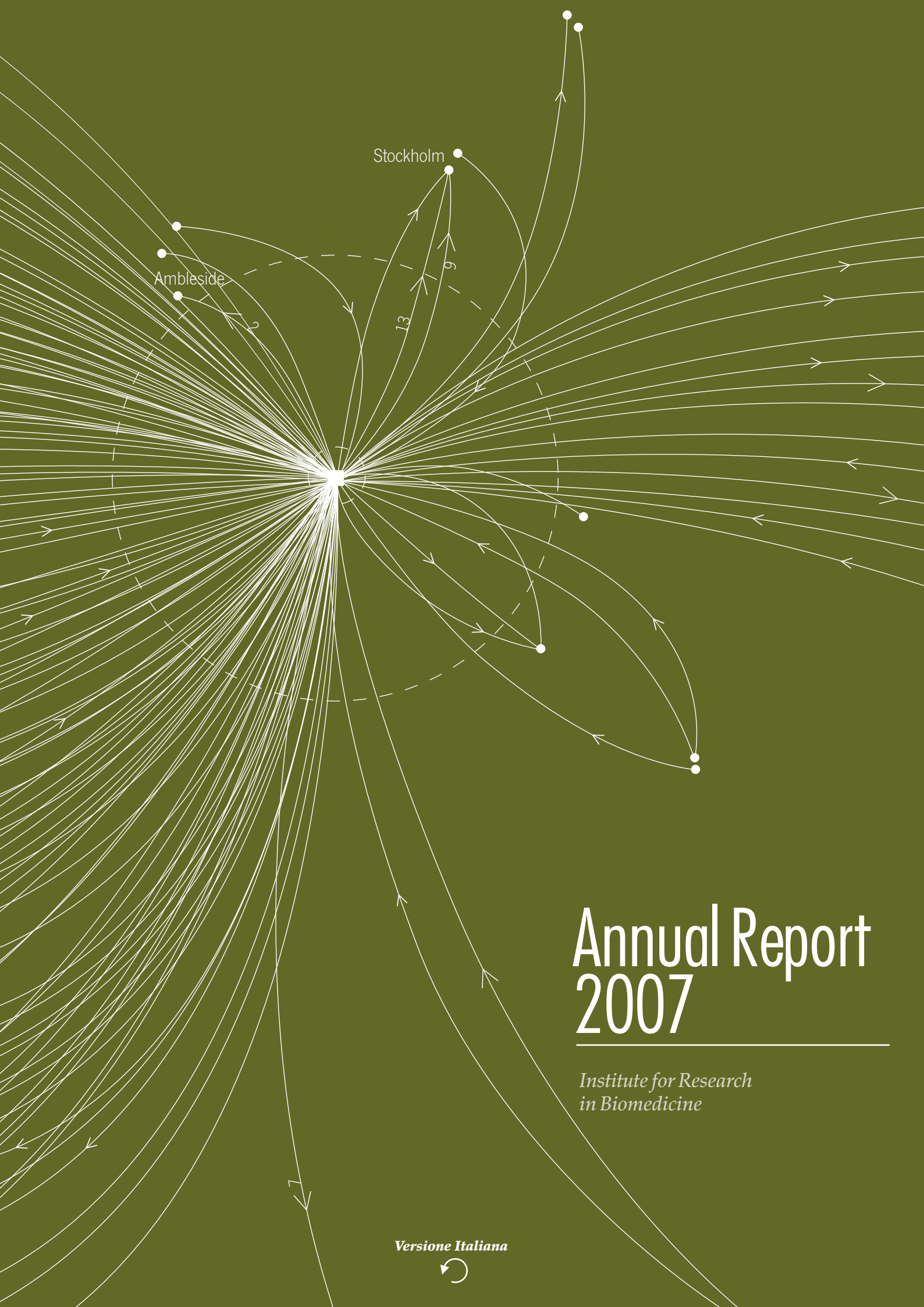
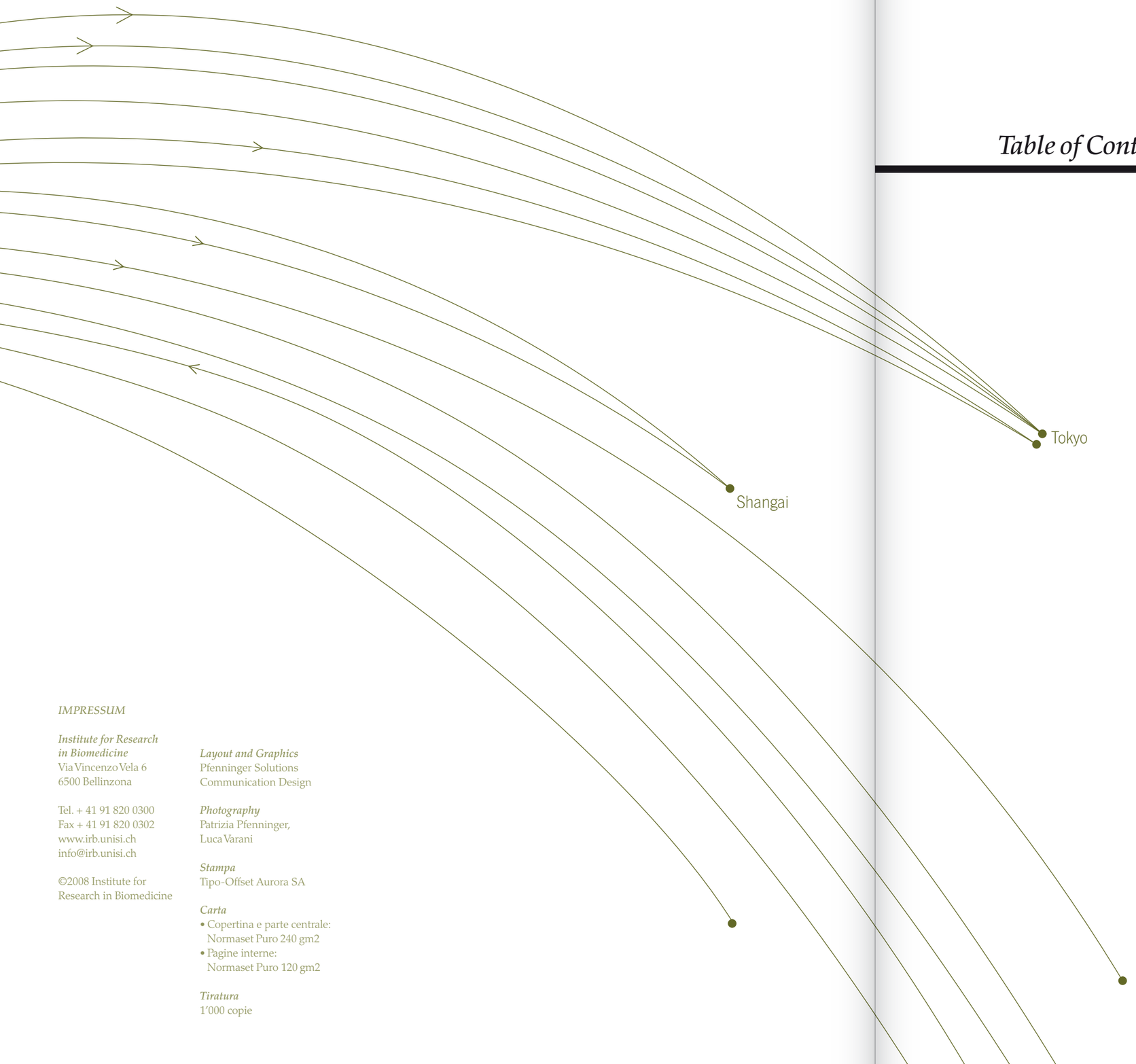


Annual Report 2007

Institute for Research in Biomedicine

Versione Italiana



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IMPRESSUM

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Professor Giorgio Noseda, President of the Foundation Council

This report describes the activity of the Institute for Research in Biomedicine (IRB) during the year 2007, a year characterized by consolidation of the institute and by the strengthening of the connections with Swiss Academe. Our researchers and students have produced relevant results and we have renewed and redoubled our efforts in offering them ideal conditions to pursue their scientific goals at the highest level. The Foundation Council of the IRB has welcomed Professor Walter Schaffner of the University of Zurich as a member.

