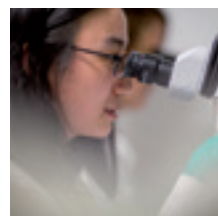


Scientific report

7th EDITION - 2017



imagine

INSTITUT DES MALADIES GÉNÉTIQUES



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Editorial



The *Imagine* foundation for scientific cooperation is 10 years old this year. We are proud to celebrate a decade of advances in our research.

The challenge of 9,000 rare and complex diseases is immense. *Imagine* is one of the foremost centers and accelerators for research in this field, drawing on our core strengths of emulation, interdisciplinary approach and broad freedom to innovate to speed up the pace of discovery. We believe that personal and professional cultural diversity plays a crucial role in driving progress. Diversity challenges us. It helps to foster and maintain our ability to probe bold ideas and push the boundaries of existing knowledge.

Realizing the dream of our former Chairman and founder, Professor Claude Griscelli, the institute has created a culture of openness and collaboration for researchers in the international scientific community and the doctors and researchers at Necker-Enfants malades hospital campus. *Imagine* is committed to dialog with patients and their families and to forging links with patient groups. Let me take this opportunity to once again acknowledge the total commitment of our Chairman who had the clarity of vision and wisdom to build *Imagine* around the principle of collaborative cross-disciplinary teams in an open model.

Professor Arnold Munnich took over from him as the Chairman of the Board of Trustees on December 14, 2016. I want to thank him for his constructive support in preparing our strategy, as well as Laure Boquet, whose tireless work in the Institute's general secretariat has been decisive in successfully implementing this strategy.

30 research teams have chosen to make *Imagine* their home. The latest additions include Mickaël Ménager's research group, which joined us in June 2017, and Alessandra Pierani's team, which is in the process of setting up at the time of publication. We are delighted and honored to have these areas of expertise to advance our knowledge of genetic diseases. *Imagine* provides the teams with the structure and resources they need to propel discoveries working in synergy and in close proximity with patients.

The quality and importance of this infrastructure are evident in recent selections of some of the major projects involving our teams.

In December 2016, the Greater Paris Region selected gene therapy as a priority research area to receive financial support under the Areas of Major Interest (DIM) program. Through the Institute, the Region will provide funding to Professor Marina Cavazzana for projects to broaden the reach and diversify the applications of gene therapy into the future.

Because the genome still has many secrets to give up, we have also launched a project to explore non-coding DNA sequences. "Devo Decode" involves no fewer than eight research groups, eight core facilities and eight centers of expertise at *Imagine* and Necker-Enfants malades hospital. It receives generous support from the Fondation MSDAvenir through to 2020. Our aim is to identify new mutations responsible for developmental disorders.

We are also privileged to lead the Sequoia project alongside Assistance Publique-Hôpitaux de Paris (the Paris University hospitals group), Institut Curie and Institut Gustave Roussy. Sequoia was selected under the French 2025 Plan for Genomic Medicine (Plan France Génomique 2025) as one of the leading platforms for genome sequencing and interpretation. Announced by the French Prime Minister on July 17 last, this decision is further proof of the confidence our teams inspire.

In further excellent news, our Cil'Lico university hospital research project was selected under the 3rd international call for projects by the French National Research Agency for the French General Commission for Investment. Our culture of collaboration, bringing together the Institute's research groups, colleagues at the Hôpital européen Georges Pompidou, Hôpital de Strasbourg, the École Polytechnique and our partner Alexion, was a decisive factor in this selection. This crucial support will advance our research into developing new therapeutic strategies for the treatment of ciliopathies.

The continued funding announced by the French Prime Minister for all major university hospital projects, subject to evaluation, sustains our hope of unlocking discoveries to provide new solutions for families affected by genetic diseases.

Our aim is to be equal to their hopes. We intend to continue to expand our activities guided by the Institute's roadmap. The excellence of our research work and the commitment of our researchers, scientists, doctors and support teams give me every confidence in our ability to transform.

Prof. Stanislas Lyonnet
Director





Imagine Institute

Imagine Institute

"NECKER-ENFANTS MALADES" was created as a pediatric hospital at the end of the 18th century. Since then, it has grown to be a reference pediatric hospital in France for all fields of medicine and surgery. Forty thousand patients from France and abroad are referred to Necker Hospital specialists every year. It is estimated that half of the recommended children are affected by an inherited disease.

On this basis, research on paediatric diseases, notably genetic diseases has successfully developed on the site: the molecular basis of more than 200 inherited disorders have been unravelled, leading to advances in pathophysiology, but also in the design of diagnostic tools and new therapeutics.

Until 2014, research activities that gather approximately 350 people were scattered in several buildings that were no longer suitable to perform competitive research. Hence the birth of the *Imagine* project in which are involved 900 collaborators. The key concept behind it consists in the ambition to foster research activities on human genetic diseases in childhood. We have built a 19.000 sq.m new institute dedicated to research, training and clinical care for genetic diseases. It is expected that new paradigms will be uncovered, notably in developmental biology, and innovative medical applications, from diagnostic tools to new therapeutics, be developed.

To do so, multiple cross-affiliations between research groups and clinical units are encouraged to tighten the link between research and medicine in a constant bi-directional movement.

A UNIQUE ENVIRONMENT

Necker-Enfants malades Hospital is affiliated to Paris Descartes University. It is primarily but not exclusively a pediatric hospital. The pediatric hospital has undergone a major renovation, including a 55,000 sq.m new building. Pediatrics are divided into 20 units covering all pediatrics fields (cardiology, dermatology, endocrinology, ENT (Ear Nose Throat), gastroenterology, general pediatrics, genetics, hematology, immunology, intensive care, neonatology, nephrology, neurology, neurosurgery, ophthalmology, orthopedics, pneumatology, psychiatry, rheumatology, transplantation) and comprise 400 beds.

OUR PUBLIC PARTNERS

Imagine is supported by INSERM and the University Paris Descartes (UMR 1163) for its research activities and the AP-HP for clinical research and development.

IMAGINE INVENTING THE MEDICINE OF THE FUTURE

More than 900 scientists, clinicians, engineers, technicians and healthcare personnel have joined together to create *Imagine* Institute. They are all passionate about the fight against genetic diseases and have a shared vision of developing state-of-the-art, patient-centered research. Internationally renowned scientists and clinicians have decided to pool their knowledge, scientific resources and medical expertise to create and implement an outstanding

research and healthcare center. The institute's organization is based on the integration of research and medical care. The Institute creates innovative solutions in diagnosis, treatment, care and education.

Imagine aims to provide the most advanced integration between clinical and research facilities including a clinical research center, a biotherapy department, a laboratory of medicine and pathology and 15 national reference centers for rare diseases.

The Necker campus has also 16 other research units in immunology, cell biology, microbiology, nephrology which form the so called Structure fédérative de recherche Necker-Enfants malades (SFR). Those additional laboratories and central core facilities are located in the University building of the campus, and are organized in another Institute focusing on molecular biology called "INEM".

The *Imagine* Institute is supplied by a foundation established in 2007. It is composed of a board in which all six founding institutions (Paris Public Hospitals group (AP-HP), the French National Institute for Health and Medical Research (INSERM), Paris Descartes University, the French Muscular Dystrophy Association (Association Française contre les Myopathies, AFM), the Hôpitaux de Paris-Hôpitaux de France charitable foundation and Paris City Council) have seats. There is an Executive Committee and a Support services department dedicated to implement the operational plan developed and validated by the Executive Committee. The international scientific advisory board (SAB) is composed of nine outstanding scientists and is a fully-independent authority designated by the Board of Trustees following proposal by the Executive Committee. It proceeds to:

- an evaluation of the teams to be recruited following international calls for proposal;
- an evaluation of the research groups of the IHU, in coordination with the quadrennial evaluation by AERES (Evaluation agency for research and higher education);
- an evaluation of the overall scientific strategy and adaptation to the objectives of the Institute.



OUR OBJECTIVES

We foster research on genetic diseases with the goals of:

- identifying mechanisms of diseases and underlying physiology;
- developing medical applications of this knowledge in terms of diagnostic tools and therapeutics;
- training MDs and PhDs in this research frame with a special emphasis on intertwining research groups with clinical departments.

