study.
Our clinical study is aimed at the definition of the molecular diagnosis of forms of genetic neuropathy, using the already proposed methodology, with the aim to continue to recruit new cases and to propose them as candidates for a molecular analysis study according to clinical-electrophysiological phenotype and associated clinical signs.

Genetic defects of metabolism and creatine transport in autistic spectrum disorders

This study was prompted by the recent report of cases with genetic defects of metabolism and of creatine transport who presented autism, severe language impairment, delayed psychomotor development, mental retardation, and epilepsy and by the fact that, for some forms, specific treatment is possible. We examined a sample of 200 subjects (152 males, 48 females; mean age 7.5 years) with diagnosis of pervasive developmental disorder according to DSM IV criteria admitted from March 2006 to June 2010, using a diagnostic protocol including the following: assay of urine level of creatinine, repeated in case of positive result; assay of creatine/GAA ratio in urine;

assay of urine creatine, repeated in case of positive result, once in males and twice in females; MR with spectroscopy in hospitalized patients, in case of positive results.
In our series, we observed no incidence of genetic metabolic disorders and creatine transport disorders. Therefore, given the possibility of phenotypic traits ascribable to the autistic spectrum in subjects with a wider range of symptoms, it is appropriate to search these diseases, rather than with a general screening, in all those subjects presenting a compatible neuropsychic phenotype.

Neurophysiological and neuropsychological study of patients with epileptogenic cortical lesions: presurgical and longitudinal evaluation of epilepsies secondary to early brain lesions

In 2012, presurgical procedures for patients with drug-resistant epilepsy candidates for possible surgical exeresis of the epileptogenic area were concluded. The activity of identification and definition of the epileptogenic area involved a multidisciplinary staff composed of child neuropsychiatrists and neurologists, with specific skills in the field of epileptology and neurophysiopathology, a neuropsycologist, for the study of correlations between epileptogenic focus and cognitive functions, neuroradiologists and neurosurgeons. In operated patients, post-surgical course was defined, and it involved child neuropsychiatrist, neuropsychologist, and physiatrist in clinical, electroclinical, cognitive-behavioural and therapeutic follow-up.
Compared to previous years, there was an increase in the frequency of candidates for neurosurgery and implant of vagal nerve stimulator. Objectives for next year are the following: selection of new cases for electrophysiological monitoring and multidisciplinary presurgical study (neuroimaging; neuropsychology); study of clinical, electrophysiological, and neuropsychological outcome of operated patients with 2 years' minimum follow-up; statistical analysis of results and preparation of scientific papers; increment of clinical trials of new antiepileptic drugs; development of multicenter studies.
In parallel, in collaboration with the Neuro-oncology unit, we started a review of the series of patients with epilepsy and brain tumors, focusing on the type of epilepsy, on drug resistance, on tumor type, on type of chemotherapy and radiotherapy used, and on underlying disease progression in each patient. On the basis of retrospectively collected data, we can start a second phase including a prospective evaluation of patients to define an approach to the patient with tumor-related epilepsy from the diagnostic, therapeutic, and rehabilitative point of view, improve management of the patient requiring integrated treatment (chemotherapy-radiotherapy-surgery), and develop an interdisciplinary approach. The study can be a multicentre study.

Study of immunomediated encephalitides in children, with particular reference to anti- N-methyl-D-aspartate (NMDA) receptor encephalitis

As an update of previous reports, we published a paper describing a patients with anti-GAD antibody-related limbic encephalitis presenting atypical clinical characteristics (Mirabelli-Badenier M et al. Anti-glutamic acid decarboxylase limbic encephalitis without epilepsy evolving into dementia with cerebellar ataxia. Arch Neurol. 2012 Aug;69(8):1064-6.) This study showed the possibility of a wider clinical phenotype of anti-GAD limbic encephalitis, first reporting in the literature the case of a presentation without epilepsy and with cerebellar signs. In addition, the description of a further case of anti-NDMA encephalitis diagnosed in a patient previously affected by Hashimoto encephalitis (Mirabelli et al. Hashimoto's encephalopathy and anti-NMDAR encephalitis: a near-miss diagnosis) is being reviewed. These papers allowed the reevaluation of diagnostic and therapeutic aspects of these rare forms in order to optimize the diagnostic procedures and planning of the therapeutic and follow-up programme, with particular focus on paraneoplastic forms. The collaboration with Prof. Angela Vincent of the University of Oxford is continued for both diagnostic and research purposes.

Epileptic genotype-phenotype correlation in Rett syndrome

Starting from the multicentre study on 165 patients, we continued our study on epilepsy in Rett syndrome, which had already produced a paper (*Pintaudi M et al, Epilepsy in Rett syndrome: Clinical and genetic features. Epilepsy Behav. 2010 Nov;19(3):296-300).*

In the same cohort, a retrospective study was carried out to evaluate medications and their efficacy in the treatment of epilepsy in these patients. The results of this study, which was started last year, underwent statistical analysis. Valproate resulted the most commonly used first choice medication, followed by carbamazepine. Lamotrigine resulted the most effective drug for patients with late onset epilepsy, whereas barbiturate resulted poorly effective. Valproate and carbamazepine had quite a good efficacy as first choice drug at onset. Among medications used at follow-up, the association valproate plus lamotrigine resulted as the most effective. The results of this study are in press.

Advances in diagnostic-therapeutic management of infantile cerebral palsies

Concerning subjects with infantile cerebral palsy and other movement disorders, a database was created for filing of clinical, electrophysiological, neuroradiological, and therapeutic data of the over 400 followed patients. Continuous update of the database and processing of correlation data on motor and cognitive symptoms is ongoing, with particular reference to diplegic and tetraplegic forms with neuroradiological picture with the aim to identify early significant prognostic parameters (Carelli et al: MRI and motor impairment in Cerebral Palsy: which predictive factors?, presented at the IV International Cerebral Palsy Conference, Pisa 2012). In addition, we are studying the electroencephalographic characteristics and, when present, the type of epilepsy of a subgroup of patients with neuroradiological picture of periventricular leukomalacia.

In particular, we are evaluating the incidence of electrical activation during sleep and its impact on motor and psychomotor skills (Carelli et al: Periventricular leukomalacia and Encephalopathy with electrical status epilepticus during slow sleep, presented in occasion of LICE congress, 2012).

In dystonic forms, we studied CSF neuromediators in order to develop possible specific drug therapies. Some peculiar syndromes with predominant motor expression were studied in detail in the following papers: De Grandis et al: De Grandis et al: Lack of SLC2A1 (Glucose Transporter 1) Mutations in 30 Italian Patients With Alternating Hemiplegia of Childhood, J Child Neurol 2012; Cerebrospinal fluid alterations of the serotonin product, 5-hydroxyindolacetic acid in neurological disorders, J Inherit Metab Dis 2010; De Grandis et al: Paroxysmal dyskinesia with interictal myoclonus and dystonia, Park Relat Disord 2008.

Concerning reorganization of services, follow-up of preterm newborns and/or newborns with neurological disorders has been functionally reorganized, with improvement of early diagnostics and the establishment of hospital-territory continuity of care with a regional multidisciplinary study: “Continuità assistenziale ospedale-territorio nel nato pretermine in Regione Liguria: Progetto Pollicino”, I.Blanchi, F.Gallino, M.S.Acutis, C.Gotta, M.Occhi and Gruppo Pollicino Regione Liguria, Istituto G. Gaslini, Asl 3 Genovese, A.O. Galliera, A.O. San Martino, Agenzia Sanitaria Regionale. Poster presented in occasion of the meeting "Nascere pretermine: follow-up e interventi. Un approccio interdisciplinare" - Bologna, 11-12 novembre 2011.

Study of clinical heterogeneity in a large cohort of patients with Rett syndrome through a biochemical-molecular approach

Rett syndrome (RTT, MIM 312750) is a progressive disorder of neurological development having an incidence of 1:10000 females. Notwithstanding the identification of three genes, the pathogenesis of the syndrome is still unknown.

The project stems from a consolidated collaboration among the Child Neuropsychiatry unit of the Istituto G. Gaslini of Genova, the Epilepsy Centre of San Paolo hospital, and the Laboratory of Cytogenetics and Molecular Genetics of the Istituto Auxologico Italiano (IAI) and the Associazione Italiana Sindrome di Rett (AIR)

Recent evidence of the important role of oxidative stress in RTT with a probable impact on the severity of symptoms is at the basis of our most recent collaboration with the Physiology unit of the University of Genova.

Aim of the study is:

1) To improve existing knowledge of the pathogenetic mechanisms responsible for Rett syndrome

2) To identify altered neurological and biochemical pathways in Rett syndrome
3) To identify factors modifying the various aspects of the clinical picture in order to choose the possible appropriate treatment of the syndrome
4) To identify new genetic defects causative of the syndrome

During the first year of the project (2012), the Neuropsychiatry units of Gaslini and San Paolo hospital reevaluated and collected the clinical history of 20 female patients (6 Genova, 14 San Paolo) with MECP2 gene mutation aged between 3 and 12 years. The patients were hospitalized or admitted to DH and underwent clinical, neurological, developmental, nutritional (BMI calculation), cardiological (ECG and Holter), auxological and/or gastroenterological, and neurophysiological (video-polygraphic EEG) evaluations, as well as evaluation of cognitive and relational aspects of bone metabolism balance.
In our unit, 40 healthy controls underwent blood sampling after obtaining informed consent for participation in the study.
In order to reach statistical significance of the data obtained, it will be necessary to recruit at least another 10 Rett female patients at the correct age range. To this end, we contacted other clinical groups and asked them to apply the project protocol or to refer their patients to our two clinical units. Clinical data were tabulated according to Kerr scale items.
The Laboratory of Physiology of Genova studied in blood the alteration of MT transcripts as compared to healthy controls and the possible imbalance of an isoform compared to the others, which indicates an imbalance of the oxidative state.
The clinical units and the Laboratory of Clinical Genetics of the Istituto Auxologico collected 22 patients with clinical diagnosis of Rett syndrome, in whom mutations and deletions of known genes had been previously excluded. Blood sampling, DNA extraction from patient and parents were performed. Data are being analysed for the selection of variants with biological significance.

Study of cerebral blood flow with Transcranial Doppler Ultrasound Examination in Alternating Hemiplegia

Infantile complex neurological diseases: new diagnostic and therapeutic approaches
Research programme funded by the Dept. of Neurosciences, Opthalmology, and Materno-Fetal Genetics, University of Genova

Research doctorate in Neurosciences, XXV cycle - Dept. of Neurosciences, Opthalmology, and Materno-Fetal Genetics, University of Genova
- Congenital Cerebellar Diseases
- Alternating Hemiplegia: genotype-phenotype correlation study

Clinical Psychology (associated)

Clinical-diagnostic analysis and software processing in R STATISTICAL COMPUTING ENVIRONMENT of psychometric and neuropsychological data in a naturalistic population of patients with specific learning disorder, in patients with borderline cognitive function and in age-matched controls; this activity is addressed to residents and trainees in clinical psychology
This annual study includes different phases. The preliminary phase will include the collection of clinical material on the basis of specific indications already established in previous years in the field of specific learning disorders in the Clinical Psychology unit of Gaslini during the daily evaluation of patients with specific learning disorders and borderline cognitive function and in age-matched controls. This phase will include periodic monitoring of activity and data collection. The subsequent phase will include software processing in R STATISTICAL COMPUTING ENVIRONMENT of collected material. This activity will be managed autonomously and will not be carried out in the Psychology outpatient service.
Processing of data collection is ultimately aimed at the completion of training of residents and trainees in clinical psychology, as a continuation of the training activity already started in previous years on the evaluation and diagnosis of specific learning disorders.