The consolidation of the institute in 2007 opens the prospective for further growth and productivity in the medium and long term. The Confederation and the Canton have renewed and increased their support of the IRB for the period from 2008-2011 in recognition of the excellence of the institute.

In April, the second site of the IRB was inaugurated in Via Murate. This building houses highly specialized laboratories built in response to urgent need for such facilities. While these immediate needs were met, we foresee an increasing need for still more space. In this new building the Swiss division of the company Humabs has rented laboratory space. Humabs is a company dedicated to developing patented technology produced by the IRB in the laboratory of the Director, Professor Antonio Lanzavecchia.

The City of Bellinzona has agreed to continue to pay the rent in our two buildings for the next ten years. Further, they have proposed to designate an important plot of land and a financial contribution toward the building of a new single site for the IRB in via Murate, near the renovated facilities.

Important investments in the infrastructure and the purchase of new instruments such as a confocal microscope, have made the IRB more competitive on an international level. Thanks to public support, the hard work of the Foundation Council, and the ability of IRB researchers to attract competitive grants, the balance sheet of the IRB has registered expenditures of 16.3 million Swiss francs, an increase of 5 million compared with 2006, and closing with an advance of 95'000 Swiss francs.

In 2007 the IRB has increased its connection within the network of Swiss academic institutions, formalizing several relationships to allow further and deeper collaborations. Among these, the Swiss Vaccine Research Institute (SVRI) is perhaps the most innovative. Founded by the IRB, the Centre Hospitalier Universitaire Vaudois/University of Lausanne (CHUV), the Ecole Polytechnique Fédérale de Lausanne (EPFL) and the Ludwig Institute for Cancer Research (LICR), the SVRI is dedicated to the research of vaccines against AIDS, malaria and tuberculosis. This institute is funded by research grants from the Bill and Melinda Gates Foundation and matching grants from the Confederation of 7 million Swiss francs for the period of 2008-2011.

At the cantonal level the IRB is involved in the creation of a network connecting the Università della Svizzera Italiana (USI), the Swiss Center for Computational Science (CSCS), the Oncology Institute of Southern Switzerland (IOSI) and the IRB through the funding of collaborative research projects in the important field of Computational Biology. Dr. Luca Varani, who recently joined the IRB from Stanford University, is working in this network on a project to study the interactions, at a molecular level, of antibodies with the virus that causes Dengue Fever.

The IRB has recently drafted a letter of understanding together with the Eidgenössische Technische Hochschule Zürich (ETH) outlining the conditions for a close association to permit and encourage powerful collaborations in teaching and research.

We are grateful to all of our donors, both public and private, for their continued and increasing support, and in particlar to the Helmut Horten Foundation and the Ruth and Gustav Jacob Foundation.

Giorgio Noseda, MD
President Foundation Council

Professor Antonio Lanzavecchia, Director of the Institute for Research in Biomedicine

The present 2007 Annual Report provides an overview of the main activities performed at the Institute for Research in Biomedicine in Bellinzona, Switzerland.

Two junior research groups have been recruited during this period. Silvia Monticelli, from Harvard University, works on micro-RNAs, an emerging field with impact in development and oncology. Luca Varani, from Stanford University, works on structural aspects of protein-protein, RNA-protein interactions. His research is performed in collaboration with the University of Southern Switzerland (USI) and the Centro Svizzero di Calcolo Scientifico (CSCS) with financial support from the Cantone Ticino.

The IRB continues to play an important role in education by training graduate students through collaborations with Swiss Universities, in particular Basel, Bern, Fribourg, Lausanne and Zurich and participates in the international PhD program with the Vita-Salute San Raffaele University in Milan, Italy, and in the EU-funded International Graduate Program in Molecular Medicine. The students at the IRB benefit from an intensive lecture series held by renowned scientist from all over the world, organized with the generous support of the Gustav & Ruth Jacob Foundation. In 2007, 29 graduate students and 2 undergraduate students have been working at the IRB and 4 students have successfully completed their doctoral training.

Research at the IRB has increasingly focused on the study of host defense mechanisms in the human system. IRB researchers have developed coherent programs that have the potential to be translated into novel therapies. Manz and colleagues have shown that mice reconstituted with a human hemato-lymphoid system can be successfully infected with viruses that target human cells but normally do not infect animals. The need to advance the study of the human immune system is illustrated by the finding by Sallusto and colleagues that the development of a particular type of inflammatory effector cells, called Th17, is differentially regulated in humans as compared to mice.

A very dynamic program stems from the development of a proprietary method to clone human memory B cells which has been licensed to a startup company, Humabs, that has established its laboratories in Bellinzona. Using this method, neutralizing antibodies against the avian infuenza A virus have been isolated and showed to protect animals from a lethal challenge with the virus. These antibodies can be used not only to confer immediate protection by passive administration to virus-exposed or infected individuals, but also as tools to identify the antigens that elicit neutralizing antibodies, a process that we defined as "analytic vaccinology".

Another example of how basic research can open new therapeutic avenues comes from Molinari's laboratory where they have shown in a model system that an antibody can inhibit the formation of Alzheimer lesions *in vivo*. The translational programs above stem directly from strong basic research, which remains the mission of the Institute. The research at the Institute in 2007 has generated 26 publications that are listed in this report.

The excellence of research performed by IRB scientists is witnessed by their success in obtaining grants from several agencies (e.g. Oncosuisse, the Swiss National Science Foundation, the European Union, the Bill & Melinda Gates Foundation, the Wellcome Trust, and the US National Institute of Health), and by the invitations to give lectures and seminars at international conferences and academic institutions.

The IRB is a Founding member of the Swiss Vaccine Research Institute (SVRI) together with the CHUV, the EPFL and the Ludwig Institute in Lausanne. The aim of the SVRI is to boost vaccine research and development via creation of common platforms and recruitment of young talent.

The urgent need to expand laboratory space, core facilities and the animal house has been partially met by the rapid refurbishment of a new building called IRBis located a few hundred meters from the main site, and by establishing a cutting edge imaging facility, generously supported by private donations and the Confederation. We are grateful to the City of Bellinzona for hosting us in these two buildings and for sharing our vision of the future.

The Institute is especially fortunate in receiving core funding from its main sponsors, the Helmut Horten Foundation, the Cantone Ticino and the Swiss Confederation. Our gratitude also goes to the many individuals who support us through donations and fellowships. We hope that the progress and achievements of the Institute will reward their dedication to the advancement of science.

Antonio Lanzavecchia, MD
Director

IRB International PhD Program in Immunology, Cell Biology and Biochemistry

The IRB provides high-level scientific education both for undergraduate students in the form of short stages and experimental diploma thesis, as well as for graduate students.

The PhD program is carried out in collaboration with Swiss and foreign universities. The experimental work is performed at the IRB under the direct supervision of a Group Leader. The program includes seminars, lessons, summer courses and an annual retreat. An International Lecture Course is organized every year as part of the IRB International PhD Program in Immunology, Cell Biology and Biochemistry. Lectures are given by visiting experts with international reputations. Currently the IRB has 29 students. Since the beginning of the program 25 PhD theses have been successfully defended.

Lectures in 2007

The PhD Lecture Series is made possible through the generosity of the Gustav and Ruth Jacob Foundation

a• *Hilde Cheroutre (USA)*
Non-classical T cells
January, 18

b• *Klaus Ley (USA)*
Cell recruitment in inflammation
February, 12

c• *Mette Rosenkilde (DE)*
Pharmacology of 7TMR antagonists
March, 1

d• *Wilhelm Krek (CH)*
Signaling networks in human diseases
March, 13

e• *Charles M. Rice (USA)*
Hepatitis C virus
March, 23

f• *Radek Skoda (CH)*
Myeloproliferative diseases
April, 20

g• *Ton N. Schumacher (NL)*
Adaptive immunotherapy of cancer
May, 24

h• *Michael McHeyzer-Williams (USA)*
Antigen specific memory B cell development
October, 10

i• *Gisou van der Goot (CH)*
Bacterial toxins
October, 31

j• *Oreste Acuto (UK)*
Signal transduction in T lymphocytes
November, 6

k• *Eric Vivier (F)*
NK cell biology
November, 14


70%
LABORATORY FILM
PARAFILM
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BROUWER
BLUE ICE HERE
Electrophoresis Power Supply - EPS 3501

Financial Data 2007

The year 2007 was very positive in terms of the financial consolidation of the institute and saw an important increase in research projects funded by international agencies. The overall costs of the institute increased from 11,3 million to 16 million, covered entirely by current revenue.