HOW TO IMPLEMENT OUR OBJECTIVES?

The design of a new research facility enables the strengthening of links between research teams and clinical activities.

During a transitory phase, we have bolstered the research platforms to be fully functional for the opening of a new research building which occurred in January 2014.

14,500 sq.m of this building are dedicated to research and 4,500 sq.m are dedicated to clinical activities. The research part accommodate space for approximately 380 people including research groups present on the campus as well as new ones to be recruited.

A new organization of the Institute, with tight links to clinical research resources and clinical departments is proposed.

THE *IMAGINE* UNIVERSITY HOSPITAL INSTITUTE

In 2010, the French government launched a call for proposals to create a small number of so-called "University Hospital Institutes" (Instituts Hospitalo-Universitaires, IHUs). The aim was to foster medical research activities as close to the patient care level as possible, in order to provide innovative treatments. The IHUs also perform teaching and technology transfer as natural ways to develop and disseminate knowledge. We therefore prepared a proposal including basic research, clinical research for innovative care, teaching and technology transfer. The IHU call for proposals fitted well with our views in the field of rare genetic disorders. It also represented a great opportunity to achieve the goals we had already defined.

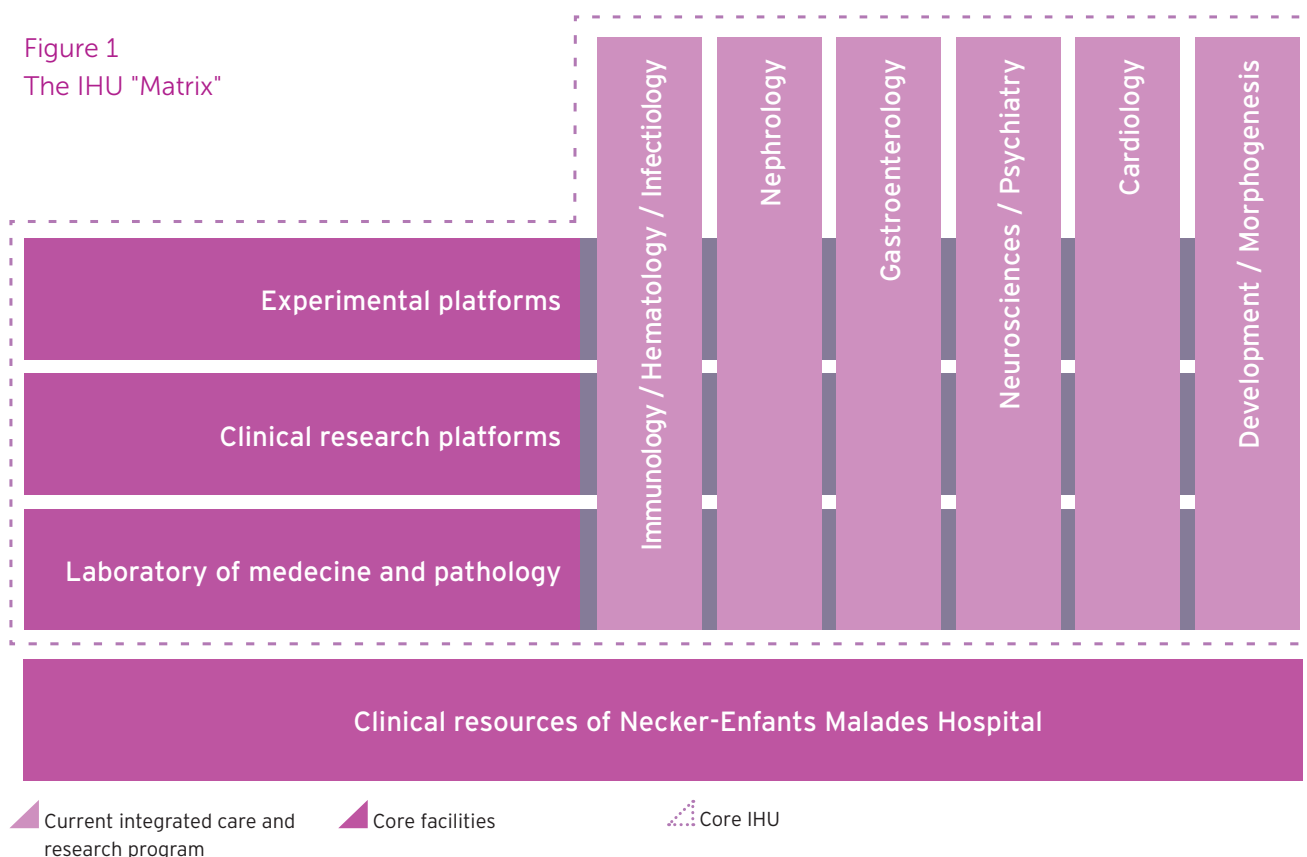
In March 2011, the *Imagine* teams were delighted to learn their application had been approved. *Imagine* is due to receive an IHU funding of 65 million euros over a 10-year period.

In July 2017, the French Prime Minister announced the extension of this IHU funding according to a specific evaluation.



The originality of *Imagine* is the integration of care and research programs organized through patients' pathway with so-called integrated care and research programs (ICaRPs) (Figure 1).

Figure 1
The IHU "Matrix"



The ICaRPs are thematic programs on rare diseases and are based on a combination of expertise in clinical care and research. These ICaRPs integrate clinical and research activities on defined topics and involve many multi-affiliated staff members (hospital/university/national institutes of research). Their work will be supported by both experimental and clinical research core facilities and Necker Hospital's central lab and pathology department. In order to strengthen our capacity for innovative care, adult medicine units with expertise in infectious diseases, haematology and nephrology have been integrated into the IHU and the relevant ICaRPs.

Two reference centers for rare diseases, Rare epilepsies (Prof. Rima Nabhout), and Genetic deafness (Dr Sandrine Marlin) have joined *Imagine* in 2015 and are contributors to an

extended ICaRP (named Octamere) on nervous system diseases in which the neuroimaging laboratory (Prof. Nathalie Boddaert) plays a central role.

The IHU intends to foster the various steps in research on genetic diseases within the indicated ICaRPs, on the following lines:

- develop cohorts and the corresponding databases on which research projects are based
- boost genomic studies of these cohorts
- foster relevant pathophysiological studies
- develop new diagnostic tools and biomarkers
- develop innovative therapeutics based on advances in pathophysiological studies.

Imagine's commitments

- Nurture world-class research, in order to understand the mechanisms of genetic diseases in children and adults.
- Implement true synergies between research and medical care activities by creating an efficient, patient-centered organization.
- Deliver the diagnostic and therapeutic solutions that patients and families are waiting for as rapidly as possible by reinforcing public-private partnerships.
- Perform the fundraising strategy that is essential for the Institute's development and manage funds transparently.

AN OVERVIEW OF OUR BEST PUBLICATIONS IN 2016 AND 2017 (UNTIL 09-2017)

	2016	01-09/2017
Cell	2	2
Nature	-	1
Science	-	-
New England Journal of Medicine	1	2
Lancet	5	2
Nature Communications	6	5
Nature Immunology	3	1
Nature Genetics	3	1
Nature Medicine	2	-
Nature Neurosciences	-	-
Nature Structural & Molecular Biology	-	-
Annual Reviews Immunology	-	-
Nature Reviews Immunology	1	-
Immunity	1	-
Journal of Clinical Investigation	1	2
Journal of Experimental Medicine	5	6
American Journal of Human Genetics	9	5
Proceedings of the National Academy of Sciences	2	1

A selection of our best publications 2016- 2017

2016

X-linked primary immunodeficiency associated with hemizygous mutations in the moesin (MSN) gene.

Lagresle-Peyrou C., Luce S., Ouchani F., Soheili T.S., Sadek H., Chouteau M., Durand A., Pic I., Majewski J., Brouzes C., Lambert N., Bohineust A., Verhoeyen E., Cosset F.L., Magerus-Chatinet A., Rieux-Laucat F., Gandemer V., Monnier D., Heijmans C., Van Gijn M., Dalm V.A., Mahlaoui N., Stephan J.L., Picard C., Durandy A., Kracker S., Hivroz C., Jabado N., De Saint Basile G., Fischer A., Cavazzana M. & Andre-Schmutz I. 2016. J Allergy Clin Immunol, 138, 1681-1689 e8.