In the third phase (October 2012-May 2013), the processed data will be shared with the outpatient service staff and will be used to define protocols for more effective psychodiagnostic evaluation aimed at responding to specific needs. In addition, the evaluation process should be considered as closely related to the proposed rehabilitation. Collected data will allow a more accurate evaluation of the different situations in the outpatient service, their frequency and specific characteristics. Therefore, it will be possible to focus on rehabilitation protocols and, if necessary, to develop more sensitive and appropriate evaluation instruments responding to the needs highlighted by the collected material.

Research programme for 2013

Research projects

Observational prospective study on the clinical features and on the prognosis of pediatric patients with non idiopathic partial epilepsies
Objective: to collect clinical and instrumental data to outline the epidemiologic characteristics of non idiopathic partial epilepsies and to monitor over time, as related to presence or absence of seizure control, the evolution of the cognitive or psychopathological profile, in order to identify early predictors of clinical and neuropsychological outcome at 2 and 5 years
Description: Children with onset of non idiopathic partial epilepsy aged between 1 month and 12 years will be recruited. The study includes patient history of critical symptomatology, clinical (neurological examination, evaluation of cognitive and psychopathological profiles) and instrumental (EEG and brain MR, prolonged recording at time 0 of sleep-wake rhythm and critical video-EEG recording) examinations.
Neuropsychological evaluation includes the administration of development scales in children aged below 5 years (Griffiths scales) and the analysis of the main cognitive functions (IQ, attention, memory, language, execution functions) through a battery of tests specific for the different age ranges in children aged over 5 years; subsequent neuropsychological controls are scheduled at 12, 24, and 60 months from onset. The psychopathological profile will be analysed through the administration of CBCL Child Beaviour Check List. The study can be conducted as a multicentre study.

Study of posterior cranial fossa diseases: clinical, neuroradiological, and genetic characterization
Objective: Clinical, neuroradiological, and genetic characterization of patients with posterior cranial fossa diseases, either malformative or hereditary-degenerative. In particular: 1. Clinical and neuroradiological study of patients; 2. Genetic-molecular analysis; 3.Correlation between clinical-neuroradiological phenotype and genotype; 3.Creation of protocols and diagnostic flow-charts.
Description: Posterior cranial fossa diseases represent a complex aspect of neurological diseases of developmental age. Notwithstanding the recent advances in the field of developmental biology, genetics, and neuroradiology, controversies still exist on classification and terminology.
The study is aimed at a retrospective and prospective evaluation of patients with cerebellar symptoms and/or neuroradiological picture involving the posterior cranial fossa. The study and correlation of clinical-neuroradiological phenotype and genotype can contribute not only to the definition of the etiological picture of each single patient, but also to a better definition of these rare diseases and to the creation of protocols and flow charts that can be used to optimize the diagnostic process.

Main collaborations

Epilepsy: C.Dravet, Member of ILAE Commission, Marseille – Laboratory ofi Genetics, Galliera hospital, Genova - E.Beghi, Laboratorio di Malattie Neurologiche, Istituto "Mario Negri", Milano. *Infantile Cerebral Palsies and Movement Disorders*: J.Campistol, Hospital Sant Joan de Déu, Universitat de Barcelona - G.Abruzzese, DiNOG, Genova - S.Soria, Presidente A.I.D.A.. *Leucoencephalopahties*: O.Boepsflug-Tanguy, Clermont-Ferrand - Marjo S.Van der Knaap, VU

University, Amsterdam. *Ceroid lipofuscinosis:* A.Simonati, Università di Verona. *Hereditary spastic paraparesis:* F.M.Santorelli, IRCCS Stella Maris di Pisa. *Peripheral neuropathies:* A.Schenone, P.Mandich, DiNOG, Genova. *Stroke*: C.Zavarone, Groupe Hospitalier Pitié-Salpêtrière, Parigi. *Opsoclonus-Myoclonus syndrome*: B.Hero, University of Cologne. *Neuroimmunology*: A.Vincent, John Radcliffe Hospital, Oxford, UK - F.Montecucco, Geneva University Hospital - A.Uccelli, DiNOG, Genova. *Alternating hemiplegia*: B.Neville, UCL Institute of Child Health, London. *Tourette syndrome and Tics:* M.M.Robertson, University of London - D.Martino, Università di Bari. *Infantile autism:* R.Faggioli, Centro per l'autismo, O. San Paolo di Milano - M.Zappella, Università di Siena - E.Micheli, Scuola di Robotica, Genova. *Sindrome di Rett*: M.Pineda, Hospital Sant Joan de Deu, Barcelona - A.Clarke, University Hospital of Wales, - B.Ben Zeev, Safra Ped. Hospital, Ramat-Gan - G.Nguyen, Rett Syndrome Europe - S.Russo, Ist. Auxologico It., Milano - A.Renieri, AOU Senese Policlinico - A.Voci e L.Vergani, Dip. Fisiologia e Biofisica, Università di Genova. *Psychopatology of childhood and adolescence:* D.Cohen, Groupe Hospitalier Pitié-Salpêtrière, Parigi - F.Gabrielli e M.Maura, AOU S. Martino, Genova - E.Franzoni, Università di Bologna - F.Neri, Università di Milano-Bicocca – Ist. Psicologia e Terapia Cognitivo Comportamentale - Centro Genovese di Terapia della Famiglia - Il Ruolo Terapeutico, Genova – PsiBA, Milano. Fragile X *Syndrome:* M.G.Torrioli, Università Cattolica, Roma. *Neuropsychomotricity:* Rete regionale del CL Terapia della Neuro e Psicomotricità dell'Età Evolutiva - P.A.Veggiotti, Fondazione Istituto Neurologico C. Mondino, Università di Pavia.

Major publications (2007-2012)

1. De novo mutations in ATP1A3 cause alternating hemiplegia of childhood. 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. NAT GENET 2012;44(9):1030-1033.
2. Anti-glutamic acid decarboxylase limbic encephalitis without epilepsy evolving into dementia with cerebellar ataxia. Mirabelli-Badenier M, Morana G, Pinto F, Uccelli A, Veneselli E, Battaglia FM, Biancheri R, Baglietto MG, Vincent A, Mancardi MM. ARCH NEUROL-CHICAGO 2012;69(8):1964-1066.
3. Rett networked database: an integrated clinical and genetic network of Rett syndrome databases. 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. HUM MUTAT 2012;33:1031-1036.
4. CC and CXC chemokines are pivotal mediators of cerebral injury in ischaemic stroke. Mirabelli-Badenier M, Braunersreuther V, Viviani GL, Dallegri F, Quercioli A, Veneselli E, Mach F, Montecucco F. Thromb Haemost 2011 105:409-20.

5. Anti -N-methyl-D-aspartate-receptor encephalitis in a four-year-old girl. Biancheri R, Pessagno A, Baglietto MG, Irani SR, Rossi A, Giribaldi G, Badenier MM, Vincent A, Veneselli E. J Pediatr 2010 156:332-4.

6. Hyccin, the molecule mutated in the leukodystrophy hypomyelination and congenital cataract (HCC), is a neuronal protein. Gazzerro E, Baldassari S, Giacomini C, Musante V, Fruscione F, La Padula V, Biancheri R, Scarfì S, Prada V, Sotgia F, Duncan ID, Zara F, Werner HB, Lisanti MP, Nobbio L, Corradi A, Minetti C. PLOS ONE 2012;7(3):e32180.

7. A 3-year-old boy with drug-resistant complex partial seizures. Striano P, Consales A, Severino M, Prato G, Occella C, Rossi A, Cama A, Nozza P, Baglietto MG. BRAIN PATHOL 2012;22:725-728.

8. Statins in the Treatment of Acute Ischemic Stroke. Montecucco F, Quercioli A, Mirabelli-Badenier M, Viviani GL, Mach F. Curr Pharm Biotechnol. 2012 Jan 1;13(1):68-76.

9. Novel mutations in the CDKL5 gene, predicted effects and associated phenotypes. Russo S, Marchi M, Cogliati F, Bonati MT, Pintaudi M, Veneselli E, Saletti V, Balestrini M, Ben-Zeev B, Larizza L. Neurogenetics 2009 10:241-50.

10. Intermittent-relapsing pyruvate dehydrogenase complex deficiency: a case with clinical, biochemical, and neuroradiological reversibility.Giribaldi G, Doria-Lamba L, Biancheri R, Severino M, Rossi A, Santorelli FM, Schiaffino C, Caruso U, Piemonte F, Bruno C. DEV MED CHILD NEUROL 2012;54:472-476.

PHYSICAL MEDICINE AND REHABILITATION

Director: Dr. Paolo Moretti

Staff

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Roberta Mantero	Ottavia Melluso	Nicoletta Orsini
Enrica Pastorino	Christian Savio	Cinzia Scano
Maria Antonietta Spanò	Daniela Spina	

Activity year 2012

Intensive rehabilitation programmes were carried out (high dosage in a short time) as well as standard low intensity rehabilitation programmes (low dosage in a long time) for recovery of the upper llimb in subjects with infantile cerebral palsy in developmental age. In addition, a series of evaluation instruments both specific for the upper limb (AHA and Besta) and general were adapted for a population of developmental age subjects with multiple and severe disabilities. All this was aimed at evaluating both basic requisites to obtain effective results in the upper limb (in terms of severity of the disability, characteristics and type of associated disabilities, and patients' age) and the "amount" of treatment required to obtain results in terms of reduction of hypertonia and improvement of muscular recruitment, and functional results.

Our unit participated in data collection and evaluation with standardized functional scales (North Star, MFM) of a population of patients with muscular dystrophy within the framework of a multicentre study for the evaluation of the efficacy of new drug treatments.

Research programme for 2013

Research project

Robotic rehabilitation of the upper limb in developmental age
Objective: Evaluation of the adaptability and efficacy of robotic systems in supporting rehabilitation in upper limb disabilities affecting developmental age subjects.
Description: Testing and use of robotic technologies in upper limb rehabilitation in developmental age subjects with disabilities due to nerve system and skeletal muscle lesions. Comparison with traditional methods. Development of evaluation and treatment protocols.

Main collaborations

- Istituto Italiano di Tecnologia
- Istituto don Gnocchi.