From the point of view of investments, 2007 should be considered exceptional in that during the year new facilities were opened with building costs of 1.7 million and equipment costs of 2.5 million. Individual donors and friends of the institute covered these extra-costs.

Balance Sheet as 31 of December 2007

ASSETS		31.12.2007	31.12.2006
1.	*Liquidity*	5'668'643	2'394'252
2.	*Various Receivables*	1'385'480	1'915'242
3.	*Temporary Receivables*	1'200'135	1'034'999
	Current Assets	*8'254'258*	*5'344'493*
4.	*Buildings*	6'129'940	5'274'945
5.	*Furnishing & Equipment*	2'802'000	3'583'000
	Fixed Assets	*8'931'940*	*8'857'944*
	Total Assets	17'186'198	14'202'438

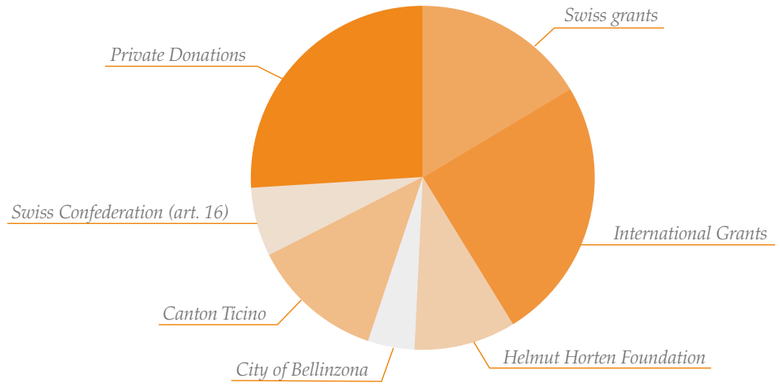
LIABILITIES		31.12.2007	31.12.2006
1.	*Debt for Delivery and Services*	1'117'970	487'441
2.	*Accruals*	341'050	272'979
3.	*Funds for Research Projects*	1'816'160	1'199'979
4.	*Funds for Laboratories*	1'559'005	1'370'250
5.	*Various Funds*	950'000	264'996
	Current Liabilities	*5'784'185*	*3'595'645*
6.	*Long Term Loans*	4'500'000	3'800'000
	Long Term Liabilities	*4'500'000*	*3'800'000*
7.	*Capital Resources*	6'806'793	8'136'725
8.	*Annual Result*	95'220	-1'329'932
	Equity of the Foundation	*6'902'013*	*6'806'793*
	Total Liabilities	17'186'198	14'202'438

Profit and Loss Account for the year 2006 and 2007 (In Swiss Francs)

COSTS		2007	2006
1.	*Personnel Costs*	5'819'323	4'903'221
2.	*Consumables*	2'203'889	1'677'051
3.	*Maintenance of Buildings and Equipment*	408'568	359'778
4.	*Investments*	2'547'655	677'524
5.	*Amortizations*	1'645'260	674'135
6.	*Rent and Related Costs*	1'117'212	883'886
7.	*Administrative Costs and Various*	1'151'127	974'792
8.	*Travel Congresses and Guests*	360'620	306'606
9.	*Various Costs for Research*	754'700	851'909
	Total Costs	16'008'354	11'308'902

REVENUE		2007	2006
1.	*Contributions from the Confederation*	1'088'000	1'105'000
2.	*Contributions from the Canton Ticino*	2'000'000	0
3.	*Contributions from the City of Bellinzona*	665'000	500'000
4.	*Contributions from the Helmut Horten Foundation*	1'500'000	1'500'000
5.	*Other Contributions*	3'826'777	974'706
6.	*Research Projects*	5'974'220	4'851'391
7.	*Other Revenue*	1'049'577	1'047'873
	Total Revenue	16'103'574	9'978'970
	ANNUAL RESULT	95'220	-1'329'932

Funding by Source

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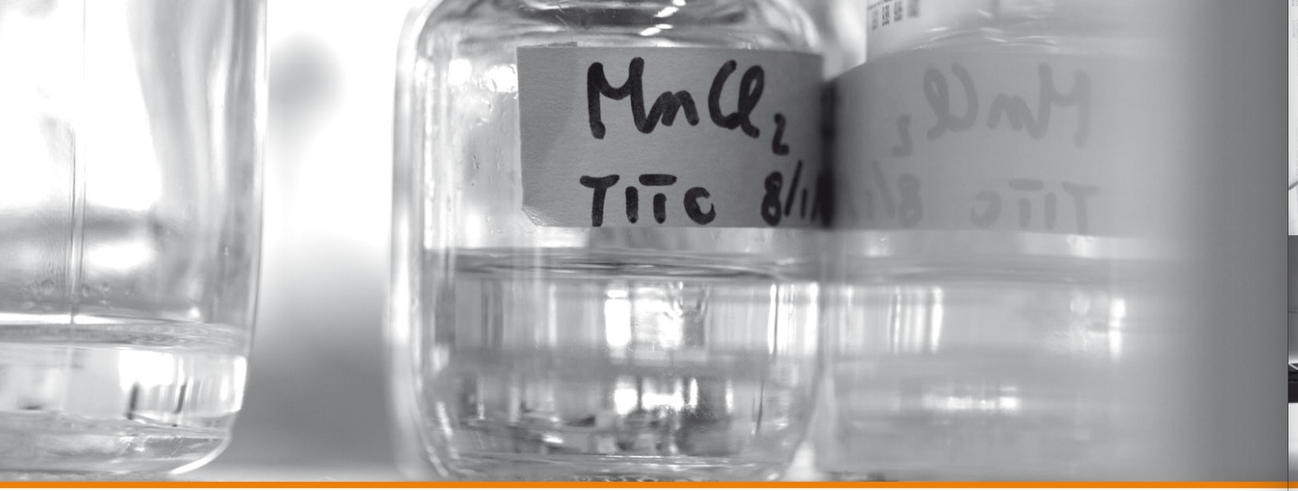
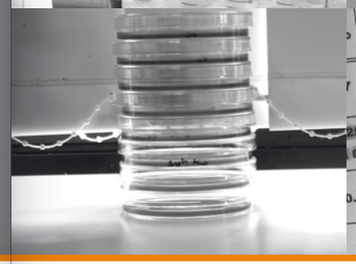
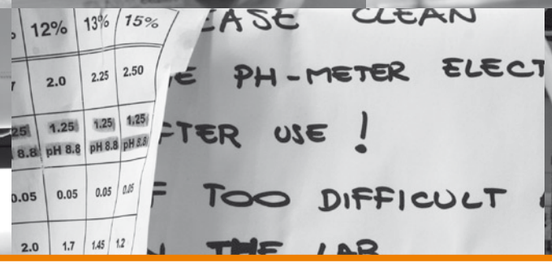






Group Leaders

MAURIZIO MOLINARI

Protein Folding and Quality Control
>> pag. 17

• Maurizio Molinari earned his PhD in Biochemistry at the ETH-Zurich in 1995. From 1996-1997 he was a post-doc in the laboratory of Cesare Montecucco at the Dept. of Biomedicine, University of Padua, Italy and subsequently in the laboratory of Ari Helenius at the ETH-Zurich (1998-2000). Since October 2000 he is a Group Leader at the IRB in Bellinzona.