Kinesin-1 controls mast cell degranulation and anaphylaxis through PI3K-dependent recruitment to the granular Slp3/Rab27b complex.

Munoz I., Danelli L., Claver J., Goudin N., Kurowska M., Madera-Salcedo I.K., Huang J.D., Fischer A., Gonzalez-Espinosa C., De Saint Basile G., Blank U. & Menasche G. 2016. J Cell Biol, 215, 203-216.

Transcriptional, epigenetic and retroviral signatures identify regulatory regions involved in hematopoietic lineage commitment.

Romano O., Peano C., Tagliazucchi G.M., Petiti L., Poletti V., Cocchiarella F., Rizzi E., Severgnini M., Cavazza A., Rossi C., Pagliaro P., Ambrosi A., Ferrari G., Bicciato S., De Bellis G., Mavilio F. & Miccio A. 2016. Sci Rep, 6, 24724.

Renal Atp6ap2/(Pro)renin Receptor Is Required for Normal Vacuolar H⁺-ATPase Function but Not for the Renin-Angiotensin System.

Trepiccione F., Gerber S.D., Grahammer F., Lopez-Cayuqueo K.I., Baudrie V., Paunescu T.G., Capen D.E., Picard N., Alexander R.T., Huber T.B., Chambrey R., Brown D., Houillier P., Eladari D. & Simons M. 2016. J Am Soc Nephrol, 27, 3320-3330.

The mutation significance cutoff: genelevel thresholds for variant predictions. I

Tan Y., Shang L., Boisson B., Ciancanelli M.J., Markle J.G., Martinez-Barricarte R., Scott E., Shah I., Stenson P.D., Gleeson J., Cooper D.N., Quintana-Murci L., Zhang S.Y., Abel L*, Casanova J.L*. 2016. Nat Methods 13: 109-10.

Interleukin-15-Dependent T-Cell-like Innate Intraepithelial Lymphocytes Develop in the Intestine and Transform into Lymphomas in Celiac Disease.

Ettersperger J., Montcuquet N., Malamut G., Guegan N., Lopez-Lastra S., Gayraud S., Reimann C., Vidal E., Cagnard N., Villarese P., Andre-Schmutz I., Gomes Domingues R., Godinho-Silva C., Veiga-Fernandes H., Lhermitte L., Asnafi V., Macintyre E., Cellier C., Beldjord K., Di Santo J.P., Cerf-Bensussan N.**; Meresse B. (2016). Immunity 45, 610-625. **Corresponding Senior author. IF: 22.8

Heterozygous Mutations in MAP3K7, Encoding TGF- β -Activated Kinase 1, Cause Cardiospondylocarpofacial Syndrome.

Le Goff C., Rogers C., Le Goff W., Pinto G., Bonnet D., Chrabieh M., Alibeu O., Nistchke P., Munnich A., Picard C., Cormier-Daire V. Am J Hum Genet. 2016 Aug 4;99(2):407-13.

Meckel's and condylar cartilages anomalies in achondroplasia result in defective development and growth of the mandible.

Biosse Duplan M., Komla-Ebri D., Heuzé Y., Estibals V., Gaudas E., Kaci N., Benoist-Lassel C., Zerah M., Kramer I., Kneissel M., Porta D.G., Di Rocco F., Legeai-Mallet L. Hum Mol Genet. 2016 Jul 15;25(14):2997-3010.

Gene-Corrected Fibroblast Therapy for Recessive Dystrophic Epidermolysis Bullosa using a Self-Inactivating COL7A1 Retroviral Vector.

Jackow J., Titeux M., Portier S., Charbonnier S., Ganier C., Gaucher S. & Hovnanian A. (2016). J Invest Dermatol 136, 1346-1354.

Recessive Mutations in TRMT10C Cause Defects in Mitochondrial RNA Processing and Multiple Respiratory Chain Deficiencies.

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2017

Finding patients using similarity measures in a rare diseases-oriented clinical data warehouse: Dr. Warehouse and the needle in the needle stack.

Garcelon N., Neuraz A., Benoit V., Salomon R., Kracker S., Suarez F., Bahi-Buisson N., Hadj-Rabia S., Fischer A., Munnich A. & Burgun, A. 2017. J Biomed Inform.

De novo mutations in SMCHD1 cause Bosma arhinia microphthalmia syndrome and abrogate nasal development.

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Mutations in MAPKBP1 Cause Juvenile or Late-Onset Cilia-Independent Nephronophthisis.

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Mutations in Borealin cause Thyroid Dysgenesis.

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Bal E., Park H.S., Belaid-Choucair Z., Kayserili H., Naville M., Mdrange M., Chiticariu E., Hady-Rabia S., Cagnard N., Kuonen F., Bachmann D., Huber M., Le Gall C., Cote F., Hanein S., Rosti R.Ö., Aslanger A.D., Waisfisz Q., Bodemer C., Hermine O., Morice-Picard F., Labeille B., Caux F., Mazereeuw-Hautier J., Philip N., Levy N., Taieb A., Avril Mf., Headon D.J., Gyapay G., Magnaldo T., Fraitag S., Crollius H.R., Vabres P., Hohl D., Munnich A., Smahi A. *Nat Med*. 2017 Sep 4.

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Scientific seminars - November 2016 - October 2017

2016

November 7: 7th Dr Claudia Waskow, Institut für Immunologie, Dresden, Germany, "Engraftment of human HSCs in mice"

November 14: Sabine Sarnacki, *Imagine*, Colorectal symposium

November 21: ICarP Endocrinology, Michel Polak, Jacques Beltrand, "Neonatal diabetes: beyond high Blood glucose, a neuroendocrine disorder"

November 28: Diana Dinca, *Imagine*, "The unusual suspects: astrocyte dysfunction in myotonic dystrophy"

December 5: Marc Deloger, Bioinformatics platform – Gustave Roussy Institute, "Precision medicine in action: how NGS and bioinformatics may improve patient cancer care?"

December 12: Pr Marina Cavazzana, *Imagine*, "Genetherapy clinical trials: advances and challenges"

December 19: IMAG2 Team, *Imagine*, "Impact of 3D MRI reconstruction on surgical strategy of pelvic tumors and malformations in children"

2017

January 9: Pablo Vargas, Systems Biology of Cell Polarity and Cell Division, UMR 144 Institut Curie/ CNRS, "Cellular requirements for fast leukocyte migration in tissues"

January 16: Olivier Hermine team, *Imagine*, "Bid cleavage and Hsp70: two check-points of human erythroid terminal differentiation"

January 23: Rita Horvath, John Walton Muscular Dystrophy Research Center Newcastle University, United Kingdom, "Molecular targets and new treatments in mitochondrial diseases"

January 30: Fernando Sepulveda, *Imagine*, "Immune homeostasis: Role of cytotoxic lymphocytes and beyond"

February 6: Daniel Hohl, University Hospital Center Vaudois, Lausanne, Suisse, "The role of the Bazex-Dupré-Christol gene ACTRT1 in primary ciliogenesis"

February 13: Lam-Son Nguyen, *Imagine*, "Role of miR-146a in differentiation and neural lineage identity determination of human progenitor stem cells: relevance for autism spectrum disorders"

February 20: Nadine Cerf-Bensussan *Imagine*, "From lymphocyte phylogeny to oncogenesis in coeliac disease"

February 23: Georg Holländer, Weather Institute of Molecular Medicine, University of Oxford, England, "The immunobiology of thymic epithelial cells - molecular and cellular mechanisms"

February 27: Sylvain Ernest, ENS, "Cis-regulation of the myo7a deafness gene in the zebrafish model"

March 6: Christophe Zimmer, Pasteur Institute, "Imaging and modeling of the nucleus and deep learning"

March 13: Alan Warren, Department of Haematology, School of Clinical Medicine, Cambridge University, United Kingdom, "New insights into the quality control of ribosome assembly from rare disease"