Major publications (2007-2012)

1. Mazzone E, Doglio L e al. "Reliability of the North Star Ambulatory Assessment in a multicentric setting" Neuromuscular Disord 2009 Jul¸19(7):458-61
2. Mazzone E. Doglio L e al "North Star Ambulatory Assessment, 6 minute walk test and timed items in ambulant boys with Duchenne Muscular Distrophy" Neuromuscular Disorders 2010 Nov; 20(11):712-6
3. Mazzone E, Doglio L e al. "Functional changes in Duchenne muscular distrophy: a 12 month longitudinal cohort study" Neurology, 2011 Jul 19; 77(3) 250-6
4. Doglio L., Pernigotti I e al. Early signs of gait deviation in Duchenne Muscular distrophy." Eur J Phys Rehabil med 2011 Dec; 27(4):587-94

Clinical Psychology

Director: Prof. Ezio Casari

Staff

Alga Gioia Fantino
Vincenza Lertora
Lucia Gatti

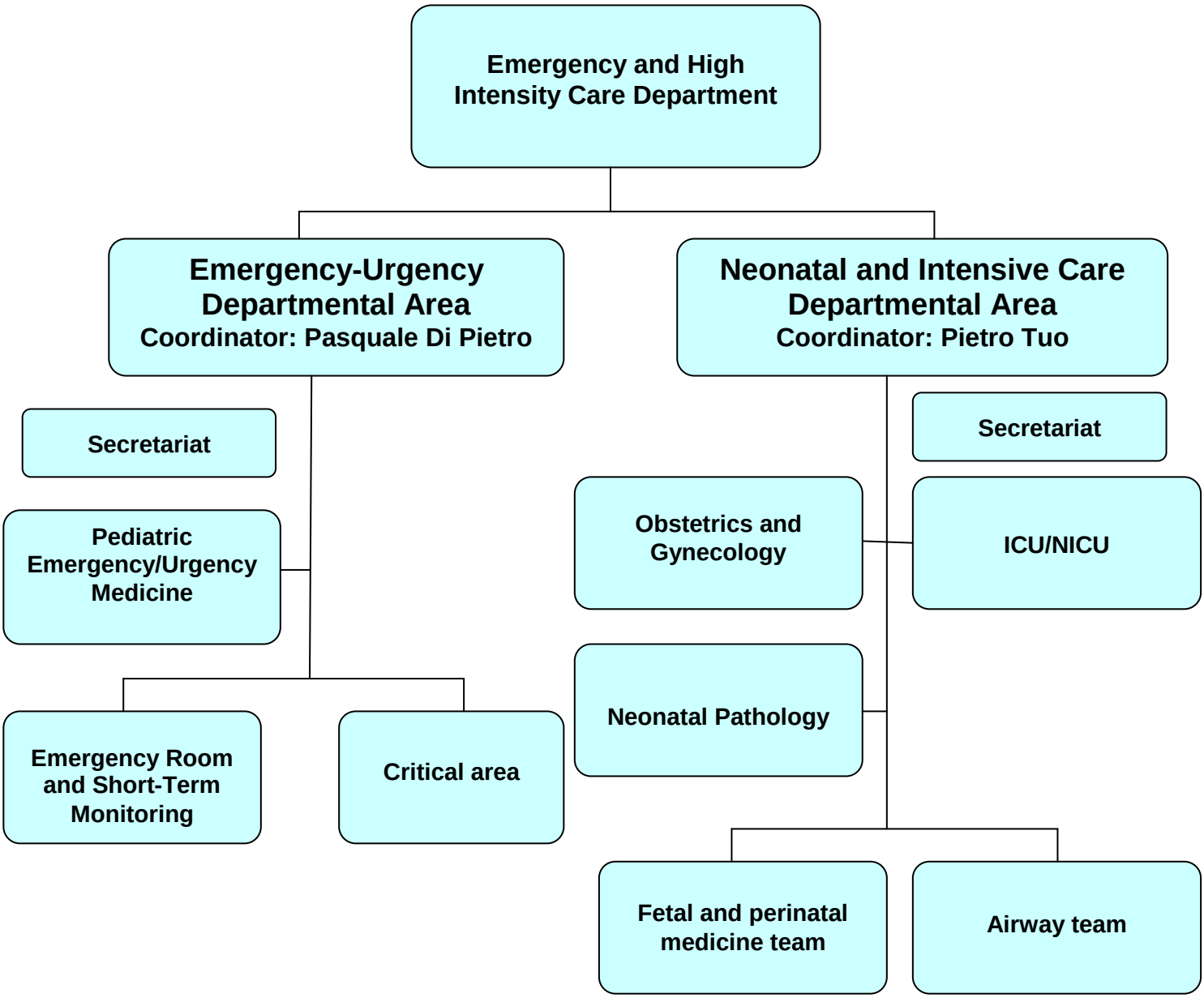
Activity year 2012

- Psychodiagnostic evaluation for specific problems or disadvantage areas in developmental age
- Evaluation of maladjustment and adjustment in chronic pediatric diseases: psychological counseling at first visits and follow-up according to operative protocols agreed upon with units
- Evaluation of somatoform diseases in developmental age. Anxiety and mood disorders (mild to moderate)
- Evaluation of recurrent abdominal disorders
- Evaluation of gender identity disorders: psychotherapy of children and preadolescents
- Evaluation of psychological support and psychotherapy for pregnancy- and puerperium-related problems

Research programme for 2013

Research and development of new clinical approaches in the following areas:

- Psychodiagnostic evaluation for specific problems or disadvantage areas in developmental age
- Evaluation of maladjustment and adjustment in chronic pediatric diseases: psychological counseling at first visits and follow-up according to operative protocols agreed upon with units
- Psychological support and counselling activity for hospital units and day hospital services in case of psychological problems, either preexisting or reactive to disease conditions, problems of adaptation and compliance with disease state and/or hospital stay of the patient and/or his/her family.
- Somatoform diseases in developmental age. Anxiety and mood disorders (mild to moderate)
- Recurrent abdominal disorders
- Gender identity disorders: psychotherapy of children and preadolescents
- Psychological support and psychotherapy for pregnancy- and puerperium-related problems


Emergency and High Intensity Care Department
Emergency-Urgency Departmental Area
Coordinator: Pasquale Di Pietro
Neonatal and Intensive Care Departmental Area
Coordinator: Pietro Tuo
Secretariat
Pediatric Emergency/Urgency Medicine
Emergency Room and Short-Term Monitoring
Critical area
Secretariat
Obstetrics and Gynecology
ICU/NICU
Neonatal Pathology
Fetal and perinatal medicine team
Airway team

PEDIATRIC EMERGENCY/URGENCY MEDICINE

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Antonella Palmieri
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Activity year 2012

1. SONDO project (supported by AIFA)
2. AIFA project: “Monitoring of safety and evaluation of appropriateness of antibiotic use in children with bronchial pneumonia, pharyngotonsillitis, and acute otitis media in Liguria region
3. SINIACA project (National Informative System of Accidents in Dwelling Places) – JAMIE

Research programme for 2013

Search and development of new clinical pathways for chronic diseases and/or diseases of scientific interest with pediatric onset, especially correlated diseases.

Main collaborations

- Contacts between SIDS centre and University of Oslo, in particular with the Director of the Department of Legal Medicine Prof. Rogum and the University of Melbourne (Prof. Mathias Dutchmann, Molecular Genetics)
- Launch of a collaborative project with the Boston Children’s Hospital – Boston, USA on procedural sedation in emergency (Dr. B. Krauss), on child protection (Dr. C. Wilson), and on advanced pediatric simulation (Dr. P. Weinstock)
- Launch of a collaborative project with the Sick Kids Hospital of Toronto, Canada (Prof. B. Stevens) on Family Child Centered Care in collaboration with the Hematology-Oncology unit and the Dept. of Nursing of the University of Genova

Major publications (2007-2012)

1 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.

2 Marchetti F, Maestro A, Rovere F, Zanon D, Arrighini A, Bertolani P, Biban P, Da Dalt L, Di Pietro P, Renna S, Guala A, Mannelli F, Pazzaglia A, Messi G, Perri F, Reale A, Urbino AF, Valletta E, Vitale A, Zangardi T, Tondelli MT, Clavenna A, Bonati M, Ronfani L. Oral ondansetron versus domperidone for symptomatic treatment of vomiting during acute gastroenteritis in children: multicentre randomized controlled trial. BMC Pediatr. 2011 Feb 10;11:15.

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5 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.

6 Palmieri A, Riccardi S, Bergamino L, Ciccone MO, Fornoni L, Piccotti E, Di Pietro P. Apparent life threatening event (ALTE): the role of the training in the follow-up. Minerva Pediatr. 2011 Apr;63(2):139-48.

7 Marchisio P, Bellussi L, Di Mauro G, Doria M, Felisati G, Longhi R, Novelli A, Speciale A, Mansi N, Principi N. Acute otitis media: From diagnosis to prevention. Summary of the Italian guideline. International Journal of Pediatric Otorhinolaryngology 74 (2010) 1209–1216

8 Indinnimeo L, Bertuola F, Cutrera R, De Benedictis FM, Di Pietro P, Duse M, Gianiorio P., Indirli G, La Grutta S, La Rosa M, Longhi R, Miceli Sopo S, Miglioranzi P, Miraglia Del Giudice M, Monaco F, Radzik D, Renna S, Snijders D, Zampogna S, Barbato A. Clinical evaluation and treatment of acute asthma exacerbations in children. Int J Immunopathol Pharmacol. 2009 Oct-Dec; 22 (4) :867-78

9 Marangoni F, Poli A, Agostoni C, Di Pietro P, Cricelli C, Brignoli O, Fatati G, Giovannini M, Riva E, Marelli G, Porrini M, Rotella CM, Mele G, Iughetti L, Paoletti R. A consensus document on the role of breakfast in the attainment and maintenance of health and wellness. Acta Biomed. 2009 Aug;80(2):166-71.

10 Palmieri A, Molinari AC, Rossi A, Gandolfo C, Lucigrai G, Pavanello M, Politanò T, Vari MS, Di Pietro P. Neurologic emergency in children's hospital. Stroke. Minerva Pediatr. 2009 Oct;61(5):461-7.

OBSTETRICS AND GYNECOLOGY

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Giuliana Ventura
Nicoletta Zerega

Activity year 2012

Research projects

Prevention of uterine cervix tumor: new screening methods
In the vaginoscopy outpatient service, cervix biopsies were examined not only for dysplasia, but in women with persistent HPV positivity and with diagnosis of L-SIL o ASC-US we evaluated the presence of p16 protein on cytologic samples.

Glucide metabolism in pregnancy: screening, diagnosis, etiopathogenesis, materno-fetal follow- up
In collaboration with the Pediatric Clinic of Gaslini, we performed controls of glucide metabolism through OGTT, seriate US examinations, evaluation of delivery, and subsequent follow-up of newborns.

RNA (RNA-based non invasive aneuploidy) study: an LTD laboratory developed test
The study was concluded in single pregnancies with optimal results (concerning referred cases, our centre ranks first in Europe and second worldwide). Further investigations are ongoing in induced and twin pregnancies and in normal population.

Prenatal diagnosis: future perspectives: the importance of the formation and activation of a perinatology multidisciplinary team
For over one year, periodical meetings involving obstetricians, neonatologists, anesthesiologists, cardiologists, cardiovascular surgeons, radiologists, etc. have allowed the achievement of improved knowledge and collaboration among specialists with improvement of timing and modalities of successful treatment of clinical cases.

Mammary carcinoma in pregnancy
Besides following the only three cases of mammary carcinoma in pregnancy, during pregnancy itself and at delivery, and evaluating the anatomic pathology aspects of the placenta as well as neonatal health and development, many pregnant women were selected for objective or anamnestic risk factors and referred to the Cancer Research Institute of Genova for US examination. In none of these women, tumor presence was observed.