MARCUS THELEN

Signal Transduction
>> pag. 17

• Marcus Thelen obtained his PhD in 1985 from the University of Bern studying the bioenergetics of mitochondria. He was a PostDoc at the Theodor-Kocher Institute in Bern from 1985 to 1989, later from 1989 to 1991 at the Rockefeller University in New York. In 1992 he was awarded a START fellowship from the Swiss National Science Foundation and headed a laboratory at the Theodor-Kocher Institute, University of Bern. Since 2000 he is a Group Leader at the IRB. In 1994 he obtained the Venia Docendi and later in 2001 was awarded an Honorary Professor title from the University of Bern where he still is member of the Medical Faculty. Prof. Thelen has published more than 60 papers. His research covers several aspects of biochemistry, cell biology and human immunology. His focus is on signal transduction in chemokine receptor mediated cell activation and migration.

FABIO GRASSI

T Cell Development
>> pag. 17

• Fabio Grassi earned his degree in Medicine at the University of Pavia and a PhD in Microbiology at the University of Milan. He worked at the University of Umeä in Sweden, the Institut Pasteur and Hopital Necker in Paris as well as the San Raffaele Scientific Institute in Milan. He has been a Special Fellow of the Leukemia & Lymphoma Society at Harvard Medical School in Boston. He is Associate Professor of Biology at the University of Milan. In September 2002, he joined the IRB as head of the T Cell Development lab. His research is focused on molecular as well as cell biology of T cell differentiation in the thymus; signal transduction of the T cell in secondary lymphoid organs and in T cell mediated inflammatory conditions.

MARKUS G. MANZ

Haematopoesis
>> pag. 18

• Markus Manz received his university degree as M.D. in 1995 at the Eberhard-Karls-University Medical School in Tuebingen, Germany, where he also finished his thesis work in 1996 at the department for Transplantation Immunology. Between 1995 and 1999, he trained in internal medicine at Tuebingen University. From 1999 to 2001 he worked as a postdoctoral fellow in the laboratory of Irving Weissman at Stanford, USA. In 2002 he became Group Leader at the IRB. Since September 2006 he is Group Leader at the IRB and attending hematologist at the Oncology Institute of Southern Switzerland (IOSI), Bellinzona. His research focuses on blood stem cells, hemato-lymphoid development, as well as on hemato-lymphoid malignancies. Recently, he also became interested in infectious agents that directly target the hemato-lymphoid system such as HIV. Markus Manz is a receipient of the Artur-Pappenheim Award of the German Society of Hematology and Oncology.

JEREMY LUBAN

Viral Replication, Pathogenesis and Immunity
>> pag. 18

• Jeremy Luban earned an M.D. at the College of Physicians and Surgeons, Columbia University in New York, in 1987. He underwent clinical training in Internal Medicine and Subspecialty fellowship training in Infectious Diseases, as well as postdoctoral training in Biochemistry in the laboratory of Stephen Goff. He became a Professor at Columbia University with dual appointments in the Department of Medicine (1993) and the Department of Microbiology (1995). In addition to teaching medical students, physicians, and PhD graduate students he served as director of the Columbia-Rockefeller Center for AIDS Research. His laboratory focuses on host factors that regulate HIV-1 replication and confer innate immunity to this deadly virus. Among the HIV-1 regulatory factors discovered by his lab are the human proteins cyclophilin A and TRIM5. Dr. Luban became a Group Leader at the IRB and relinquished his position at Columbia University in 2007.

MARIA–GRAZIA UGUCCIONI

Chemokines
>> pag. 19

• Mariagrazia Uguccioni received a degree in Medicine from the University of Bologna (Italy) where she specialized in Haematology in 1994. From 1993 to 2000 she was a member of the Theodor Kocher Institute, University of Bern (Switzerland), and since 2000 she is Head of the Chemokine Expression and Function Laboratory at the IRB. She is Adjunct Professor of Immunology at the School of Rheumatology, University of Bologna, since 2000. Dr. Uguccioni's research has covered aspects of human haematology and immunology: chemokine activities, leukocyte activation and traffic, natural chemokine antagonists, and chemokine expression in human pathology. Recently, her group is focusing on chemokine activities in human pathology and has identified a novel regulatory mechanism of leukocyte trafficking induced by synergy-inducing chemokines.

FEDERICA SALLUSTO

Cellular Immunology
>> pag. 20

• Federica Sallusto received her degree in Biology at the University of Rome La Sapienza. Between 1989 and 1996 she worked at the Department of Immunology of the Italian National Institute of Health first as a postdoctoral fellow and then as a research scientist. She worked at the Basel Institute for Immunology as a visiting scientist from 1993 to 1994 and as a member from 1996 to 2000. Her research is focused on dendritic cell biology, T cell activation, differentiation and T cell traffic. Among her original contributions are the development of a method to culture human dendritic cells, the discovery that Th1, Th2 and Th17 cells express distinct sets of chemokine receptors and the definition of central and effector memory T cell subsets. She has published more than 80 papers and was the recipient of the Pharmacia Allergy Research Foundation Award in 1999. Since 2000 Federica Sallusto is the Head of the Cellular Immunology Laboratory at the IRB.

ANTONIO LANZA–VECCHIA

Immune Regulation
>> pag. 21

• Antonio Lanzavecchia earned a degree in Medicine at the University of Pavia where he specialized in Paediatrics and in Infectious Diseases. From 1983 to 1999 he was a member of the Basel Institute for Immunology and since 1999 he is the founding director of the IRB in Bellinzona. He has been Professor of Immunology at the University of Genoa and at the University of Siena. Awarded the EMBO medal in 1988 and the Cloëtta prize in 1999, Dr. Lanzavecchia has published more than 200 papers. His research has covered several aspects of human immunology: antigen processing and presentation, dendritic cell biology, lymphocyte activation and traffic, T and B cell memory. Recently he developed a method for the efficient isolation of human monoclonal antibodies from memory B cells, which has been successfully applied to infectious diseases such as SARSCoV, H5N1, HCMV, Dengue, Malaria and HIV-1.

SILVIA MONTI–CELLI

Molecular Immunology
>> pag. 21

• Silvia Monticelli earned a PhD. in Biology at the University of Milan where she specialized in Molecular Biology. From July 2000 to January 2007 she was a post-doc in Anjana Rao's laboratory at the Center for Blood Research, Harvard Medical School in Boston (USA), and in February 2007 she joined the IRB in Bellinzona as Group Leader. Dr. Monticelli has published several papers covering various aspects of the molecular mechanisms underlying the immunopathology of allergy and asthma. Recently she focused her research efforts on the role of microRNAs, a relatively new class of regulatory molecules, in the development and function of cells of the immune system.

LUCA VARANI

Structural Biology
>> pag. 22

• Luca Varani graduated in chemistry at the University of Milan (Italy) with a thesis in structural biology. He then moved to the MRC-Laboratory of Molecular Biology, obtaining a PhD degree at the University of Cambridge (UK) in 2000. His PhD research focused on the role of RNA and protein interactions in regulation of gene expression at the post-transcriptional level, culminating in the determination of the largest NMR structure and one of only 3 RNA-protein complexes available at the time. He also contributed to showing the role of RNA structure in dementia, proving the viability of RNA as a therapeutic target. After a brief spell in Florence, he moved to Stanford University (USA) as a postdoctoral fellow, being awarded an "EMBO Fellowship" in 2003. At Stanford he completed the first NMR study on TCR-pMHC complexes, proposing a novel approach to the systematic characterization of protein-protein interactions. In October 2007 he joined the IRB as a Group Leader in Structural Biology.

Protein Folding and Quality Control

Group Leader: Maurizio Molinari, PhD

Laboratory

Members: Carmela Galli-Molinari, *Researcher* • Riccardo Bernasconi, *PhD student* • Tito Calì, *PhD student* • Silvia Olivari, *PhD student* • Omar Vanoni, *PhD student* • Siro Bianchi, *Technician* • Verena Calanca, Technician • Tatiana Soldà, *Researcher*
Awards: Research Award Aetas 2007

Cystic fibrosis, Alzheimer's disease, Parkinson's disease, Hungtington disease, Creutzfeld-Jakob's disease, diabetes mellitus. This is a very short selection of the several hundreds of human diseases with profoundly different traits but common aethiology: "protein misfolding". Several of these diseases are hereditary and most of them are rare, affecting less than 1 in 2000 individuals. For some of them, as an example for all neurodegenerative syndromes affecting old people, a sharp increase in frequency is expected in the next decades due to the extension of the human life span. Proteins are fundamental components of all living cells and include many substances, such as enzymes, hormones, and antibodies that are necessary for the proper functioning of an organism. They are fabricated in a specialized organelle present in all our cells and named the endoplasmic reticulum.