March 14: Pr Jean-François Mattéi, French Academy of Medicine, "From eugenics to post-humanism"

March 27: Metodi Metodiev, *Imagine*, "Mitochondrial translation defects in human pathology"

April 3rd: David Fitzpatrick, MRC Human Genetics Unit, University of Edinburgh, United Kingdom, "Proving Pathogenesis in Developmental Disorders; Coding Variants and Beyond"

April 10: Federico Mingozzi, Immunology and Liver Gene Transfer Unit, Genethon, Evry, "Progress and challenges in the development of in vivo gene therapies for inherited diseases"

April 24: iCarp Cardiology, Damien Bonnet, Lucile Houyel, Stanislas Lyonnet, Sigolène Meilhac, "Left/right, a matter of the heart"

May 3rd: Richard REDON, Institute of thorax (Inserm/CNRS/University of Nantes/CHU Nantes), "A genetic approach to sudden cardiac death: from exomes to genomes through GWAS"

May 22: Laurent Abel, *Imagine*, "Human genetics of tuberculosis"

May 29: Laure Bally Cuif, Pasteur Institute, "Maintenance and recruitment of telencephalic adult neural stem cell pools: what the zebrafish can teach us"

June 12: Harry Sokol, Gastroenterology Department St Antoine Hospital, Inserm U1157 &

INRA Micalis, "Dangerous liaisons between gene and microbiota: the example of Card9 in IBD"

June 19: Romain Roncagalli, CIML, Marseille, "Disentangling the complexity of the TCR signaling pathway by using systems biology approaches"

June 20: Michelle Kerns, John Hopkins, Baltimore, USA, "Vive la différence: Sexual dimorphism in response to an NRF2 inducer in a model for pachyonychia congenita"

June 26: Angela Gritti, San Raffaele Telethon Institute for Gene Therapy, Milano, Italy, "Patient-specific iPSCs for disease modeling and cell therapy applications in lysosomal storage diseases"

June 29: Alexandre Colas, The Sanford Burnham Prebys Medical Discovery Institute Neuroscience Center, California, USA, "Regulatory Network of Cardiac Mesoderm Specification in Vertebrates"

July 3: Pr Danny Chan, University Hong Kong, "Plasticity of skeletal cells: Don't let me die, it will be a waste"

July 10: Christophe Lamaze, Curie Institute, "Membrane dynamics and trafficking selectively control JAK/STAT signaling by interferons"

July 17: Dr Edor Kabashi, Ecole des Neurosciences, "Fishing for Genes and Therapy in Amyotrophic Lateral Sclerosis"

September 8: Michaël Ploquin, 10X Genomics, "Single cell transcriptomics by 10X Genomics"

September 11: Mickaël Ménager, *Imagine*, "Inflammatory responses and transcriptomic networks"

October 2nd: Alessandra Pierani, *Imagine*: "Transient moving organizers: life and death in cortical development, evolution and pathology"

October 9: Terry Rabbitts, Weatherall Institute of Molecular Medicine, University of Oxford, United Kingdom, "From intracellular antibodies to small molecule inhibitors of mutant KRAS"

October 16: Sylvain Latour, *Imagine*, "CD70-CD27-ITK, a critical pathway in immunity to Epstein Barr virus infection"



The actors

The actors

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8 ASSOCIATED CLINICAL DEPARTMENTS

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The scientific advisory board



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KARL TRYGGVASON
Department of Medical Biochemistry
and Biophysics, Karolinska Institute,
Stockholm, Sweden

The executive committee



STANISLAS LYONNET is Director of the *Imagine* Institute. He is Professor of Genetics at Paris Descartes University since 1995, and a clinical geneticist at Necker-Enfants Malades Hospital. As the principal investigator of an INSERM group (Genetics and embryology of malformations), founding member of the *Imagine* Institute, he has conducted several studies aiming to localize and identify the genes involved in inborn errors of development. He is the author or co-author of 350 publications in peer-reviewed journals. He is responsible for the European Master of Genetics (Paris Descartes-Paris

Diderot), and served as a member of the INSERM Scientific Advisory Board. He was responsible for launching the Rare Diseases Research Program of the French National Agency for Research (ANR). He is a section editor of the European Journal of Human Genetics, and a member of the editorial board of Human Molecular Genetics. S. Lyonnet was awarded the Jean Hamburger prize in 2006, the INSERM Research Prize in 2009, and the Colliery Prize (National Academy of Medicine) in 2012. He was elected President of the European Society of Human Genetics in 2013.



LAURENT ABEL is Head of Research at INSERM. He received his MD from the University of Paris Descartes in 1988 and a PhD in Genetic Epidemiology from the University of Paris-Sud in 1993. In 2000, he co-founded with Jean-Laurent Casanova the Laboratory of Human Genetics of Infectious Diseases (University Paris Descartes/INSERM Unit 550) at the Necker Medical School, and has co-directed it with him since then. He studies human genetics of infectious diseases, with the goal of identifying the main human susceptibility/resistance genes controlling the

response to infection by various microbes (in particular, mycobacteria and oncogenic viruses), and the development of the associated infectious diseases. He is the author or co-author of more than 200 publications in peer-reviewed journals since 1986. He is the recipient of the 1999 André Lwoff prize from the Pasteur-Weizmann Council and the French Academy of Sciences. In 2009, he was appointed as a visiting professor at The Rockefeller University of New York, and in 2011 he was awarded an ERC advanced grant.



ISABELLE ANDRÉ-SCHMUTZ is a research director at INSERM and leads the research "Human lymphohematopoiesis" laboratory at *Imagine* Institute. Her main research focuses on the development of the human hematopoietic immune system, and cell therapy pre-clinical studies for inherited and acquired disease of the hematopoietic system. The research group she leads studies not only how to succeed hematopoietic stem cell transplantation in humans but also the differentiation of mouse and human stem cells towards lymphocyte lineages. She has recently identified key steps in the production of T cells, key players of immunity generated throughout the life of an individual within the thymus. This work led to the development of an artificial thymus, which will be tested in a clinical trial to reduce the immune deficiency period after bone

marrow transplantation. Her team also identified new genes involved in severe forms of inherited immune deficiencies in children and demonstrated genotoxicity of anti-viral drugs, such as AZT, used to prevent transmission of HIV during pregnancy. She is involved in several clinical trials that are based on the use of ex vivo gene modified hematopoietic stem cells to treat patients with inherited disorders. She is the author or co-author of one patent and of about 50 publications in peer-reviewed journals and was awarded with several national and European grants. She is an active member of the scientific and medical committee of the French Biomedicine Agency, the program evaluation committee of the National Agency for Research (ANR) and the committee "Immunology and Hematopoiesis" of the French League Against Cancer (La Ligue).



CORINNE ANTIGNAC is Professor of Genetics since 2001, in the Department of Genetics at Hospital Necker, University Paris Descartes. She is the Head of the INSERM Research Laboratory "Hereditary Nephropathies and Kidney Development" at *Imagine*. She studied medicine in Paris and received her degree of Doctor in Medicine in 1982, her certification in Nephrology and in Pediatrics in 1988, and a PhD in Human Genetics in 1994. Her research programs are devoted to the

identification of genes involved in rare hereditary renal diseases and to the characterization of the proteins encoded by these genes. She is the author or co-author of around 130 publications in peer reviewed journals since 1985. She is serving in the editorial board of Journal of the American Society of Nephrology and Kidney Int. She was awarded the French Medical Research Foundation prize in 2000 and the Éloi Colliery prize from the French National Academy of Medicine in 2001.