Research programme for 2013

Research projects

Immunohistochemical study of protein p16 as marker of low-grade squamous lesion progression
Objective of the study is to evaluate the potential of this protein as prognostic marker in women with persistent positivity for HR-HPV DNA and with diagnosis of L-SIL or ASC-US.
The aim is to differentiate patients at higher risk of progression and therefore needing repeated controls.
The patients admitted to the Vaginoscopy Outpatient Service are selected according to the above-mentioned parameters and sampled material is sento to anatomic pathology unit.

Study of early diagnosis of preeclampsia by assay of maternal serum levels of fms-like tyrosine kinase (sFlt)-1 and placental growth factor (PlGF) associated with doppler evaluation of uterine arteries in the 1st trimester of pregnancy. Early screening of patients at risk for preeclampsia.
This study could be carried out in collaboration with our laboratories (dr. Salvatore Mangraviti) and with the Prenatal Diagnosis Outpatient Service at patient admission for the execution of the combined test.
Angiogenetic and antiangiogenetic factors (sFlt-1 and PlGF) are involved in the mechanisms underlying PE development. Plasma concentration of sFlt-1, PlGF and sFlt-1/PlGF ratio have a positive predictive value for PE diagnosis and probably for diagnosis of PE atypical forms. This assay could also be useful for the identification of patients with chronic hypertension that can subsequently develop PE.
In association with these assays, the use of US for the determination of the resistance index of uterine arteries can increase the sensitivity of diagnosis in this group of patients.

Pregnancy in adolescents: retrospective analysis from 2000 to 2012 and prospective analysis in 2013
The study is aimed at evaluating and preventing risk factors related to young age and giving an answer to unsolved questions. The study will use more specific diagnostic-therapeutic methods for the adolescent as compared to the adult pregnant woman.

Adolescence and prevention of cervico-vaginal disease
The approach to young female patients through the pluriennial presence of a gynecological outpatient service specific for children and adolescents can make it possible to prevent cervico-vaginal diseases, especially those related to HPV.
The study will be carried out through the following:

a- Primary prevention (vaccination)
b- Secondary prevention (Pap-test, vaginoscopy, HPV-test and, if necessary, biopsy) since the long latency time between infection and appearance of intracervical lesion allowed the creation of consolidated preventive approaches.

Development and validation of OSATS (Objective Structured Assessment of Technical Skills) for the simulation of difficult delivery
OSATS is a validated method largely used in English-speaking countries for the evaluation of competence in the use of a particular technique. Our objective is to develop appropriate OSATS to manage difficult delivery with high fidelity human patient simulations and to validate their efficacy.

During the training course “Difficult vaginal delivery simulated with *Prompt brithing simulator*”, we will use objective observation forms to evaluate technical and team work abilities according to OSATS method. On the basis of data obtained with simulation tests, new forms will be created and submitted to a panel of experts according to Delphi method. The opinions collected anonymously by the experts will be used by researchers to deveop new observational OSATS methods to be used in subsequent retraining editons. At the end of retraining, changes will be made and submitted again to the expert panel according to Delphi method. This will allow the validation and preparation of OSATS specific for high fidelity human patient simulation in obstetrics.

Reduction of prevalence of cesarean section by manual rotation of the occiput in occipito-posterior positions

Occipito-posterior positions during delivery are an important cause of dynamic and mechanical dystocia. Aim of the project is to show the possibility of rotating manually fetal head and of reducing the prevalence of cesarean sections for dystocia.

Prospective observational study. With the training course “Difficult vaginal delivery simulated with *Prompt brithing simulator*”, obstetricians and gynecologists will be trained to perform the procedure of manual rotation of posterior occiput through frontal lessions and high fidelity human patient simulations. In all cases of delivery with suspected occipito-posterior position or dystocia, US examination will be performed to evaluate fetal position. In cases of occipito-posterior position, trained staff will perform the procedure of manual rotation of the occiput. At the end of 2013, a preliminary evaluation of the prevalence of cesarean sections for dystocia with occipito-posterior position will be performed in our unit and compared with the data obtained in 2012. Data collection will continue also in 2014.

Main collaborations

- San Martino hospital: gynecology and obstetrics unit
- San Martino hospital: infectious disease clinic
- Cancer Research Institute, Genova
- Fatebene Fratelli hospital-Roma

Major publications (2007-2012)

1. J Matern Fetal Neonatal Med. 2012 Apr;25(4):339-42. doi: 10.3109/14767058.2011.576722. Epub 2011 May 24. Defective placental adhesion in voluntary termination of second-trimester pregnancy and risk of recurrence in subsequent pregnancies. Morotti M, Podestà S, Musizzano Y, Venturini PL, Bentivoglio G, Fulcheri E, Ferrero S. Department of Obstetrics and Gynecology, University of Genoa, Genoa, Italy. PMID: 21609201 [PubMed - indexed for MEDLINE]
2. Eur J Immunol. 2012 Sep;42(9):2459-70. doi: 10.1002/eji.201242375. Epub 2012 Jul 25.Receptor modulation and functional activation of human CD34+ Lin- -derived immature NK cells in vitro by Mycobacterium bovis Bacillus Calmette-Guerin (BCG). Marras F, Bozzano F, Bentivoglio G, Ugolotti E, Biassoni R, Moretta L, De Maria A. G. Gaslini Istitute, Genova, Italy. © 2012 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. PMID: 22736333 [PubMed - in process]
3. J Reprod Med. 2010 Sep-Oct;55(9-10):423-9. Evaluation of patients' satisfaction of cervical ripening using dinoprostone by either intravaginal gel or pessary: an open-label, randomized, prospective study. Ferraiolo A, Dellacasa I, Bentivoglio G, Ferrero S, Ragni N. Department of Obstetrics and Gynecology, San Martino University Hospital, Genoa, Italy. PMID: 21043369 [PubMed - indexed for MEDLINE]
4. Arch Gynecol Obstet. 2010 Feb;281(2):183-8. doi: 10.1007/s00404-009-1170-5. Epub 2009 Aug 5. Peripartum cardiomyopathy. Moioli M, Valenzano Menada M, Bentivoglio G, Ferrero S.

Department of Obstetrics and Gynaecology, San Martino Hospital, University of Genoa, Largo R. Benzi 1, 16132, Genoa, Italy. melitamoioli@libero.it PMID: 19655159 [PubMed - indexed for MEDLINE]

5. Expert Rev Neurother. 2008 Jun;8(6):979-88. doi: 10.1586/14737175.8.6.979. Myasthenia gravis during pregnancy. Ferrero S, Esposito F, Biamonti M, Bentivoglio G, Ragni N. Department of Obstetrics & Gynecology, San Martino Hospital & University of Genoa, Largo R. Benzi 1, 16132, Genoa, Italy. dr@simoneferrero.com PMID: 18505362 [PubMed - indexed for MEDLINE]
6. Childs Nerv Syst. 2011 Jul;27(7):1073-81. doi: 10.1007/s00381-010-1372-y. Epub 2011 Jan 5. Maternal periconceptional factors affect the risk of spina bifida-affected pregnancies: an Italian case-control study. De Marco P, Merello E, Calevo MG, Mascelli S, Pastorino D, Crocetti L, De Biasio P, Piatelli G, Cama A, Capra V. U.O. Neurochirurgia, Istituto G. Gaslini, Largo G. Gaslini, 5, 16148, Genua, Italy. laboratorioNCH@ospedale-gaslini.ge.it PMID: 21207040 [PubMed - indexed for MEDLINE]
7. J Matern Fetal Neonatal Med. 2009 Dec;22(12):1194-6. doi: 10.3109/14767050903067337. Stepwise sequential screening for trisomy 21 in assisted reproduction pregnancies. Pastorino D, Canini S, Prefumo F, Buffi D, Pugliese M, Venturini PL, de Biasio P. U.O. Ostetricia e Ginecologia, Istituto G. Gaslini, Università di Genova, Italy. PMID: 19916716 [PubMed - indexed for MEDLINE]
8. Fetal Diagn Ther. 2008;24(1):35-8. doi: 10.1159/000132403. Epub 2008 May 27. Acute premature constriction of the ductus arteriosus after maternal self-medication with nimesulide. Prefumo F, Marasini M, De Biasio P, Venturini PL. Department of Obstetrics and Gynaecology, Institute G Gaslini, Genova, Italy. federico.prefumo@libero.it Copyright 2008 S. Karger AG, Basel. PMID: 18504378 [PubMed - indexed for MEDLINE]
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10. Prenat Diagn. 2007 May;27(5):483-4. Apparently isolated borderline ventriculomegaly and lissencephaly. Pastorino D, Prefumo F, Rossi A, Crocetti L, Pugliese M, Buffi D, Venturini PL, de Biasio P. PMID: 17471604 [PubMed - indexed for MEDLINE]

INTENSIVE CARE/NEONATAL INTENSIVE CARE

Director: Dr. Pietro Tuo

Staff

Nicola Disma Gaia Giribaldi Leila Mameli Giovanni Montobbio

Activity year 2012

Research projects

Multisite RCT comparing regional and general anestesia for effects on neurodevelopmental outcome in infants – The GAS Study.

This study is aimed at determining whether general and regional anesthesia have equivalent neurocognitive outcomes. Recruitment of patients started in 2008 and was concluded on January 31, 2013. 27 children's hospital in 7 countries have reached the target of 720 newborns. Neurocognitive evaluation is ongoing and will be performed at 2 and 5 years of age with standardized tests. Post-anesthesia apnea will be tho scope of a publication.

Comparative study of sterofundin and physiological solution in major surgery in patients aged below 36 months.

The study is aimed at determining hydroelectrolytic methods after administration of two different intraoperative fluids.

Research programme for 2013

Efficacy of tranexamic acid in surgery of craniostenosis. TXA study

Objective: to determine the efficacy, pharmacokinetics and pharmacogenomics of tranexamic acid administered with two different dosage schemes in surgery of craniostenosis

Description: patients aged between 3 months and 6 years, scheduled for surgical correction of craniostenosis, will be treated with tranexamic acid to reduce intraoperative bleeding and consequent exposure to blood transfusion. Tranexamic acid will be administered according to two different administration schemes. Pharmacokinetics will be determined through assay of blood and urine levels of tranexamic acid. Demographic factors determining the different response of the population to drug administration will be identified through the study of PAI genetic polymorphism.

Main collaborations

- Royal Children's Hospital, and Murdoch Childrens Research Institute, Melbourne, Australia
- Children's Hospital Boston, Boston, US
- Royal Hospital for Sick Children, Glasgow, UK
- Montreal Children's Hospital, Quebec, Canada

Major publications (2007-2012)

1. 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.
2. 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.
3. 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.

4. 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. 2011Aug;27(8):839-46.
5. 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.
6. Pini Prato A, Rossi V, Avanzini S, Mattioli G, Disma N, Jasonni V. Hirschsprung's disease: what about mortality? Pediatr Surg Int. 2011 May;27(5):473-8.
7. 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.
8. Røeggen II, Olischar M, Davidson A, Disma N. Sleep and the EEG in infants. Paediatr Anaesth. 2010 Apr;20(4):368-9.
9. Mattioli G, Buffa P, Torre M, Pini-Prato A, Disma N, Avanzini S, Guida E, Rapuzzi G, Costanzo S, Rossi V, Leggio S, Jasonni V. Preperitoneoscopic approach for bladder neck sling suspension in a boy: preliminary experience. J Laparoendosc Adv Surg Tech A. 2010 Jun;20(5):497-501.
10. Ullmann N, Sacco O, Gandullia P, Silvestri M, Pistorio A, Barabino A, Disma NM, Rossi GA. Usefulness and safety of double endoscopy in children with gastroesophageal reflux and respiratory symptoms. Respir Med. 2010 Apr;104(4):593-9.