To be functional, proteins must acquire a specific structure in the endoplasmic reticulum in a series of tightly regulated processes defined as "protein folding". Failure to do so will result in the destruction of the defective protein and in the loss of its activity. The cell and the organism will eventually suffer as a consequence of the absence of this specific protein's function and this elicits a disease state.

The aim of our work is to understand how our cells fabricate the proteins. How correct protein folding is ensured, what happens if protein folding is not possible, how misfolded proteins are destroyed. We are convinced that a detailed knowledge of the processes that regulate protein production in our cells will allow intervention to alleviate symptoms, to delay disease onset and even to arrest and revert disease progression for all human pathologies caused by defects in acquisition of the functional protein shape.

Signal Transduction

Group Leader: Marcus Thelen, PhD

Laboratory

Members: Sylvia Thelen, *PhD* • Tiziana Apuzzo, *PhD student* • Ulrike Naumann, *PhD student* • Silvia Volpe, *PhD student*

Cell migration is essential for development and survival of multicellular organisms. Generally, single cells move along cues to reach their destination. The process requires polarization, i.e. the formation of a morphologically distinct front and rear end of the cell along the axis of attraction. The intracellular pathways that sense the attracting signal and transduce it into remodeling of the actin cytoskeleton and the sequential activation of adhesion molecules is a central focus of our research.

Leukocyte trafficking is largely regulated by chemokines and their respective receptor. Migration of cells expressing subsets of receptors is further controlled by spatially restricted secretion of chemokines. The mechanism is important for immune homeostasis, but is also essential for acute and chronic immune responses such as inflammation. In addition, some cancer cells appear to use the chemokine systems for metastasis.

T Cell Development

Group Leader: Fabio Grassi, MD, PhD

Laboratory

Members: Ursula Schenk, *PhD* • Anna Casati, *PhD student* • Michela Frascoli, *PhD student* • Isabella Scheu, *PhD student*

The experiments performed in the lab are principally focused on the characterization of signal transduction pathways at different developmental stages of the murine T cell. A first aim is to define signaling microdomains, which are involved in transducing the signal by the pre-T cell receptor (pre-TCR) and promote T cell as well as thymus development. A second aim pursued in the lab is to characterize signaling pathways controlled by Ca2+ during immunopathological T cell responses leading to inflammation and tissue destruction. Another topic studied by our group is the impact of T cell activation during an inflammatory response on hematopoiesis and bone homeostasis.

Haematopoesis

Group Leader: Markus G. Manz, MD

Laboratory

Members: Hitoshi Takizawa, *PhD* • Patrick Ziegler, *PhD* • C. Sekhar Boddupalli, *PhD student* • Chiara Borsotti, *PhD student* • Dior Kingston, *PhD student* • Michael A. Schmid, *PhD student* • Steffen Boettcher, *MD student*

Throughout life, a small fraction of hematopoietic stem cells (HSCs) self-renew in the bone marrow and generate all cells of the hemato-lymphoid system, a system with very high cellular turn-over. Because of its ready accessibility, hematopoiesis is currently one of the best studied mammal adult stem cell differentiation systems, and is likely paradigmatic for other physiologic (e.g. liver, skin, central nervous system) and pathologic (tumors, leukemia) stem cell regenerated compartments. Beyond its model character for basic research, hematopoietic stem cell transplantation is so far the only successfully working clinical stem cell therapy, mostly applied for the treatment of malignant hematologic disease or immunodeficiencies. Also, hematopoietic stem cells currently provide the major gateway for clinical gene therapy.

The hierarchically structured differentiation process from HSCs to terminally differentiated cells involves progressive loss of self-renewal ability, proliferation capacity, and lineage differentiation potentials. In my laboratory, we are studying regulation of hematopoietic stem cell turn-over and hemato-lymphopoid differentiation in physiologic steady–state conditions as well as in inflammation and neoplasia in both mice and men. In depth understanding of maintenance and differentiation pathways from HSCs to mature cells of the hematopoietic system will eventually provide new insights and improved therapeutic methods to treat hematopoietic and immune system diseases.

Viral Replication, Pathogenesis and Immunity

Group Leader: Jeremy Luban, MD

Laboratory

Members: Caterina Strambio de Castillia, *PhD* • Susanne Maertens, *PhD* • Silvia Olivari, *PhD* • Martha Neagu, *MD, PhD student* • Thomas Pertel, *PhD student* • Nadia Rahm, *PhD student* • Claudio Realini, *Technician*

Study of retroviruses has led to major advances in fundamental biology, most notably the discovery of oncogenes and the modification of the central dogma. In this spirit, we investigate mechanisms of HIV-1 replication and pathogenesis with the goal of advancing understanding of the basic workings of the cell. Through the development of genetic and biochemical screens we attempt to identify cellular factors of importance to HIV-1 and, more generally, to cell physiology. In effect, we exploit HIV-1, using the virus to elucidate mechanisms of cell cycle progression and cytokinesis, signal transduction and cytokine expression, protein folding and degradation, as well as pathogen recognition and antigen presentation. Our research is basic in nature but by shedding light on mechanisms of HIV-1 replication and immune system evasion we hope to contribute to the development of drugs and vaccines that target this virus.

Chemokines

Group Leader: Mariagrazia Uguccioni, MD

Laboratory

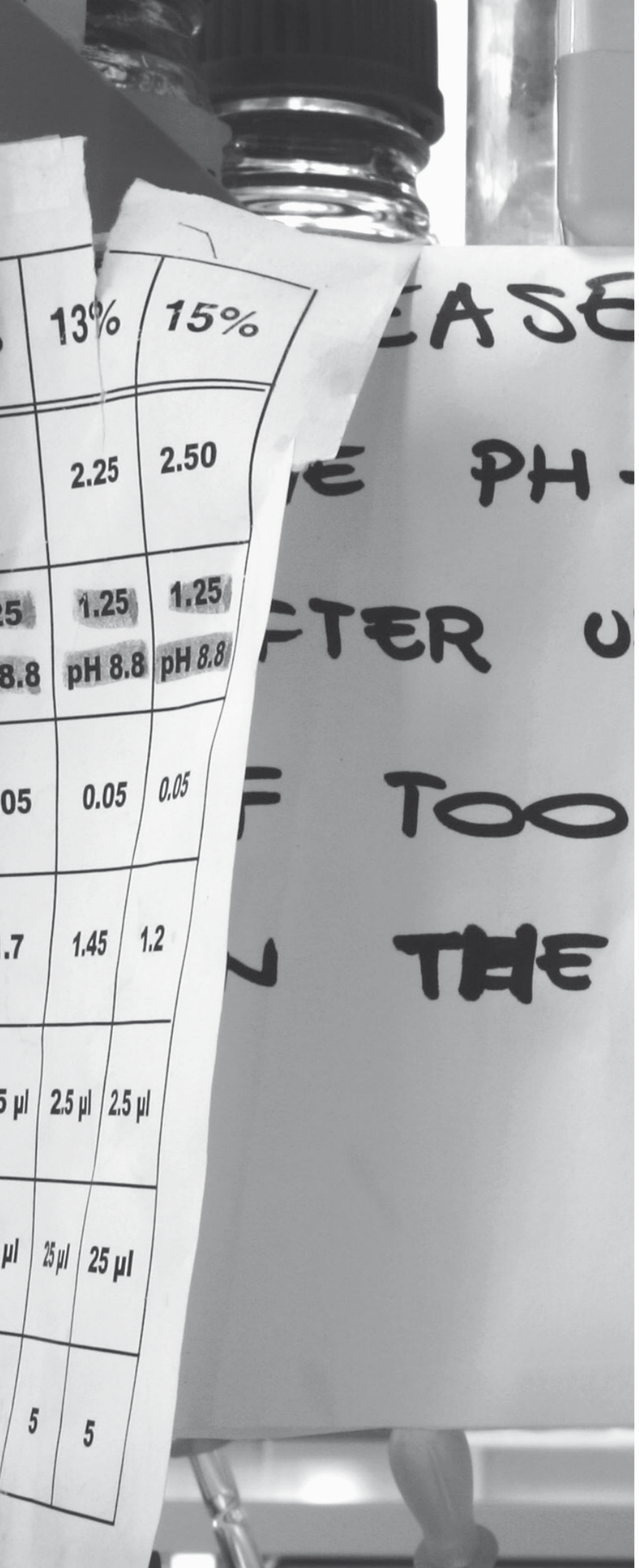
Members: Tamara Visekruna, *PhD* • Katrin Kuscher, *PhD student* • Milena Schiraldi, *PhD student* • Daniel Venetz, *MD, PhD student* • Denise Bottinelli, *undergraduate student* • Maria Gabriela Danelon, *Technician*