OLIVIER HERMINE After a medical education at Paris Descartes, Olivier Hermine received his MD in 1992, and his PhD in 1995, and is Professor of Hematology since 1999, director of the department of Adult Hematology since 2009, coordinator and founder of the reference centre for mastocytosis (CEREMAST) since 2007, director of the CNRS ERL 8254/INSERM U1163 "Cellular and molecular basis of haematological disorders and their therapeutic implications" since 2013, and is member of the executive committee of the *Imagine* Institute at Necker Hospital since 2011. He is co founder and coordinator of the Laboratory of excellence on red cells (GRex) and scientific director of the INTS (institut national de la transfusion sanguine). He is co-founder and director of the scientific committee of the biotechnologies AB science specialized in tyrosine kinases development and Inatherys specialized in the development

of antibodies against IgA receptors including transferrin receptor. He is author and co-author of 15 patents and of 485 publications in peer-reviewed journals. He is an active member of the International retrovirology association, the Lysa, the EMCL and EBMT and he is particularly involved in clinical and translational studies of Mantle cell lymphoma and virus related lymphoma particularly HTLV-1 and HCV, and mastocytosis. His topics of basic science cover erythropoiesis regulation and erythroid disorders, immune regulation, mast cell and mastocytosis, viral lymphomagenesis, and leukaemogenesis. He was awarded the Olga Saint prize from Ligue de Paris de recherche contre le cancer, the Jean Bernard prize from French medical research foundation in 2008, the prize of the French Medical Research Foundation in 2011, the Grand prix de la Fondation de France in 2012, and the French Academy Etancelin prize in 2014.



FRÉDÉRIC RIEUX-LAUCAT is a research director at INSERM and leads the research Laboratory "Immunogenetics of Pediatric Autoimmune diseases" at *Imagine* Institute. His main research focuses on the genetic bases and the pathophysiological mechanisms underlying juvenile autoimmune diseases such as the autoimmune lymphoproliferative syndrome (ALPS), the Evans syndrome and the juvenile Systemic Lupus Erythematosus (pSLE). His research group made seminal discoveries in the field of ALPS (germline and somatic mutations of FAS) leading to a new concept on the genetic inheritance of pediatric autoimmune diseases. Recently, his group identified the first activating mutations of TMEM173/STING, a key regulator of the type-I interferon production in patients presenting with autoinflammatory, autoimmune vasculopathies and lung fibrosis. Beyond the identification of new gene defects

in self-tolerance and autoimmunity, his team's projects also focus on a better characterization of the immunological mechanisms involved in these diseases allowing the identification of new therapeutic targets. He is involved in basic and translational research projects in local, national and European networks. He is the author or co-author of more than 90 publications in peer-reviewed journals (including Science, NEJM and JCI as senior author) and was awarded with several national and European grants as well as with the Jacques Oudin Prize in 2006. In the last years he was the president of the scientific committee in immunology and microbiology at INSERM (CSS7, 2012-2016), of the Immunology and hematology committee at the Ligue Nationale Contre le Cancer (2009-2012), and he is an active member of the executive committee and the administrative council at *Imagine*.



AGNÈS RÖTIG is Research Director at INSERM. She is the head of the laboratory "Genetics of Mitochondrial Disorders" at the *Imagine* Institute, INSERM UMR1163, University Paris Descartes. She received her PhD in Biology in 1987 from the university Pierre et Marie Curie in Paris. As a post-doctoral fellow in Necker-Enfants malades Hospital she has built her research group in the field of mitochondrial disorders in very close collaboration with the Genetic Unit of Necker Hospital. She

obtained an INSERM research position in 1990 and she developed various technologies and tools to investigate mitochondrial functions in patients with mitochondrial disorders. She was twice member of the INSERM scientific committee CSS2. She was awarded the A. Gagna & Ch. Van Heck prize in 2008 and the Fondation Claude Pompidou prize in 2015. She is the author or co-author of more than 200 publications in peer reviewed journals since 1988.

Workpackage coordinators:

WP1: To further develop exceptional cohorts – **Rémi Salomon**

WP2: To develop genomic and bioinformatics platforms – **Corinne Antignac**

WP3: To foster pathophysiological studies – **Isabelle André-Schmutz & Agnès Rötig**

WP4: To develop innovative therapies – **Marina Cavazzana**

WP5: To recruit new talents – **Stanislas Lyonnet**

WP6: To develop teaching that fulfills new research, care and industry needs – **Frédéric Rieux-Laucat**



RÉMI SALOMON is Professor of Paediatrics since 2008, working in the department of Paediatric Nephrology at Hospital Necker, University Paris Descartes. He coordinates the Reference Centre for Renal Hereditary Diseases in Children and Adults (Marhea). He studied medicine in Paris and received the degree of Doctor of Medicine in 1992 and a PhD in Genetics in 2000. His main

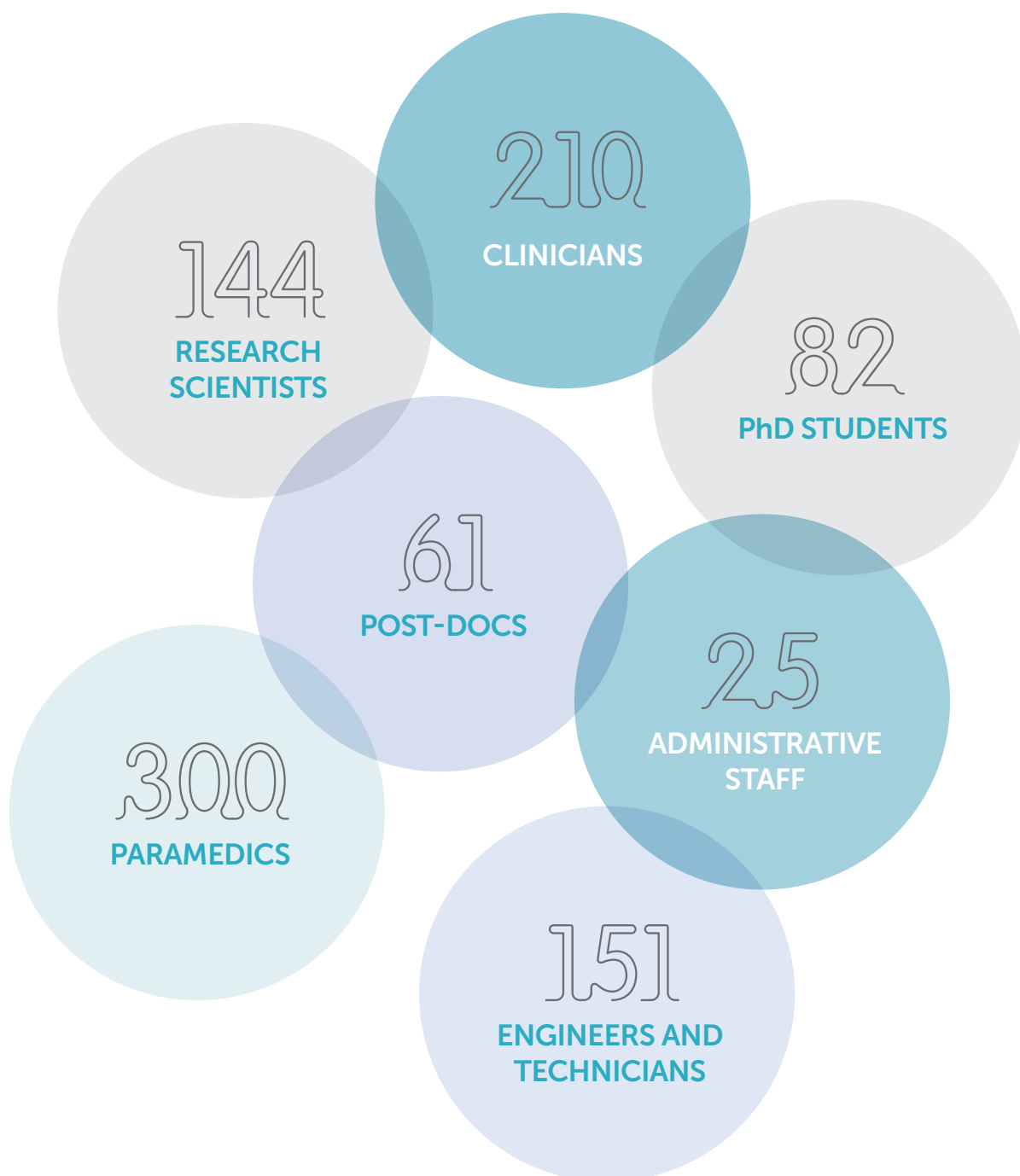
research interests are development of the kidneys and genetic diseases of the urinary system. His research activities take place in the INSERM U574 laboratory directed by Corinne Antignac. He coordinates several multicentric clinical research programs notably on nephronophthisis and renal hypodysplasia in children and fetuses in collaboration with obstetrician and fetopathologists.