NEONATAL PATHOLOGY

Director: Dr. Luca Antonio Ramenghi

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Francesco Traverso
Matteo Bruschettini
Roberta Da Rin Della Mora
Anna Rita Natalizia
Andrea Sannia
Cristina Traggiai

Research programme for 2013

Research projects

Identification of the best technique for weanining from mechanical ventilation for neuroprotection
Objective: identification of the best ventilation technique allowing the lowest number of failures at extubation and of episodes of intraventricular bleeding.
Description: the study will compare two mechanical ventilation techniques (conventional and volume guarantee) in very low weight preterm newborns at high risk of developing hemorrhagic brain lesions. Analysis of the incidence of this disease will be performed through brain echography and MR studies.

Prospective randomized controller trial (proof of concept) on early treament with either high or standard dose caffeine in very preterm infants to evaluate the effects on visual function and respiratory morbidity
Objective: to evaluate: 1) whether a higher dose can improve visual function and respiratory outcome in preterm newborns as compared to the standard dose; 2) whether such a higher dose can improve white matter development measured by MR; 3) pharmacokinetics and pharmacodynamics of both doses in terms of safety and visual function.
Description: Single centre, single blind, randomized, parallel group prospective study. Comparison between two different caffeine dosaages: standard dose vs fourfold dose. Inclusion criteria: newborns with gestational age below 32 weeks admitted to the Neonatal Pathology unit within 24 hours from birth; absence of complete informed consent. Caffeine administration up to 34 weeks of age and until when the newborn has been stable for at least 5 days without the use of positive pressure. Caffeine doses are tapered or suspended in case of signs of toxicity. Statistical data: *closed sequential design*; sample size: 40 patients.
Main collaborations

Neonatology Department, Lund (Sweden) and Stockholm (Karolinska Hospital): Prevent – ROP (EU-funded) study on i.v. administration of IgF1 for the presention of neovascularization of ROP. At Gaslini, visual function test and MR study of maturation of optic pathways will be performed.

Major publications (2007-2012)

1. *Neonatal stroke*. Rutherford MA, Ramenghi LA, Cowan FM. Arch Dis Child Fetal Neonatal Ed. 2012 Sep;97(5):F377-84. doi: 10.1136/fetalneonatal-2010-196451. Review. PMID:22933099
2. Development of the optic radiations and visual function after premature birth. Groppo M, Ricci D, Bassi L, Merchant N, Doria V, Arichi T, Allsop JM, Ramenghi L, Fox MJ, Cowan FM, Counsell SJ, Edwards AD. Cortex. 2012 Mar 8. PMID:22482694
3. Impaired brain growth and neurodevelopment in preterm infants with posthaemorrhagic ventricular dilatation. Jary S, De Carli A, Ramenghi LA, Whitelaw A. Acta Paediatr. 2012 Jul;101(7):743-8. doi: 10.1111/j.1651-2227.2012.02686.x. Epub 2012 Apr 28. PMID:22452585

4. Deep medullary vein involvement in neonates with brain damage: an MR imaging study. Arrigoni F, Parazzini C, Righini A, Doneda C, Ramenghi LA, Lista G, Triulzi F. AJNR Am J Neuroradiol. 2011 Dec;32(11):2030-6. doi: 10.3174/ajnr.A2687. Epub 2011 Sep 29. PMID:21960491

5. The proper tidal volume target using volume guarantee ventilation in the course of neonatal respiratory distress syndrome: a crucial endpoint. Scopesi F, Risso FM, Sannia A, Traggiai C, Arioni C, Zullino E, Campone F, Mezzano P, Massocco D, Baldi F, Serra G. J Matern Fetal Neonatal Med. 2010 Jul;23(7):692-4. doi: 10.3109/14767050903440448. Review. PMID: 19951009

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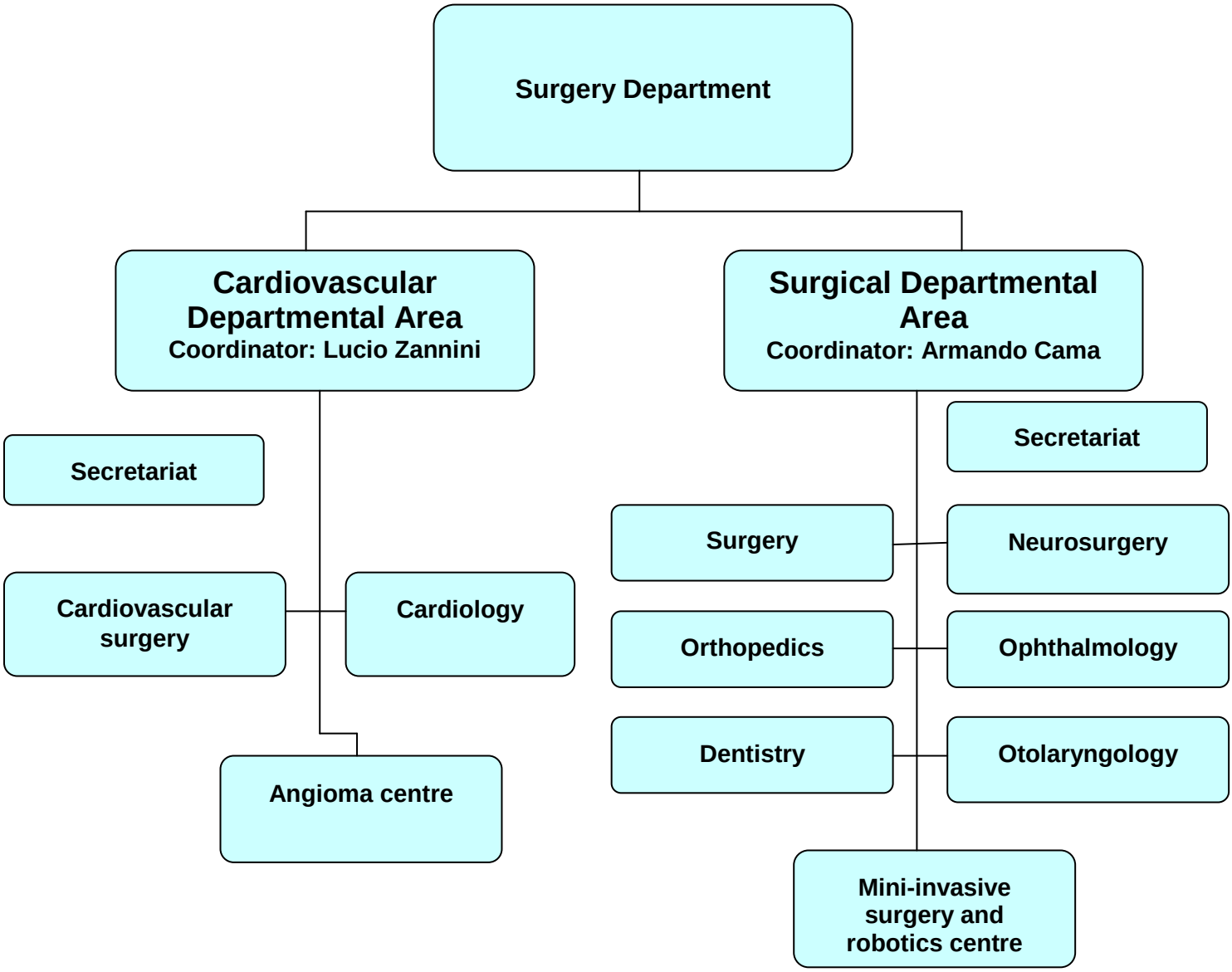
8. Biomarkers of brain damage in preterm infants. Risso FM, Sannia A, Gavilanes DA, Vles HJ, Colivicchi M, Ricotti A, Li Volti G, Gazzolo D. J Matern Fetal Neonatal Med. 2012 Oct;25 Suppl 4:101-4. doi: 10.3109/14767058.2012.715024. PMID: 22958034

9. Lymphatic dysplasias in newborns and children: the role of lymphoscintigraphy. Bellini C, Boccardo F, Campisi C, Villa G, Taddei G, Traggiai C, Bonioli E. J Pediatr. 2008 Apr;152(4):587-9, 589.e1-3. doi: 10.1016/j.jpeds.2007.12.018. PMID: 18346521

10. Vulnerability versus resilience to prenatal stress in male and female rats; Implications from gene expression profiles in the hippocampus and frontal cortex. Van den Hove DL, Kenis G, Brass A, Opstelten R, Rutten BP, Bruschettini M, Blanco CE, Lesch KP, Steinbusch HW, Prickaerts J. Eur Neuropsychopharmacol. 2012 Nov 27. doi:pii: S0924-977X(12)00308-2. 10.1016/j.euroneuro.2012.09.011. PMID:23199416


Surgery Department
Cardiovascular Departmental Area
Coordinator: Lucio Zannini
Surgical Departmental Area
Coordinator: Armando Cama
Secretariat
Cardiovascular surgery
Cardiology
Angioma centre
Secretariat
Surgery
Neurosurgery
Orthopedics
Ophthalmology
Dentistry
Otolaryngology
Mini-invasive surgery and robotics centre

CARDIOVASCULAR SURGERY

Director: **Dr. Luzio Zannini**

Staff

Giuseppe Cervo	Lauralba Di Sabato	Pietro Dalmonte
Giuseppe Panizzon	Elena Ribera	Francesco Santoro
Nadia Vercellino	Alfredo Virgone	

Activity year 2012

Research projects

Efficacy of fenoldopam mesylate in the control of splancnic ischemia during extracorporeal circulation in pediatric patients

Objective: to evaluate whether treatment with Fenoldopam mesylate at the dose of 0.2 γ/Kg/min is able to improve perfusion of the splancnic district and to limit the occurrence of lactic acidosis during CPB in pediatric patients. Treatment will be considered effective if the percentage of patients with hyperlactatemia at the end of CPB results reduced from about 40%, expected value according to our retrospective analysis, to 20%.

Description: The study enrolled 54 patients and was concluded in the first half of 2012. Data were filed in a dedicated database and underwent statistical analysis. Results are being defined and a paper is being prepared.

The primary end point was reached and no drug-related adverse events were reported The following aspects will be evaluated also as secondary objectives: variations of daily diuresis during CPB and during the first 6 postoperative hours and variations of plasma lactates during the first 6 postoperative hours.

Gene expression profile in advanced heart failure: **identification and validation of new biomarkers**

Objective: To identify new biomarkers starting from the analysis of gene expression profile of the cardiac muscle in children with heart failure in congenital cardiopathies undergoing surgery in the Cardiovascular Surgery unit of Gaslini.