Our research interest remains focused on CHEMOKINE activities in physiology and pathology, with emphasis on mechanisms governing the fine tuning modulation of their expression and activity. Chemokines are produced constitutively or upon specific induction in virtually all tissues of the human body. The migration of leukocytes at the site of inflammation is largely determined by their response to chemokines.

While the chemokine specificities and expression patterns of chemokine receptors are well defined, it is still a matter of debate how cells integrate the messages provided by different chemokines that are concomitantly produced in physiological or pathological situations *in vivo*. Previous work from our laboratory identified a novel regulatory mechanism of leukocyte trafficking. Many chemokines, which per se have no effect on a particular chemokine receptor, can greatly augment the cellular response to specific receptor agonist(s).

The studies undergone in our laboratory demonstrated that the responses mediated by the CCR7 and CCR4 agonists could be enhanced by unrelated, non-agonistic chemokines. Western blot and binding experiments have shown the formation of heteromeric complexes suggesting these complexes as the cause of the observed synergism. Synergy-inducing chemokines could bind only in the presence of selective receptor ligands. This would induce conformational changes of the receptor enabling triggering, or conversely, the heterocomplex could lock the agonist into a higher-affinity conformation.

We have hypothesized that the synergism induced by heteromeric chemokine interactions may be a widespread phenomenon, positively regulating diverse chemokine activities such as chemotaxis, cellular adherence, receptor internalization, and protein kinase phosphorylation. Therefore, we are conducting additional *in vitro* studies to dissect in detail the mechanisms governing these activities. In addition, we study the breakdown in the control of leukocyte mobilization, induced by chemokines, which contributes to the pathogenesis of chronic inflammation as well as tumour development.



Cellular Immunology

Group Leader: Federica Sallusto, PhD

Laboratory

Members: Eva V. Acosta-Rodriguez, *PhD* • Martina Beltramello, *PhD* • Thomas Duhen, *PhD* • Annalisa Macagno, *PhD* • Alfonso Martin-Fontecha, *PhD* • Dirk Boumjohann, *PhD student* • Miroslav Hons, *PhD student* • Rebekka A. Geiger, *PhD student* • Andrea Reboldi, *PhD student*

Specific immune responses require the timely interaction of various cell types within specific microenvironments. In the primary response the rare antigen specific naive T cells need to maximize the possibility of encounter with antigen. They do so by continuously recirculating through secondary lymphoid organs where they are stimulated by antigen-presenting mature dendritic cells (DCs). Soluble antigens can reach the lymph node directly but in most cases they are carried by migrating DCs that capture antigen in peripheral tissues and subsequently move through the lymphatics to the draining lymph node.

One goal of our laboratory is to understand how the number, localization and activation state of DCs in the lymph node impact on T cell priming and immune responses.

A second goal of our research is to dissect the signals by which DCs determine differentiation of proliferating T cells towards the Th1, Th2 or Th17 lineage and how migratory capacity and effector function are coordinately regulated in differentiating T cells. Based on their migratory capacity and effector function we have originally characterized two subsets of memory T cells: central memory T cells (TCM) express homing receptors for lymph nodes and have no or low level effector function. In contrast effector memory T cells (TEM) lack lymph node receptors and have immediate effector function.

We are investigating the molecular basis underlying the functional properties and the differentiation potential of TCM and TEM, their heterogeneity and the signals required for their generation and maintenance. We are also interested to define the composition of memory subsets in different pathological and physiological conditions to gain insights into the role these subsets play in the immune responses.

Immune Regulation

Group Leader: Antonio Lanzavecchia, MD

Laboratory

Members: Afonso Almeida, *PhD* • Nadia Bernasconi, *PhD* • Giulia Di Lullo, *PhD* • Giorgio Napolitani, *PhD* • Janine Stubbs, *PhD* • Davide Corti, *PhD student* • Greta Guarda, *PhD student* • Debora Pinna, *PhD student* • Isabella Giacchetto-Sasselli, *Technician* • Chiara Silacci, *Technician* • Fabrizia Vanzetta, *Technician*

The research of our group remains focused on three main themes. First, we study the impact of innate immunity on the adaptive immune response with special emphasis on the activation of dendritic cells and the regulation of polarizing cytokines such as IL-12, IL-23, IL-1 and IL-6.

Second, we continue to test in different experimental systems the role of the cumulative strength of stimulation (SoS) on the generation of effector and memory T cells. Current results from our group as well as others support our initial proposition that SoS is the critical factor in determining the extent of CD4 and CD8 T cell differentiation. We are particularly interested to understand the mechanisms that control the generation of T and B memory cells and the dynamics of memory cells in the central and effector compartment.

A third new avenue of research which is progressively expanding is prompted by two methods that have been originally developed in our laboratory that allow an accurate analysis of memory B cell frequencies and the efficient retrieval of human monoclonal antibodies from cells obtained from immune donors.

We feel that our research has the potential to impact the field of vaccination in at least three areas: i) development of novel adjuvants capable of driving strong and selected immune responses; ii) identification of *in vitro* correlates of the immune status to evaluate vaccine efficacy and iii) adoptive immunotherapies with antigen-specific T cells or human monoclonal antibodies retrieved from the memory repertoire.

Molecular Immunology

Group Leader: Silvia Monticelli, PhD

Laboratory

Members: Ramon Jesus Jove Mayoral, *PhD student*

MicroRNAs are a class of small, non-coding RNAs, found in organisms ranging from worms to plants and humans, where they function mostly as repressors of protein-coding genes. It is well known that cell development is controlled or modulated by an intricate network of growth and transcription factors that simultaneously regulate the commitment, proliferation, death and maturation of progenitor cells. MicroRNAs appear ideally suited to rapidly adjust protein concentrations in cells, as would be expected to be required during cell differentiation. Accordingly, certain microRNAs are expressed in a stage-specific fashion. Moreover, consistent with the discovery that microRNAs modulate gene expression, altered microRNA expression has been found to affect cancer development. Indeed, altered expression of specific microRNAs has been shown to promote tumorigenesis.

The aim of our study is to understand the mechanisms of microRNA regulation, as well as the role played by microRNAs in the development and function of cells of the immune systems. Specifically, we are investigating the role played by microRNAs in mast cell differentiation and function. This is particularly important in view of the fact that mast cells are specialized cells of the immune system that reside particularly in tissues such as the skin that are more exposed to the environment, acting as sentinel cells at sites of antigen entry.

Besides being of fundamental relevance to our understanding of gene regulation, elucidation of the general molecular mechanisms that control mast cell differentiation, proliferation and functions have substantial potential for clinical application in the treatment of allergy and asthma, as well as of mast cell malignancies.

Structural Biology

Group Leader: Luca Varani, PhD

Laboratory

Members: Luca Simonelli, *PhD student*

Each molecule in a living organism needs to adopt a specific three-dimensional shape (structure) to function, which usually requires interaction with other molecules. Characterizing molecular structures and their interactions is therefore important to understanding the cellular mechanisms and develop strategies to interfere with them when necessary.