MARINA CAVAZZANA is a pediatrician, Professor of Hematology since 2000, Director of the Department of Biotherapy at Necker Hospital, Paris Descartes University. She is the Director of the Inserm / Assistance Publique - Hôpitaux de Paris GHU Ouest Biotherapy Clinical Investigation Center and leads the research "Human lymphohematopoiesis" Laboratory at *Imagine* Institute. Her main research and clinical interests are the development of the hematopoietic immune system, and cell and gene therapy for inherited and acquired disease of the hematopoietic system. Her group studies the means to improve the clinical results of hematopoietic stem cell transplantation, crossing HLA-barriers, and the differentiation of mouse and human stem cells towards lymphocyte lineages. She has initiated several clinical trials based on the use of ex vivo

gene modified hematopoietic stem cells to treat patients with inherited disorders, the preliminary clinical results of which are encouraging. She is the author or co-author of one patent and of more than 240 publications in peer-reviewed journals and was awarded 2 ERC (2011 and 2016). Her work was rewarded by the American Society of Hematology (Award on Clinical Research in Gene Therapy in 1999), by the French Academy of Sciences (Special Medical Award in 2000 and Jean-Pierre Lecocq Award on Gene Therapy in 2004). She was awarded the title of Officier de l'Ordre National de la Légion d'honneur in 2011, and given the Irène Joliot Curie 2012 award "Scientific Women of the Year" (Science Academy and French Ministry of Education and Research). In 2016 she was awarded the French National Medicine Academy Prize.

Overall staff of the IHU Imagine project





The scientific groups

The scientific groups

There are 27 research groups in the *Imagine* Institute. They are grouped in 6 units affiliated to Inserm or CNRS units and Paris Descartes University.



L. ABEL

Human genetics of infectious diseases: complex predisposition



Y. CROW

Neurogenetics and neuroinflammation



C. ANTIGNAC

The molecular basis of kidney diseases: cystinosis and hereditary nephrotic syndrome



G. GOURDON

CTG repeat instability and myotonic dystrophy



J-L. CASANOVA

Human genetics of infectious diseases: Mendelian predisposition



O. HERMINE

Laboratory of molecular mechanisms of hematologic disorders and therapeutic implications



M. CAVAZZANA & I. ANDRÉ-SCHMUTZ

Human Lymphohematopoiesis Laboratory



A. HOVNANIAN

Genetic skin diseases : from disease mechanisms to therapies



N. CERF-BENSUSSAN

Intestinal immunity



S. LATOUR

Lymphocyte activation and susceptibility to EBV



L. COLLEAUX

Laboratory of developmental brain disorders



S. LYONNET & J. AMIEL

Embryology and genetics of malformations



C. COLNOT

Origins and functions of skeletal stem cells in bone regeneration



S. MEILHAC

Heart morphogenesis



V. CORMIER-DAIRE & L. LEGEAI-MALLET

Molecular and Physio-pathological bases of osteochondrodysplasia



M. MÉNAGER

Inflammatory responses and transcriptomic networks in diseases



A. MICCIO

Chromatin and gene regulation during development



A. PIERANI

Genetics and Development of the Cerebral Cortex



A. RAUSELL

Clinical bioinformatics Lab



F. RIEUX-LAUCAT

Immunogenetics of pediatric autoimmune diseases



A. RÖTIG

Genetics of mitochondrial diseases



J.-M. ROZET

Genetics in ophtalmology



G. DE SAINT-BASILE

Normal and pathological homeostasis of the immune system



S. SAUNIER

The molecular bases of the hereditary kidney diseases nephronophthisis and renal hypodysplasia



M. SIMONS

Epithelial biology and disease



A. SMAHI

Genetics of monogenic auto-inflammatory diseases



J.-P. DE VILLARTAY & P. REVY

Genome dynamics in the immune system

ASSOCIATED LABORATORIES:



N. BODDAERT

Image at *Imagine*



M. POLAK

Molecular basis of several congenital or neonatal endocrine disorders and establishment of new therapeutic strategies



S. SARNACKI & I. BLOCH

Imag2 - Computational anatomy for image-guided minimally invasive surgery in pediatric tumoral and developmental diseases

INFLAMMATORY RESPONSES AND TRANSCRIPTOMIC NETWORKS IN DISEASES



Mickaël Ménager, PhD completed his thesis under the direction of Geneviève de St Basile at Necker-Enfants malades hospital in 2008. He then moved to New York University School of Medicine to continue his studies. Aged 36, he has contributed papers to prestigious scientific journals. In June 2017, he returned from the United States to *Imagine* to head up the "Inflammatory Responses and Transcriptomic Networks in Diseases" research group. Laureate of the French ATIP-Avenir Program for the Promotion of Young Researchers in 2016, Mickaël Ménager has also just been announced as the winner of the French National Institute of Health and Medical Research (INSERM) CR1 research competition.

His research work will boost *Imagine*'s pool of expertise in immunology (teams working with Isabelle André-Schmutz and Marina Cavazzana, Nadine Cerf-Bensussan, Yanick Crow, Geneviève de Saint Basile, Sylvain Latour and Frédéric Rieux-Laucat), in bioinformatics (Antonio Rausell's team, director of the Clinical Bioinformatics lab, which joined *Imagine* in March 2016), and in virology.

MAIN RESEARCH AREAS OF INTEREST

The originality of Mickaël Ménager's approach lies in combining high-end transcriptome analysis at individual cell level and chromatin accessibility experiments with powerful new computational biology tools as a novel and impartial model for exploring complex innate immune responses and autoinflammation. The idea is to use the emerging field of network inference analysis based on transcriptome data to open up a deeper and impartial understanding of the diversity of molecular mechanisms behind autoinflammatory diseases.

Mickaël Ménager is also interested in the interactions between dendritic cells and HIV approached via two complementary research routes. The first studies dendritic cell responses to HIV infection, while the second approach seeks to discover the molecular and cellular aspects of HIV transmission between the dendritic cells and T lymphocytes to assess the importance of this process in particular diseases.

For further information on his research, go to:
<http://institutimagine.org/fr/la-recherche/25-laboratoires-de-recherche/255-inflammatory-responses-and-transcriptomic-networks-in-diseases.html>

GENETICS AND DEVELOPMENT OF THE CEREBRAL CORTEX



Alessandra Pierani, *Imagine* Institute and Institute of Psychiatry and Neurosciences of Paris, France

Alessandra Pierani is Director of Research at the National Center for Scientific Research (CNRS). She heads the team "Genetics and Development of the Cerebral Cortex" with a dual affiliation at the *Imagine* Institute (Institute of genetic diseases, Necker Hospital, Paris) and the Institute of Psychiatry and Neurosciences of Paris (IPNP, St Anne Hospital, Paris).

She obtained two PhDs in Biology at the University of Florence (1986) and University of Paris XI (1994) and trained first as a molecular biologist and biochemist at the Rockefeller University (New York) where she provided the first evidence of the existence of "co-activators" as mediators of tissue-specific transcriptional control. She then began her work on neural development at the Institut Curie (Orsay) and pursued it at Columbia University (New York) and the École Normale Supérieure (Paris).

In particular, she focused on the mechanisms controlling patterning of the nervous system and the function of the Dbx1 transcription factor in the identity of spinal cord interneurons using mouse genetics, cell tracing and ablation. Her work demonstrated that these neurons play key roles in physiological processes such as left-right alternation during locomotion and breathing. In 2006 she established her group at the Institut

Jacques Monod in Paris working on the role of the Dbx1 gene and its progeny in patterning of the cerebral cortex.

Her team has since made major contributions in the field of cortical development by identifying novel populations of neurons, including Cajal-Retzius subtypes and Cortical Plate Transient neurons, with unique characteristics of long-range migration, signalling activity and transient life during development. They have shown that these neurons serve as organizers of cortical patterning and glutamatergic neuron production.