Description: The identification of new biomarkers with higher sensitivity and specificity is essential to improve heart failure management. These markers allow the optimization of current therapeutic approaches with benecifical effect for the patient and reduction of hospital stay. Children with selected congenital cardiopathies were enrolled and underwent surgery in the Cardiovascular Surgery unit of Gaslini. In collaboration with the Laboratory of Molecular Biology, where the collected material is studied, the centralization of samples in the biobank-BIT of Gaslini is continued. The collected material is studied through analysis of gene expression profile of the cardiac muscle through microarray technology.

Research programme for 2013

Gene expression profile in advanced heart failure: identification and validation of new biomarkers

The number of enrolled patients is still insufficient. We will continue to collect samples of heart tissue during cardiosurgery and to study gene espression profiles through microarray technology.

Main collaborations

- *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 the neonatal period.
- *Prof Patrick Diner* – Hôpital Trousseau, Paris: Reconstructive maxillofacial plastic surgery for cervico-facial vascular malformation

- *Prof Claude Laurian* - Hopital Saint Joseph, Paris: Surgery of complex musculoskeletal vascular malformations.
- *Dr Michel Wassef*- Hopital Lariboisiere, Paris: Pathologic and cytologic anatomy of complex vascular malformations.

Cooperation projects

Training of medical-nursing staffs and 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.

Major publications (2007-2012)

1. Intra-articular venous malformations of the knee. Dalmonte P, Granata C, Fulcheri E, Vercellino N, Gregorio S, Magnano G. J Pediatr Orthop 2012 32:(4):394-8
2. A case of congenital hypothyroidism in PHACE syndrome. J Pediatr Carinci S, Tumini S, Consilvio NP, Cipriano P, Di Stefano A, Vercellino N, Dalmonte P, Chiarelli F.Endocrinol Metab. 2012;25(5-6):603-5
3. Selective pulmonary artery embolization in two patients with single ventricle and acquired pulmonary vein occlusion. Bondanza S, Derchi M, Marasini M. Catheter Cardiovasc Interv. 2012 Jul 1;80(1):101-6. doi: 10.1002/ccd.23272. Epub 2011 Dec 12.
4. Use of a telescopic system for transcatheter radiofrequency perforation and balloon valvotomy in infants with pulmonary atresia and intact ventricular septum. Bondanza S, Derchi M, Tuo G, Zannini L, Marasini M. Cardiol Young. 2012 Apr 26:1-6. [Epub ahead of print]
5. Impact of prenatal diagnosis on outcome of pulmonary atresia and intact ventricular septum. Tuo G, Volpe P, Bondanza S, Volpe N, Serafino M, De Robertis V, Zannini L, Pongiglione G, Calevo MG, Marasini M. J Matern Fetal Neonatal Med. 2012;25(6):669-74
6. Dexamethasone prophylaxis in pediatric open heart surgery is associated with increased blood long pentraxin PTX3: potential clinical implications. Lerzo F, Peri G, Doni A, Bocca P, Morandi F, Pistorio A, Carleo AM, Mantovani A, Pistoia V, Prigione I. Clin Dev Immunol. 2011:730828 Epub 2011 Jul 9.
7. Tracheal compression by aberrant innominate artery: clinical presentations in infants and children, indications for surgical correction by aortopexy and short- and long-term outcome Chiara Gardella, Donata Girosi, Giovanni A. Rossi, Michela Silvestri, Paolo Tomà, Gianlauro Bava and Oliviero Sacco J Ped Surgery 2010; 45,564-573

8. The Scimitar Syndrome: An Italian Multicenter Study Vladimiro L. Vida, Simone Speggiorin, Massimo A. Padalino, Giancarlo Crupi, Carlo Marcelletti, Lucio Zannini, Alessandro Frigiola, Alessandro Varrica, Duccio Di Carlo, Roberto Di Donato, Bruno Murzi, Massimo Bernabei, Giovanna Boccuzzo, Giovanni Stellin Ann.Thorac.Surg. 2009 Aug;88(2):440-4.

SURGERY

Director: Dr. Piero Buffa

Staff

Giovanni Maria Bisio
Fabio Faranda
Giuseppe Fratino
Lorenzo Leonelli
Alberto Michelazzi
Alessio Pini Prato
Valentina Rossi
Michele Torre
Marcello Carlucci
Silvio Ferretti
Katarina Holm
Girolamo Mattioli
Manuela Mosconi
Luca Pio
Fabio Sanfilippo
Antonella Vaccaro
Sara Costanzo
Monica Firrisi
Federica Icardi
Cinzia Mazzola
Ludovico Muller
Emilio Podestà
Piero Scarsi

Activity year 2012

In 2012, we continued to enroll patients with Hirschsprung's disease. Family history was investigated for previous episodes of enterocolitis and other useful data for the completion of a complex integrated database. All the patients consecutively enrolled in our Institute were also inserted in a programme of genotype and phenotype screening + intestinal tissue sampling for immunologic study (in case of surgery) and stool sampling for meta-genomic study (performed at NIH – Bethesda). Up to November 30, 2012, overall 139 patients were enrolled: 98 of them underwent full screening and therefore could be used for the definition of the phenotype variability of Hirschsprung's disease, for genotype/phenotype correlation, and for the search for possible risk factors.

Research project

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 November 30, 2012, the second year of the three-year project was completed. Since December 1, 2012, we enrolled overall 110 patients, 32 of them undergoing intestinal tissue sampling for immunological study, 110 peripheral blood sampling for DNA extraction (50 trios = proband + both parents), and 89 peripheral blood sampling for the study of gene expression on circulating immune cells. We submitted to *Plos-One* a paper analyzing the preliminary results of the study and focusing on the evaluation of RET proto-oncogene expression on various cell lines of circulating immunity, in patients with Hirschsprung's disease, and on the effect, in the same patients, of RET stimulation on up- or down-regulation of specific inflammatory genes.

Research programme for 2013

Research project

Miniinvasive approach in pediatric surgery: clinical audits, risk management, and guidelines
Introduction: Over the last three decades, mini-invasive surgery (laparoscopy, thoracoscopy, retroperitoneoscopy) progressively imposed itself both in adults and in children. The first laparoscopic cholecystectomy dates back to 1985, though at that time it was considered almost as nonsense. In a few years, however, this procedure became the *gold standard* for the surgical treatment of gallbladder calculosis. Similarly, other surgical interventions, once performed only through a conventional approach, were replaced with the mini-invasive approach (diagnostic laparoscopy, gynecologic laparoscopy, colorectal surgery, splenectomy, etc). Subsequently, miniinvasive surgery was successfully used also in thoracic surgery, urology, and oncologic surgery. Even though pediatric laparoscopic surgery imposed itself later than in the adult, the Pediatric Surgery unit of the Istituto Giannina Gaslini has soon adopted the mini-invasive approach.

To date, a few thousands of diagnostic and/or therapeutic procedures were performed through a mini-invasive approach in our Institute.
Objective: To define the applicability, reliability, and efficacy of endoscopic surgery in pediatrics and to identify any possible critical aspects; to optimize fast-track and costs related to miniinvasive surgery; to define approaches and guidelines to make the optimal results obtained to date reproducible and consistent.
Materials and methods: We will collect preoperative clinical data, diagnosis, surgical description, hospital stay duration, cosmetic and functional result, possible complications, and long-.term follow-up of all patients treated with miniinvasive approach from January 1992 to January 2013. The study period can be extended prospectively when useful and/or indicated according to sample size or medium-term results. The patients will be subdivided into age groups and disease groups. Complications will be divided into perioperative, intraoperative, and postoperative, short-term, and long-term. Functional results will be defined using validated international scores (i.e Visik score), while cosmetic results will be based on subjective impression of patients and their families. Further analyses of procedure-related costs and risk management proactive analyses (i.e. FMECA) will be applied to selected patient groups.
Expected results: We will conduct audits on appendectomy, endorectal pull-through for Hirschsprung's disease, ileo-rectal anastomosis with J-pouch for ulcerative colitis, resection of tumors, positioning of CVC, reconstruction of congenital abdominal malformations, reconstruction of the thoracic wall for pectus excavatum and/or Poland syndrome, and reconstruction of congenital abdominal thoracic, and urologic malformations. Given the present epidemiological incidence observed in our Institute, we will probably analyze data on over 1,000 patients, thus guaranteeing (without additional costs or even with cost restriction) and even improving excellence of care for our patients.

Main collaborations

- Prof. Agostino Pierro, 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

Major publications (2007-2012)

1. 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
2. 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
3. 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
4. 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
5. 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
6. Pini-Prato A, Mattioli G, Giunta C, Avanzini S, Magillo P, Bisio GM, Jasonni V. Redo surgery in

Hirschsprung disease: what did we learn? Unicentric experience on 70 patients. J Pediatr Surg. 2010 Apr;45(4):747-54

7. Pini Prato A, Musso M, Ceccherini I, Mattioli G, Giunta C, Ghiggeri GM, Jasonni V. Hirschsprung disease and congenital anomalies of the kidney and urinary tract (CAKUT): a novel syndromic association. Medicine (Baltimore). 2009 Mar;88(2):83-90
8. Mattioli G, Palomba L, Avanzini S, Rapuzzi G, Guida E, Costanzo S, Rossi V, Basile A, Tamburini S, Callegari M, DellaRocca M, Disma N, Mameli L, Montobbio G, Jasonni V. Fast-track surgery of the colon in children. J Laparoendosc Adv Surg Tech A. 2009 Apr;19 Suppl 1:S7-9
9. Torre M, Buffa P, Jasonni V, Cama A. Long-term urologic outcome in patients with caudal regression syndrome, compared with meningomyelocele and spinal cord lipoma. J Pediatr Surg. 2008 Mar;43(3):530-3
10. Mattioli G, Castagnetti M, Verrina E, Trivelli A, Torre M, Jasonni V, Perfumo F. Laparoscopic-assisted peritoneal dialysis catheter implantation in pediatric patients. Urology. 2007 Jun;69(6):1185-9

NEUROSURGERY

Director: Dr. Armando Cama

Staff

Valeria Capra, Patrizia De Marco, Maria Luisa Garrè, Samantha Mascelli, Elisa Merello, Alessandro Raso

Activity year 2012

Identification of candidate genes involved in the pathogenesis of Neural Tube Defects (NTD)

Neural Tube Defects have a complex hereditary mechanism, due to the interaction of genetic factors with environmental factors, characterized by incomplete penetrance and phenotype variability within the same family. Genetic predisposition to NTD is modulated by the effect of multiple genetic variations, both common and rare, that can play a role in individual risk. It was demonstrated that genes of the Planar Cellular Polarity (PCP) signalling pathway, also called non-canonical *Wnt*, a cascade of molecular events with the ultimate goal of directional polarization of cells on the plane of an epithelium, are involved in NTD pathogenesis both in animal models and in humans. Over the last few years, our group, in collaboration with Dr. Kibar (CHU Sainte Justine Research Center and University of Montreal, Montreal, Canada) identified in overall 629 patients 74 rare mutations (mainly missense) in 7 essential genes of this signalling pathway, including *VANGL1, VANGL2*, *PRICKLE1*, *CELSR1*, *FZD6, DVL2,* and *DVL3,* and in a regulating gene (*FUZ*), that are absent in all analyzed controls. For 51 of these rare variants a pathologic effect was demonstrated on the function of the encoded protein on the basis of both predictive sofware and of *in vitro* and *in vivo* biological tests. These mutations can account for 8-10% of both open and closed NTD cases. These data confirm a model of NTD inheritance in which multiple rare variants in genes of the same signalling pathway have a synergic effect on NTD risk threshold.