Studying the atomic details of molecular conformations as well as their thermodynamic properties is the scope of structural biology. Our group uses computational, biochemical and biophysical tools to determine the structure of proteins and RNA and to characterize their interactions with other proteins, RNAs and small molecules.
The ultimate goal is to help design new molecules (drugs) to treat infectious disease.

The group was started in October 2007.
Current projects involve the study of RNA-small molecule interactions in Frontotemporal dementia; determining the structure of protein receptors in cytomegalovirus (a major cause of birth defects) and characterizing antibody-protein interactions in the Dengue virus, a disease which every year affects millions of people in tropical regions.

Publications 2007

This list covers publications for the year in chronological order.

1. Membrane translocation of P-Rex1 is mediated by G protein beta gamma subunits and phosphoinositide 3-kinase.
Barber MA, Donald S, Thelen S, Anderson KE, M. Thelen M, Welch HC.
J.Biol.Chem. 2007; 282:29967-29976.

2. Human pregnancy-associated malaria-specific B cells target polymorphic, conformational epitopes in VAR2CSA.
Barfod L, Bernasconi NL, Dahlback M, Jarrossay D, Andersen PH, Salanti A, Ofori MF, Turner L., Resende M, Nielsen MA, Theander TG, Sallusto F, Lanzavecchia A, Hviid L.
Mol.Microbiol. 2007; 63:335-347.

3. The role of lysine 186 in HIV-1 integrase multimerization.
Berthoux, L., S. Sebastian, M.A. Muesing, J. Luban.
Virology 2007; 364:227-236.

4. Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells.
Acosta-Rodriguez, E.V., G. Napolitani, A. Lanzavecchia, and F. Sallusto
Nat.Immunol. 2007

5. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells.
Acosta-Rodriguez, E.V., L. Rivino, J. Geginat, D. Jarrossay, M. Gattorno, A. Lanzavecchia, F. Sallusto, and G. Napolitani
Nat.Immunol. 2007; 8:639-646.

6. Distinct expression pattern of IFN-alpha and TNF-alpha in juvenile idiopathic arthritis synovial tissue.
Gattorno, M., L. Chicha, A. Gregorio, F. Ferlito, F. Rossi, D. Jarrossay, A. Lanzavecchia, A. Martini, and M.G. Manz
Rheumatology (Oxford) 2007; 46:657-665.

7. The central nervous system in mucosal vaccination of rhesus macaques with simian immunodeficiency virus Deltanef.
Georgsson G., Stahl-Hennig C., Tenner-Racz K., Uberla K., Stoiber H., Uguccioni M., Dierich M., Ignatius R., Steinman R. M., and Racz P.
Neuropathol.Appl.Neurobiol. 2007

8. L-selectin-negative CCR7 - effector and memory CD8+ T cells enter into reactive lymph nodes and kill dendritic cells.
Guarda G., Hons M., Soriano S.F, Huang H.Y., Polley R., MartIn-Fontecha A., Stein J.V., Germain R.N., *Lanzavecchia A. and Sallusto F. Nat.Immunol. 2007; 8:743-752.*

9. Toll-like receptors and innate immunity in B-cell activation and antibody responses.
Lanzavecchia, A. and F. Sallusto
Curr.Opin. Immunol.2007

10. Cyclophilin A, TRIM5, and resistance to human immunodeficiency virus type 1 infection.
Luban, J.
J.Virol. 2007; 81:1054-1061

11.Duration, combination and timing: the signal integration model of dendritic cell activation.
Macagno, A., G. Napolitani, A. Lanzavecchia, and F. Sallusto
Trends Immunol.2007; 28:227-233

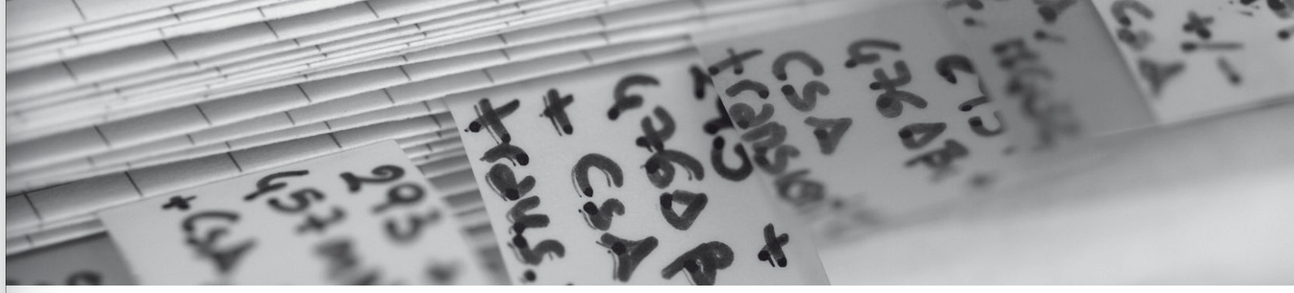
12. Human-Hemato-Lymphoid-System Mice: Opportunities and Challenges.
Manz, M.G.
Immunity. 2007; 26:537-541

13. A hypomorphic R229Q Rag2 mouse mutant recapitulates human Omenn syndrome.
Marrella V., Poliani P. L., Casati A., Rucci F., Frascoli L., Gougeon M. L., Lemercier B., Bosticardo M., Ravanini M., Battaglia M., Roncarolo M. G., Cavazzana-Calvo M., Facchetti F., Notarangelo L. D., Vezzoni P., Grassi F., and Villa A.
J.Clin.Invest 2007; 117:1260-1269

14. Glycoprotein Folding and the Role of EDEM1, EDEM2 and EDEM3 in Degradation of Folding-Defective Glycoproteins.
Olivari, S. and Molinari, M.
FEBS Lett. 2007; 581, 3658-3664.

15. N-glycan structure dictates extension of protein folding or onset of disposal.
Molinari, M.
Nat.Chem.Biol. 2007; 3:313-320

16. Flt3 in regulation of type-I interferon producing and dendritic cell development.
Onai, N., A. Obata-Onai, M.A. Schmid, and M.G. Manz.
Ann.N.Y.Acad.Sci. 2007



17. Division of labor with a workforce of one: challenges in specifying effector and memory T cell fate.
Reiner, S.L., F. Sallusto, and A. Lanzavecchia
Science 2007; 317:622-625.

18. Bcl10 controls TCR- and FcgammaR-induced actin polymerization.
Rueda D., Gaide O., Ho L., Lewkowicz E., Niedergang F., Hailfinger S., Rebeaud F., Guzzardi M., Conne B., Thelen M., Delon J., Ferch U., Mak T. W., Ruland J., Schwaller J., and Thome M.
J.Immunol. 2007; 178:4373-4384.

19. The Retroviral Restriction Factor TRIM5-alpha.
Sebastian, S. and J. Luban
Curr.Infect.Dis. 2007; Rep. 9:167-173.

20. Prophylactic and therapeutic efficacy of human monoclonal antibodies against H5N1 influenza.
Simmons C. P., Bernasconi N. L., Suguitan A. L., Mills K., Ward J. M., Chau N. V., Hien T. T., Sallusto F., Ha do Q., Farrar J., de Jong, Lanzavecchia A., and Subbarao K.
PLoS.Med. 2007; 4:e178.

21. Substrate-specific requirements for UGT1-dependent release from calnexin.
Solda, T., C. Galli, R.J. Kaufman, and M. Molinari
Mol.Cell 2007; 27:238-249.

22. A single vaccination with attenuated SIVmac 239 via the tonsillar route confers partial protection against challenge with SIVmac 251 at a distant mucosal site, the rectum.
Stahl-Hennig C., Eisenblatter M., Franz M., Stoiber H., Tenner-Racz K., Suh Y. S., Jasny E., Falkensammer B., Ugucchioni M., Georgsson G., Baroni C., Dierich M. P., Lifson J. D., Steinman R. M., Uberla K., Racz P., and Ignatius R.
Front Biosci. 2007; 12:2107-2123.

23. Vif counteracts a cyclophilin A-imposed inhibition of simian immunodeficiency viruses in human cells.
Takeuchi H., Buckler-White A., Goila-Gaur R., Miyagi E., Khan M. A., Opi S., Kao S., Sokolskaja E., Pertel T., Luban J., and Strebel K.
J.Virol. 2007; 81:8080-8090.