The group recently showed that transient variations in the kinetics of arrival of migrating signalling neurons during early development or of their death at the end of corticogenesis have profound consequences on the construction of normal and pathological circuits. Dr. Pierani's research focuses on the role of transient neuronal populations in cerebral cortex development, evolution and pathology.

She was awarded a CNRS-ATIP grant (1999), a City of Paris prize (2006), an Equipe FRM grant in 2013 and the Foulon Prize of the French Academy of Science in 2012.

Dr. Pierani has mentored the work of 8 PhD and 21 undergraduate students, 12 postdoctoral fellows and 6 technicians. She delivers courses (ENS Paris, ENS Lyon, University Paris Diderot and Descartes, UPMC, Sweden, Italy, Argentina) and is an invited speaker nationally and internationally. She is a reviewer for over 20 scientific journals and over 15 national and international granting agencies.

GENE THERAPY RECOGNIZED AS A "MAJOR AREA OF INTEREST" (DIM) BY THE PARIS REGION.

On December 15, 2016 the Paris region revealed its new "major Areas of interest" (DIM) for the 2017–2020 period. The "gene therapy" DIM, coordinated by prof. Marina Cavazzana and supported by *Imagine* Institute, was chosen to further the development of gene therapy and consolidate its reputation as one of the most innovative and promising treatments in the field of personalized medicine. Under the auspices of the DIM, key players in Paris region (doctors, scientists, facilities, manufacturers) will receive the coordination and support they need to progress current and future developments and widen the scope to include treatments for common diseases.

The multi-year budget set aside for the "Gene Therapy" DIM will be used mainly to recruit internationally renowned scientists, associate scientists, post-doctoral candidates, PhD

students, engineers or technicians, and to establish and share technological platforms.

The designation of "Gene Therapy" as a DIM will enable us to:

1. Consolidate a functioning ecosystem that brings together all the players necessary for the development of this treatment: academics, medics, manufacturers, the associative sector and social economists;
2. Make the Paris region more attractive to international experts from academia and industry;
3. Promote the development and production of new gene-therapy protocols for patients suffering from rare and more common diseases. Moreover, this designation recognizes the Paris region community's pioneering and highly innovative approach in the field of gene therapy.



Team:

Researchers:

Alexandre Alcaïs
Aurélien Cobat
Jean-Philippe Jais

Post-doctoral fellows:

Matthieu Bouaziz
Jeremy Manry

Students:

Frédérique About
Chaima Gzara
Fabienne Jabot-Hanin
Gaspard Kerner
Jocelyn Quistrebart

Research assistants:

Cécile Patissier
Soraya Boucherit
Vimel Rattina

Publications:

1. Cobat A, Gallant CJ, Simkin L, .../..., Casanova J-L, Abel L, Hoal EG, Schurr E, Alcaïs A. Two loci control tuberculin skin test reactivity in an area hyperendemic for tuberculosis. *J. Exp. Med.* 2009;206:2583–2591.

2. Patin E, Kutalik Z, Guernon J, .../..., Pol S, Bochud PY, Abel L. Genome-Wide Association Study Identifies Variants Associated With Progression of Liver Fibrosis from HCV- Infection. *Gastroenterology*. 2012; 143: 1244-52.

3. Grant AV, El Baghdadi J, Sabri A, .../..., Rasolofo V, Casanova JL, Abel L. Age-dependent association of pulmonary tuberculosis with common TOX variants in the 8q12-13 linkage region. *Am J Hum Genet* 2013. 92:407-14.

4. Belkadi A, Bolze A, Itan Y, Cobat A, Vincent QB, Antipenko A, Shang L, Boisson B, Casanova JL, Abel L. 2015. Whole-genome sequencing is more powerful than whole-exome sequencing for detecting exome variants. *Proc Natl Acad Sci USA* 112: 5473-8.

5. Belkadi A, Pedergnana V, Cobat A, Itan Y, Vincent QB, Abhyankar A, Shang L, Alcaïs A, Boisson B, Casanova JL, Abel L. 2016. Whole-exome sequencing to analyze population structure, parental inbreeding, and familial linkage. *Proc Natl Acad Sci USA* 113: 6713-8.

HUMAN GENETICS OF INFECTIOUS DISEASES: COMPLEX PREDISPOSITION

Our group aims to identify the main genes and the corresponding variants involved in the determinism of common infectious diseases. It is also involved in the development of statistical methods in human genetics, since data analyses often raise methodological issues that then we seek to resolve. In particular, we have developed several approaches to improve and optimize the analysis of next generation sequencing (NGS) data. Our studies of infectious diseases mainly focus on infections caused by virulent mycobacteria and certain oncogenic viruses. Our main results over recent years include:

1. In leprosy, after the identification by positional cloning of two major leprosy susceptibility variants (in PARK2/PACRG and LTA genes), we successfully replicated and refined the role of some HLA-C alleles, as well as the role of variants in genes also involved in Crohn's disease, validating the striking overlap in the genetic control of this disease with leprosy.

2. In tuberculosis (TB), we identified variants in the gene TOX that are strongly associated with the development of early-onset pulmonary TB (before 25 years of age). Moreover, we discovered additional cases of Mendelian predisposition in disseminated forms of TB in children, due to mutations in TYK2 in particular. Finally, we recently showed replication of the TST1 locus involved in resistance to TB infection in populations of different ethnic origin.

3. In Hepatitis C virus (HCV) infection, we conducted the first genome-wide association study (GWAS) on liver fibrosis caused by chronic HCV infection. We identified several susceptibility loci for HCV-induced liver fibrosis related to the apoptosis pathway, providing new insights into the mechanisms underlying fibrosis development and paving the way for novel therapeutic strategies. We also identified another susceptibility loci for HCV-induced liver fibrosis

4. From a methodological point of view, we extended family-based association tests to accommodate variants that are imputed in large GWAS. More recently, we are developing methods to facilitate the interpretation and the identification of disease-causing mutations from NGS data of patients with the same disease. We also showed that whole genome sequencing (WGS) was more powerful than whole exome sequencing (WES) for detection of exonic variants, and that WES data could be used for analysis of population stratification as well as for linkage analyses.

We are extending our work on TB and leprosy by studying new phenotypes (subjects highly resistant to TB infection and reversal reactions in leprosy) and collecting new samples. We have an ongoing project on the genetic basis of Buruli ulcer, the third most common mycobacterial disease. We will continue our work on the most severe HCV- and HBV-related complications such as liver cirrhosis and hepatocarcinoma. Our strategy combines a candidate gene/pathway strategy with genome-wide (GW) approaches. In particular, we are now investigating the role of rare variants with strong individual effects using WES and WGS studies which needs the development of specific analysis methods. All these projects are being performed in large field studies that we are coordinating and involve many collaborators.

Together with the other research group in the laboratory (JL Casanova), we are also investigating the genetic control of some of these infections from the perspectives of both Mendelian predisposition to rare phenotypes (e.g. severe TB or fulminant hepatitis) and complex predisposition to common phenotypes (e.g. pulmonary TB or HCV/HBV infection). The identification of host genes involved in human infectious diseases will provide new keys to understanding the pathogenesis mechanisms underlying disease development, with potentially major practical implications for the control of infectious diseases.



Team: Research scientists and clinicians:

Géraldine Mollet
Olivia Boyer
Aude Servais

Graduate students:

Sara Goncalves
Guillaume Dorval
Giulia Menara
Francesco Miscia

Research assistants:

Olivier Gribouval
Christelle Arrondel
Bruno Estebe
Julie Patat
Sonia Keddani

Post-graduate fellows:

Frances Tilley
Daniel Pouly

Publications:

1. Braun D et al. Mutations in KEOPS-complex genes cause nephrotic syndrome with primary microcephaly. *Nat Genet.* 2017 Aug 14. doi: 10.1038/ng.3933.