Genetic-molecular study of pediatric brain tumors

The study is mainly focused on low-grade glial tumors in children. Even though they are benign tumors, at least 12% of patients show disease progression. It was demonstrated that a genetic polymorphism of *TP53* gene is associated with negative prognosis in those cases that have not received complete resection. In addition, through functional studies on primary tumor cell lines, it was possible to investigate the potential pathogenicity and drug-resistance of these tumors.

Research programme for 2013

Research projects

Sequencing of the whole genome and/or exome in familial and sporadic NTD cases by massive New Generation Sequencing (NGS)

Objective: Sequencing of the whole genome and/or exome of a selected group of affected individuals not included in the group of familial NTD cases by last generation high processivity sequencing technology of Illumina/Solexa platform.

Description: Given the very high clinical and genetic heterogeneity of NTD, in addition to the limited number of known genes, other genes must still be identified both for cases with familial recurrence and for sporadic cases. We intend to adopt a large scale approach using state-of-the-art last generation sequencing technology (Illumina/Solexa platform) to identify rare mutations that can confer susceptibility to NTD. The protocol establishes the preparation of libraries and the generation by PCR of hundreds of millions of clonal clusters that are sequenced by synthesis through the use of dideoxy-reversibile terminators. The produced reads will be aligned on a reference genome, then rare variants will be identified and recorded after filtration through a database of common variants; finally, candidate variants, after validation using gold standard methods (Sanger sequencing), will be interpreted biologically.

Medulloblastoma stem cells: molecular characteristics related to drug resistance

Objective: Biological characterization of medulloblastoma stem cells and identification of molecular characteristics related to drug resistance

Description: Among CNS tumors, medulloblastoma (Mbl) is the most common malignant tumor of pediatric age. Even though. Over the last few years, the survival rate of patients has increased, the more highly aggressive forms still result refractory to conventional therapeutic approaches. Numerous studies show that the aggressiveness of these tumors is due to a subpopulation of tumor cells with stem cell characteristics (*Tumor Initiating Cells*: TICs). In fact, TICs show tumorigenesis ability, resistance to chemo/radiotherapy and high levels of anti-apoptotic factors. We will perform the biological characterization of cells with stem cell phenotype present in Mbl, in order to identify the specific genetic anomalies able to alter their peculiar se*lf-renewal* and differentiation abilities.

Main collaborations

- Dr. Z. Kibar, Department of Obstetrics and Gynecology, CHU Sainte Justine Research Center and University of Montreal, Montreal, Canada
- Dr. Guido Frosina, Istituto Nazionale Ricerca Cancro, Dept. Of Epidemiology, Prevention and Special Functions, Molecular Mutagenesis and DNA repair, Largo Rosanna Benzi 10, 16132 Genova

Major publications (2007-2012)

1. 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
2. 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
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 Mut 2012 Feb;33(2):384-90
4. 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.
5. Seo JH, Zilber Y, Babayeva S, Liu J, Kyriakopoulos P, De Marco P, Merello E, Capra V, Gros P, Torban E. Mutations in the Planar Cell Polarity gene, Fuzzy, are associated with Neural Tube defects in humans. Hum Mol Genet 2011 Nov 15;20(22):4324-4333.
6. 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.
7. P. Nozza, M. L. Casciana, A. Rossi, A. Cama, C. Milanaccio, A. Raso, M. Ravegnani, G. Morreale, M. L. Garre`. Post-chemotherapy maturation of a pineoblastoma. Acta Neuropathol. 2010;119(5):651-3. PMID: 20224924.
8. Kibar Z, Bosoi CM, Kooistra M, Salem S, Finnell RH, De Marco P, Merello E, Bassuk AG, Capra V, Gros P. Novel Mutations in VANGL1 in Neural Tube Defects. Hum Mutat. 2009 Jul;30(7):E706-15.

9. Raso A, Negri F, Gregorio A, Nozza P, Mascelli S, De Marco P, Merello E, Milanaccio C, Ravegnani M, Cama A, Garrè ML, Capra V. Successful isolation and long-term establishment of a cell line with stem cell-like features from an anaplastic medulloblastoma. Neuropathol Appl Neurobiol. 2008; 34(3):306-15. PMID: 17995922.

10. Z. Kibar, E. Torban, J.R. McDearmid, A. Reynolds, J. Berghout, M. Mathieu, I. Kirillova, P. De Marco, E. Merello, J.M. Hayes, J.B. Wallingford, P. Drapeau, V. Capra, and P. Gros. Mutations in VANGL1 are associated with neural tube defects. New England Journal of Medicine, 2007;356: Apr 5;356(14):1432- 1437.

ORTHOPEDICS AND TRAUMATOLOGY

Director: Dr. Silvio Boero

Staff
Maria Beatrice Michelis
Simone Riganti

Activity year 2012

Research project

Retrospective study of axial corrections and limb lengthening in patients with osteochondrodysplasia
The study analyses a cohort of 46 patients aged between 8 and 19 years, including a group of 25 patients with genetically confirmed diagnosis of achondroplasia and a control group of 21 patients with congenital lower limb length discrepancy.
Between January 1994 and December 2007, all the patients underwent lower limb lengthening by femoral and/or tibial osteotomy abd distraction of bone callus with Ilizarov or monoaxial external fixator.
During surgery, in selected patients of both groups, a sample of osteoblastic cells was cultured in vitro to study its differentiation process.
The combined analysis of clinical and in vitro results showed that the significant differences between the two groups in terms of lengthening obtained, consolidation time, and healing index must be ascribed not only to a chondrogenic alteration in achondroplastic patients, as unversally agreed in the literature, but also to alterations in the osteoblastic differentiation processes that would lead to abnormal early mineralization of the matrix in achondroplastic patients.

Research programme for 2013

Research project

Use of guided growth technique in congenital lower limb length discrepancies and in post-traumatic axial deviations in association with de-epiphysiodesis.
Objective: Validation of an original surgical technique which, in the first case, allows the reduction of the number of surgical interventions aimed at the correction of axial deformities associated with limb lengthening, in the second case the correction of deformities due to growth plate injury of the lower limb.
Description: Retrospective analysis of results obtained by surgery, taking into account axial correction and time of correction of deformities in the two diseases according to patients' age.

Major publications (2007-2012)

1. Boero S, Michelis MB, Riganti S.: Use of eight-plate for angular correction of knee deformities due to idiopathic and pathologic physis: initiating treatment according to etiology. J Child Orthop 2011; 5: 209-216.
2. Mantero E, Carbone M, Calevo MG, BS.: Diagnosis and treatmentof pediatric chronic osteomyelitis in developing countries: prospective study of 96 patients treated in kenya. Muscoloskeletal surg. 2011,95: 13-18.
3. Michelis MB, Boero S: trattamento intraosseo di osteonecrosi asettica con concentrato piastrinico e cellulare autologo ed osso sintetico: case report in eta' pediatrica. 2011.www.touchmculoskeletal.com
4. Di Stadio M., Becchetti F., Boero S.: Correction of pronation syndrome by subtalar arthrodesis with talar cone-shaped screw in developmental age. j orthop traumat, 2009, 10 supp.1, s29.
5. Boero S, Sénès FM, Catena N. Pediatric cubital tunnel syndrome by anconeus epitrochlearis: a case report. J Shoulder Elbow Surg. 2009 Mar-Apr;18(2):e21-3.

Staff

Filippo M. Sénès
Nunzio Catena

Activity year 2012

Research project

Medium-long-term review of the treatment of brachial plexus obstetrical palsies
The authors have completed a medium-term retrospective study on 32 patients with brachial plexus obstetrical palsy, treated by selective neurotization (use of a healthy nerve to resuscitate a damaged nerve) of muscular groups that did not recover their function, either as first surgical act during incomplete spontaneous recovery or after primary nerve repair of the brachial plexus.
The study is original in that reinnervation of muscular groups was performed later compared to surgical interventions reported in the international literature, exploiting the ability of nerve regeneration in the child that allows longer treatment time than in the adult.
Statistical analysis, carried out in collaboration with prof. Ivano Repetto from the Department of Statistical Analysis of the University of Genova, showed that, in patient age groups, older age at surgery did not correspond to increased negative results, thus supporting the surgical indication even long after the perinatal nerve injury.

Research programm for 2013

Research project

Proposal of a new surgical technique for the correction of flexed elbow as a sequela of brachial plexus obstetrical palsy.
Objective: Validation of an original surgical technique allowing cosmetic and functional improvement of contracture in flexed elbow as a sequela of brachial plexus obstetrical palsy.
Description: Retrospective analysis of results obtained with parcellar resection of olecranon and elbow anterior arthrolysis, with a subjective evaluation of the patient by the administration of the DASH test (international test on disabilities of arm, shouder and hand) and an objective evaluation of surgeons, taking into account pre- and post-surgical range of motion, measured by clinical and radiographic examination of the elbow.

Major publications (2007-2012)

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. 2011 Nov 22.
6. Senes FM, Campus R, Becchetti F, Catena N. Upper limb nerve injuries in developmental age. Microsurgery. 2009;29(7):529-35.

7. Torre M, Baban A, Buluggiu A, Costanzo S, Bricco L, Lerone M, Bianca S, Gatti GL, Sénès FM, Valle M, Calevo MG. Dextrocardia in patients with Poland syndrome: phenotypic characterization provides insight into the pathogenesis. J Thorac Cardiovasc Surg. 2010 May;139(5):1177-82.

8. Senes FM, Campus R, Becchetti F, Catena N. Sciatic nerve injection palsy in the child: early microsurgical treatment and long-term results. Microsurgery. 2009;29(6):443-8.

9. Catena N, Sénès FM. Obstetrical chondro-epiphyseal separation of the distal humerus: a case report and review of literature. J Perinat Med. 2009;37(4):418-9.

10. Boero S, Sénès FM, Catena N. Pediatric cubital tunnel syndrome by anconeus epitrochlearis: a case report. J Shoulder Elbow Surg. 2009 Mar-Apr;18(2):e21-3.

11. Senes FM, Campus R, Becchetti F, Catena N. Lower limb nerve injuries in children. Microsurgery. 2007;27(1):32-6.

SCOLIOSIS CENTRE

Staff

A. Andaloro
F. Becchetti
A. Barbangelo

Activity year 2012

Research Project

Study of the bone-metal interface in vertebral implants
Studies carried out in collaboration between the Orthopedics unit of Gaslini and the Dept. if Applied Mechanics (DI.MEC.) of the University of Genova have been completed. These studies, aimed at the analysis of biocompatibility of vertebral implants, allowed the understanding of some triggering mechanisms of implant rupture, on the basis of their structure and material. The results obtained, included in a University degree thesis and presented in occasion of international meetings, will be published in a scientific journal.

Research programme for 2013

Research project
Vertebral tuberculosis in pediatric patients
Objective: Testing and proposal of diagnostic-therapeutic pathways
Description: Analysis of a series of patients with vertebral tuberculosis, taking into account clinical picture, diagnostic tools, and therapy.