24. Lymphocyte activation.
von Andrian, U.H. and F. Sallusto
Curr.Opin.Immunol. 2007; 19:247-248.

25. Cyclophilin A participates in the nuclear translocation of apoptosis-inducing factor in neurons after cerebral hypoxia-ischemia.
Zhu C., Wang X., Deinum J., Huang Z., Gao J., Modjtahedi N., Neagu M. R., Nilsson M., Eriksson P. S., Hagberg H., Luban J., Kroemer G., and Blomgren K.
J.Exp.Med. 2007; 204:1741-1748.

26. Potent cross-reactive neutralization of SARS coronavirus isolates by human monoclonal antibodies.
Zhu Z., Chakraborti S., He Y., Roberts A., Sheahan T., Xiao X., Hensley L. E., Prabakaran P., Rockx B., Sidorov I. A., Corti D., Vogel L., Feng Y., Kim J. O., Wang L. F., Baric R., Lanzavecchia A., Curtis K. M., Nabel G. J., Subbarao K., Jiang S., and Dimitrov D. S.
Proc.Natl.Acad.Sci.U.S.A 2007; 104:12123-12128

27. In and Out of the ER: Protein Folding, Quality Control, Degradation and Related Human Diseases.
Hebert, D.N. and Molinari, M.
Physiol Rev. 2007; 87, 1377-1408

2007 at the Institute

JANUARY

- *IRB Foundation President, Giorgio Noseda, wins the 2006 Swiss Award*
- *IRB seeks funding for powerful new confocal microscope*
- *Patronage Committee to be founded to help support the IRB*
- *Silvia Monticelli Joins the IRB as a Junior Group Leader*

- ***PhD programme Lectures:***

>Hilde Cheroutre: Non-classical T cells

- ***Seminars:***

> Hilde Cheroutre: Stirring up the melting pot of memory: mucosal T cells and memory differentiation
> Kevin Marsh: Measuring immunity to malaria

FEBRUARY

- *FP7: The future of European Union Research Policy outlined*

- ***PhD programme Lectures:***

> Klaus Ley: Cell recruitment in inflammation

- ***Seminar:***

> Klaus Ley: Role of IL-17-producing T cells in neutrophil homeostasis

MARCH

- *Fabio Grassi, Markus Manz and Federica Sallusto receive funding from the Swiss National Fund*
- *IRB particpates in Cantonal activity "Promoting Careers in Science"*
- *Molinari receives research fellowship from AETAS, Swiss Foundation for Ageing Research.*
- *Mrs. Ruth Jacob, sponsor of the IRB PhD Program, visits*

- ***PhD programme Lectures:***

Klaus Ley: Cell recruitment in inflammation
> Mette Rosenkilde: Pharmacology of 7TMR antagonists
> Wilhelm Krek: Signaling networks in human diseases

- ***Seminars:***

> Charles Rice: Hepatitis C: The end of the beginning or the beginning of the end?
> Mette Rosenkilde: Molecular interaction of nonpeptide agonists and antagonists with chemokine receptors
> Olivier Schwartz: HIV, dendritic cells, and CD4+ lymphocytes: immunological and virological synapses
> Wilhelm Krek: The metabolic basis of disease: insights from animal models of VHL pathway components

APRIL

- *EMBO Fellowship awarded to Janine Stubbs*
- *Integrase, a new target for HIV Drugs published in Virology*
- *Young Apprentices Visit the IRB*
- *PhD awarded to Silvia Olivari from Molinari's lab*

- ***PhD programme Lectures:***

> Radek Skoda: Myeloproliferative diseases
> Ton N. Schumacher: Adaptive immunotherapy of cancer

- ***Seminars:***

> Barbara Cassani: Molecular mechanisms of immune deficiency in Adenosine Deaminase-deficient SCID patients: implications for stem cell gene therapy
> Radek Skoda: The genetics of Myeloproliferative disorders

MAY

- *2007 Annual Student Retreat held in Bigorio*
- *A model for OMENN Syndrome published by Fabio Grassi*
- *Interleukin-17 Producing T cells Characterized: published by Sallusto*
- *IRB Report card on Equality*
- *Moving In: The IRBis is coming to life*
- *Musica e Molecole 3: Morricone*
- *The Patrizzi of Bellinzona Visit the IRB as part of their annual meeting*

- ***Seminars:***

> Alfred Wittinghofer: Signalling via Ras-like G proteins
> Edward Clark: Regulation of dendritic cell cytokine production and lifespan
> Ton Schumacher: Tracing T cell responses with conditional MHC ligands and molecular barcodes

JUNE

- *Automatic Imaging System Installed at IRB*
- *Gates Foundation Grand Challenge meeting held in Lugano*
- *IRB Fund raising goal reached for new-microscope!*
- *Lanzavecchia Bird Flu antibodies shown to protect and cure*
- *Cover of Nature Immunology for June 2007 by Federica Sallusto*
- *Trafficking Seminar Held in Curzutt above Monte Carasso*
- *World Cup underlines the international character of the IRB*

- ***Seminars:***

> Felix Rey: Functional insights from structural studies of viral membrane fusion proteins
> Richard Flavell: Regulation of immune response by cells and cytokines

JULY

- *PhD Awarded to Denise Ferrara from Grassi Lab*

- ***Seminars:***

> Elisabetta Cameroni: Quiescence: I go for it! The yeast enbosulfines are central regulators of GO
> Giovanna Musco: Molecular interactions of the autoimmune regulator PHD finger with Histone H3

AUGUST

- ***Seminars:***

> Daniele Gaudiosi: Chromatin-associated functions of the CDK inhibitor p27KIP1
> Michael S. Diamond: Innate and adaptive immune system protection against West Nile virus

SEPTEMBER

- *Michelin Calmy Rey, President of the Confederation visits the IRB*
- *New Student in the lab of Silvia Montecelli: Ramon Jesus Jose Mayoral*
- *La Zushan, Governor of China, visits IRB*

OCTOBER

- *Confocal Microscope Arrives!*
- *First meeting of the new IRB Executive Committee*
- *IRB Scientific Advisory Board meets to review scientific program of the institute*
- *Luca Varani Joins IRB as Group Leader*
- *Nature Immunology Article: Markus Manz*
- *New Members in Fabio Grassi Lab: Michela Frenscoli and Stefano Volpi*
- *Visit from the Balerna Middle School*

- ***PhD programme Lectures:***

> Gisou van der Goot: Bacterial toxins
> Michael McHeyzer-Williams: Antigen specific memory B cell development

- ***Seminars:***

> Emmanuel Delamarche: H1125ONI – Using IBM technology for checkmating a pandemic
> Gisou Van der Goot: From anthrax toxin endocytosis to Wnt signaling
> Michael McHeyzer-Williams: Regulating Adaptive Immunity: The Clonal Selection and the Development of Effector Function

NOVEMBER

- *Confocal Microscope Up and Running!*
- *IRB elects new Member of the Board: Walter Schaufler of the University of Zurich*
- *Musica e Molecole 4: Hungarian Girls Choir*

- ***Seminars:***

> Daniela Bossi: Identification of the haematopoietic target cell of acute promyelocytic leukaemia (APL) in a PML-RARa transgenic mouse model
> Eric Vivier: Detection, Education and Traffic of Natural Killer cells
> Maurizio Ceppi: Fine-tuning of Dendritic Cells activation: lost in translation?
> Onsite Acuto: Signal transduction in T lymphocytes
> Paul Barren: Antiinflammatory Activity of IgG4 antibodies by Dynamic Fab Arm Exchange

DECEMBER

- *Telethon Ticino holds televised "Musica e Molecole" concert at the IRB*

- ***Seminars:***

> Jaap Goudsmit: Cross-reactive human monoclonal antbodies to avian influenza: analysis of the human B cell reservoir
> Thomas Calzascia: Boosting T cell immunity to cancer and chronic viral infections using IL-7 therapy

English Version

Rapporto Annuale 2007

Istituto di Ricerca in Biomedicina

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