Major publications (2007-2012)

1. “Correction of pronation syndrome by subtalar arthrodesis with talar cone-shaped screw in developmental age” M. Di Stadio, F. Becchetti, S. Boero. J Orthop Traumat, 2009 10 Supp. 1, S29

Staff

Mauro Di Stadio

Activity year 2012

Research projects

Morphological changes of the cartilagineous and fibro-ligamentous components of the foot
For several years, in the Orthopedics unit of Gaslini, Ponseti method has been adopted for the correction of congenital clubfoot.
From the anatomic pathology point of view, the deformity consists of malpositions of tarsal bones, which undergo extreme flexion, abduction, and inversion, all maintained by capsular, ligamentous, and tendineous retractions.
The technique includes a progressive correction by reducing cavus deformity and talonavicular subluxation, and by recreating the correct talocalcaneal angle through weekly manipulations followed by the immediate application of immobilizations involving the whole lower limb.
Bones and joints are remodeled at each new immobilization since, in very young subjects, the properties of connective tissue, cartilage, and bones allow a response to the exerted mechanical stimuli.
Our study seems to confirm the good results obtained by Ponseti and other orthopedic surgeons who use his technique, provided that adherence to treatment is complete, with use of a fixator, after reaching correction, for few hours a day until 3 to 4 years of age.

Research programme for 2013

Research project

Morphological changes of the cartilagineous and fibro-ligamentous components of congenital clubfoot
Objective: Clinical and instrumental validation of a treatment (Ponseti method) that has revolutionized in newborns the therapeutic approach to one of the most frequent lower limb malformations, avoiding the adoption of more or less invasive surgical techniques that showed important limitations over time.
Description: Retrospective analysis of the results obtained by comparing clinical pictures with the corresponding instrumental examinations such as CT, X-ray, and/or MR before, during, and after treatment.

Major publications (2007-2012)

1. “Il piede torto congenito equino-varo-supinato. Trattamento incruento: quali opzioni?” M. Di Stadio, R. Schiavon. Progressi in Medicina e Chirurgia del Piede “Il piede pediatrico” 19 (2010) pag. 99-107, Timeo Editore, Bologna.
2. “Aspetti ortopedici nella Sindrome Proteus” M. Di Stadio. Atti del Convegno “Aspetti ortopedici nelle malattie rare” pag. 28-31, Genova 2011.
3. “Correction of pronation syndrome by subtalar arthrodesis with talar cone-shaped screw in developmental age” M. Di Stadio, F. Becchetti, S. Boero. J Orthop Traumat, 2009 10 Supp. 1, S29.

OPHTHALMOLOGY

Director: Prof. Paolo Capris

Staff

Paola Camicione
Enrico Priolo
Elisa Tassara
Riccardo De Marco
Carlo Sburlati
Simona Panarello
Enrica Spaletra

Activity year 2012

Research projects:

- Non-interventional, prospective, longitudinal cohort study for the evaluation of safety of long-term treatment with Xalatan in the pediatric population
- Study n. A6111143 supported by Pfizer
- Study on patients with congenital glaucoms under treatment
- Morphological evaluation of the papilla by optical coherence tomography in Sturge-Weber angiomatosis

Research programme for 2013

Research project

Non-interventional, prospective, longitudinal cohort study study for the evaluation of safety of long-term treatment with Xalatan in the pediatric population - Study n. A6111143 supported by Pfizer

Objective: evaluation of side effects of the topical use of anti-glaucoma drug Xalatan in patients with congenital glaucoma in pediatric age, in particular mutations of iris color, lashes, and corneal thickness
Description: enrolment of pediatric patients admitted to Istituto Giannina Gaslini under treatment with Xalatan for at least 1 month and recording of eye parameters by diagnostic examinations (pachymetry, photograph of anterior and posterior segments, measurement of corneal diameters and tonometry).

Main collaborations

- Ophthalmology Clinic, University of Genova
- “David Chiossone” Institute

Major publications (2007-2012)

1. Barabino Arrigo, Gandullia Paolo, Calvi A, Vignola Silvia, Arrigo Serena, De Marco Riccardo. Sudden blidness in a child with Crohn's disease. World J Gastroentero 2011;17(38):4344-6.
2. Iester M, Capris E, De Feo F, Polvicino M, Brusini P, Capris Paolo, et Al. Agreement to detect glaucomatous visual field progression by using three different methods: a multicentre study. Brit J Ophthalmol 2011;95:1276-83.
3. Iester M, Corallo G, Capris E, Capris Paolo. Agreement in detecting glaucomatous visual field progression analysis and Humphrey overview printout. Eur J Ophthalmol 2011;21(5):573-9.
4. Midena E, Vujosevic S, Cavarzeran ScD, for the Microperimetry Study Group, Capris Paolo. Normal values for fundus perimetry with the microperimeter MP1. Ophthalmology 2010;117:1571.

5. Camicione P, Fodor E, Pannarello S, Barabino S. Retinal peripapillary nerve fiber layer thickness in a 13-year-old boy with neuromyelitis opticaEur J Ophthalmol. 2010 Mar-Apr;20(2):485-8..Ophthalmology Unit, Giannina Gaslini Institute, Genova, Italy.

OTOLARYNGOLOGY

Director: Dr. Vincenzo Tarantino

Staff

Roberto D'Agostino
Andrea Melagrana
Adelina Porcu

Activity year 2012

Pediatric ENT diseases: clinical and epidemiological aspects
In the field of diagnosis and treatment of laryngeal and tracheal diseases, we started a retrospective study on the incidence of laryngomalacia (LM) in newborns, on the number of surgically treated patients (both absolute and relative percentages), and on the association between best anesthesiology procedure and more effective and conservative surgical procedure. To this end, the availability of a double laser instrument (CO2 and diods) allows the treatment of a wide range of patients with personalized anesthesiology techniques according to age, degree of LM, and anatomical conditions of the laryngeal district. In addition, we evaluated the possibility of an endoscopy-based classification of LM severity to be associated with clinical classification, in order to reach a more accurate staging of LM, based on endoscopy and symptomatology, and therefore a more objective identification of cases to be treated surgically.

Research programme for 2013

Research project

Pediatric ENT diseases: clinical and epidemiological aspects
Objective: Identification of LM etiopathogenesis and new anesthesiology/surgical procedures.
In order to identify the etiopathogenesis of this disease, which is still not clear, we developed a detailed questionnaire to be submitted to parenst of newborns with LM. This questionnaire explores many moments of the life and behaviour of mother and fetus during pregnancy, useful to evaluate their possible effect on onset of LM.
Concerning the improvement of surgical techniques and further increase in patient safety and intra- and postoperative risk reduction, we will evaluate the possible application of Jet-ventilation anesthesiologic technique to laryngo-tracheal endoscopic surgery in children. This technique, which is not new, has been improved by further acquisitions and changes over the last few years, however at present it is applied in the adult or at older ages compared to our reference age range.

Main collaborations

- Tracheal team
- Reumatology (PFAPA)
- Physical Therapy - Radiology – Neuromuscular Diseases – Neurosurgery – ICU/NICU – Swallowing disorders
- Otolaryngology, Audiology, and Phoniatrics – University of Pisa- Prof. Stefano Berettini
- CHUV Lausanne – ENT Department – Prof. Philippe Monnier

Major publications (2007-2012)

1. A.Melagrana, S.Casale, M.C.Calevo, V.Tarantino: MB11 BERAphone and auditory brainstem response in newborns at audiologic risk: comparison of results. Int. J. Ped. Otorhinolaryngology: 71, 1175, 2007.
2. S. Casale, A.Melagrana, P.Di Pietro, P.O.Gianiorio, O.Sacco, R.Vallarino, V.Tarantino: Foreign bodies in airways. Ital. J. Pediatr. 33, 226, 2007.

3. E.Rognone, A.Rossi, M.Conte, P.Nozza, V.Tarantino, A.Fibbi et al: Laryngeal schwannoma in a 8-year-old boy with inspiratory dyspnea. Head and Neck surgery: 310, 17, 2007
4. M.G. Calevo, P. Mezzano, E. Zullino, P.Padovani, F. Scopesi, G. Serra, V.Tarantino et all.: Neonatal hearing screening model: An Italian regional experience. J. Mat.Fet. Neon. Ned. Med.: 441, 20, 2007
5. R.D'Agostino, V. Tarantino, M.G. Calevo: Blunt dissection versus electronic molecular resonance bipolar dissection for tonsillectomy: operative time and intraoperative time intraoperative and postoperative bleeding and pain. Int. J. Ped. Otorhinolaringology: 72, 1077, 2008.
6. R.D'Agostino, V. Tarantino, M.G.Calevo: Post-tonsillectomy late haemorrage: it is a preferablynight-time event? Int. J. Ped. Otorhinolaringology: 73, 713, 2009.
7. 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
8. G. Motta, P. Cassano, S.Conticello, V.Tarantino et al. A multicentric study on: guidelines and (Adeno-)Tonsillectomy. Acta Otorhinolaringol. 5, 32, 2011.
9. 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.

DENTISTRY

Director: Dr. Roberto Servetto

Staff

Enrico Calcagno
Laura Ailunno

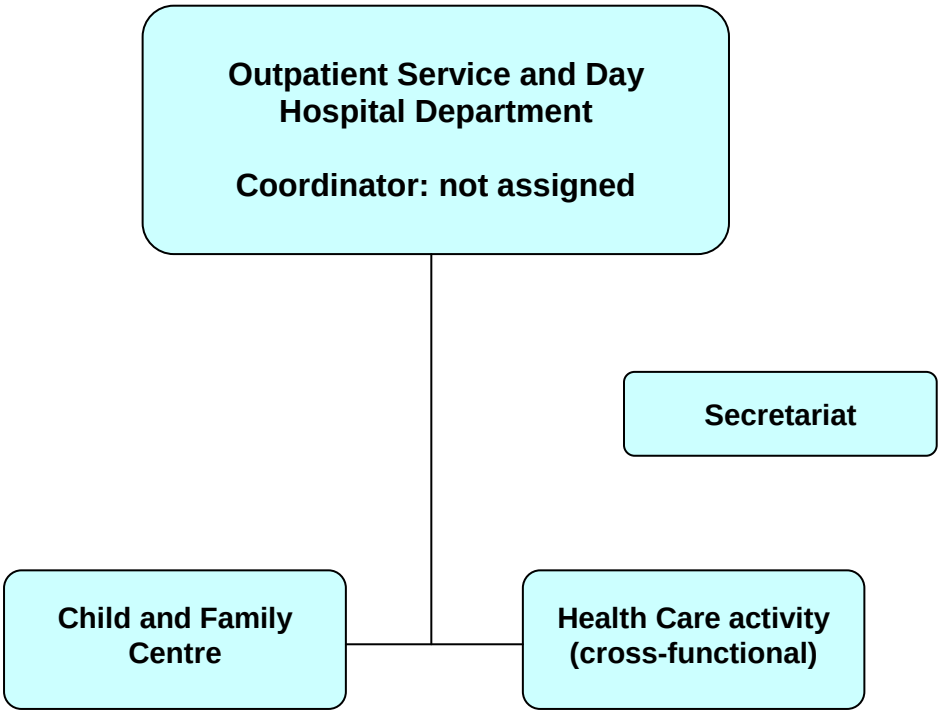
Activity year 2012

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 2013

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
Coordinator: not assigned
Secretariat
Child and Family Centre
Health Care activity (cross-functional)