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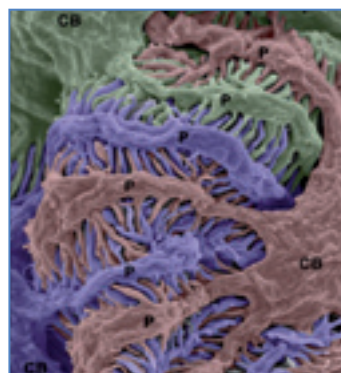
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THE MOLECULAR BASES OF KIDNEY DISEASES: CYSTINOSIS AND HEREDITARY NEPHROTIC SYNDROME

The research projects of our team are focused on two major topics; cystinosis and hereditary nephrotic syndrome. These projects stem from the seminal work done by our group that identified the *CTNS* gene involved in cystinosis in 1998, and the *NPHS2* gene encoding podocin in 2000, the first gene identified in steroid-resistant nephrotic syndrome (SRNS).

Cystinosis is an inherited lysosomal storage disorder characterized by a defective lysosomal efflux of cystine, a proximal tubulopathy being the main and earliest renal symptom of the disease. The causative gene, *CTNS*, encodes a glycosylated lysosomal membrane protein, cystinosin, which acts as a cystine-proton symporter. We recently showed that cystinosin is a component of the mTORC1 pathway and that absence of cystinosin (and not cystine accumulation) lead to a delayed and/or blunted activation of the mTORC1 pathway upon amino acid stimulation in proximal tubular cell lines, thereby identifying an additional role for cystinosin beyond lysosomal cystine export (3). We are now further dissecting the **role of cystinosin in the mTORC1 signaling pathway** in the early course of the disease in young *Ctns*^{-/-} mice and in renal organoids developed from induced pluripotent stem cells (iPSC) from patients with various types of mutations. In addition, we further characterize the role of cystinosin in the amino acid sensing machinery by assessing its role in the v-ATPase/Ragulator/Rags interactions.

Nephrotic syndrome is a clinical entity characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia and edema. The identification of genes involved in rare familial forms of SRNS has highlighted the crucial role played by the podocyte, a highly specialized glomerular cell, in the integrity of the glomerular filtration barrier. Almost 50 genes have been identified to date that, if mutated, are responsible for monogenic forms of SRNS. Most of these genes encode proteins expressed in the podocyte, particularly structural proteins and actin network regulators.



Podocyte are traditionally divided into three kinds of subcellular compartment, cell body (CB), primary process. Conventional SEM image shows the luminal surface of all three kinds of podocyte subcellular compartments. Three neighboring podocytes are individually colored with blue, green, and red.
From Ichimura et al., 2015 (PMID:25759085) @creative commons.

We have have described the crucial role of podocin dimerization in the pathogenicity of NPHS2 mutations, leading to incomplete penetrance of some associations of mutations⁵. Mutations in this gene, originally found by our group, are responsible for more than 40% of SRNS and these results have a direct impact on patients care, both clinically and for genetic counseling, and open new perspectives for evaluating the pathogenicity of mutations in autosomal recessive diseases.

We have also identified mutations in several genes mutated in syndromic forms of SRNS, such as SGPL1 allowing us to describe a novel phenotypic association comprising SRNS, adrenal deficiency, ichthyosis and immunodeficiency². In addition, our group has identified the first genes involved in Galloway-Mowat syndrome (GAMOS), associating microcephaly and SRNS: (WDR73)⁴ as well as, more recently, four genes, encoding all subunits of the highly conserved KEOPS complex¹. Mutations in these genes affect both the kidney and the nervous system, in line with growing evidence that podocytes and neurons share a large set of common features. Moreover, our discovery of mutations in genes such as TTC21B and WDR73 has highlighted the emergent role of proteins involved in microtubule dynamic and organization in podocyte pathophysiology.

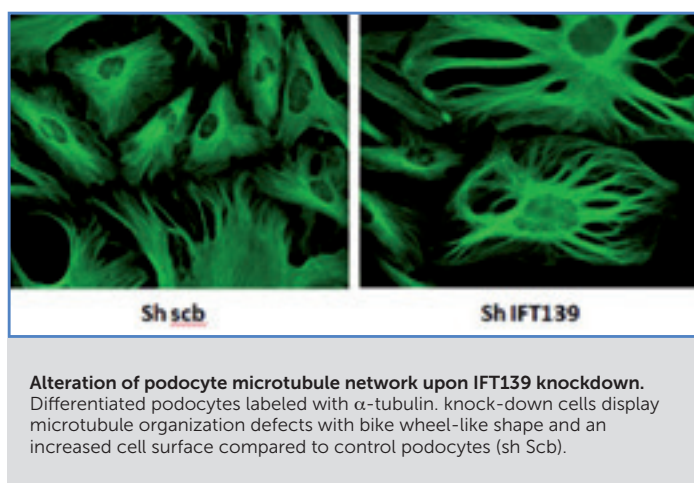
The main objective of our group is to unravel new actors and molecular networks driving podocyte differentiation and/or maintenance, and to identify new pathophysiological mechanisms leading to SRNS, especially those related to actin/microtubule networks and cell survival.

Our projects comprise:

1) the study of podocin biogenesis, trafficking and degradation, as well as screening of molecules modifying podocin folding and trafficking with the aim of testing new and innovative therapies,

2) the identification of new genes involved in SRNS (especially in GAMOS) by next-generation sequencing and the characterization of their gene products by using cellular models, as well as knock-in and knock-out animal models (fruit fly *Drosophila melanogaster*, zebrafish and mouse) generated with the CRISPR/Cas9 technology.

3) the modeling of hereditary nephrotic syndrome in kidney organoids derived from iPSCs of patient's cells with isolated SRNS (especially GAMOS) in order to generate new insights into the molecular pathways altered in these disorders.





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HUMAN GENETICS OF INFECTIOUS DISEASES: MONOGENIC PREDISPOSITION

Our team aims to determine the molecular basis of the monogenic determinism of rare and common infectious diseases in children. We hypothesize that a substantial fraction of children with severe infectious diseases suffer from novel single-gene inborn errors of immunity, resulting in a specific susceptibility to one or a few microorganisms. During the last years, we have provided further evidence supporting this hypothesis, with the discovery of the molecular genetic basis of:

The syndrome of Mendelian predisposition to mycobacterial disease (MSMD), severe pediatric tuberculosis, and syndromic forms of mycobacterial disease, due to mutations of IFN- γ immunity. We discovered new recessive etiologies of mycobacterial disease, in patients carrying specific mutations of: 1) ISG15 in patients with mycobacterial disease and auto-immunity, 2) TYK2 in patients with mycobacterial and viral infections, and 3) RORC in patients with mycobacterial and fungal infections.

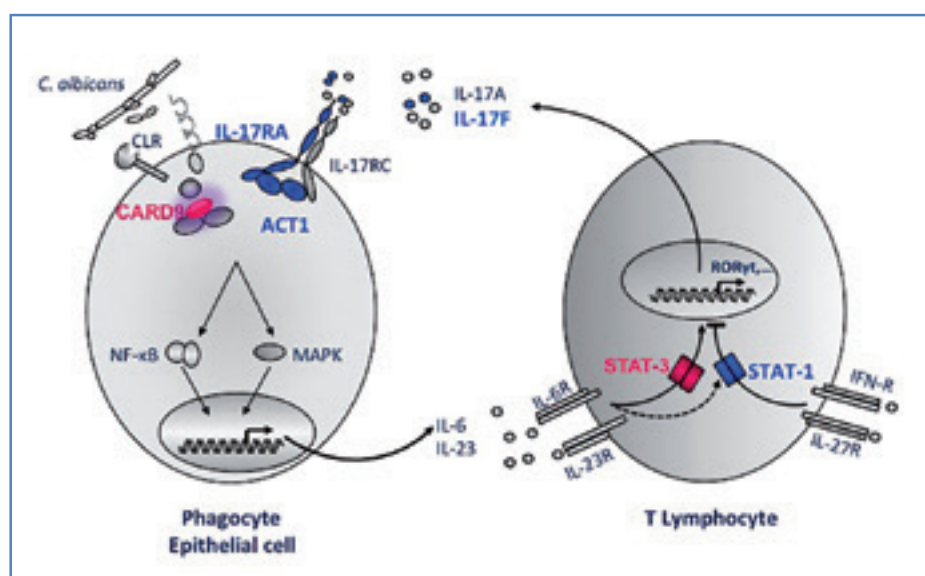
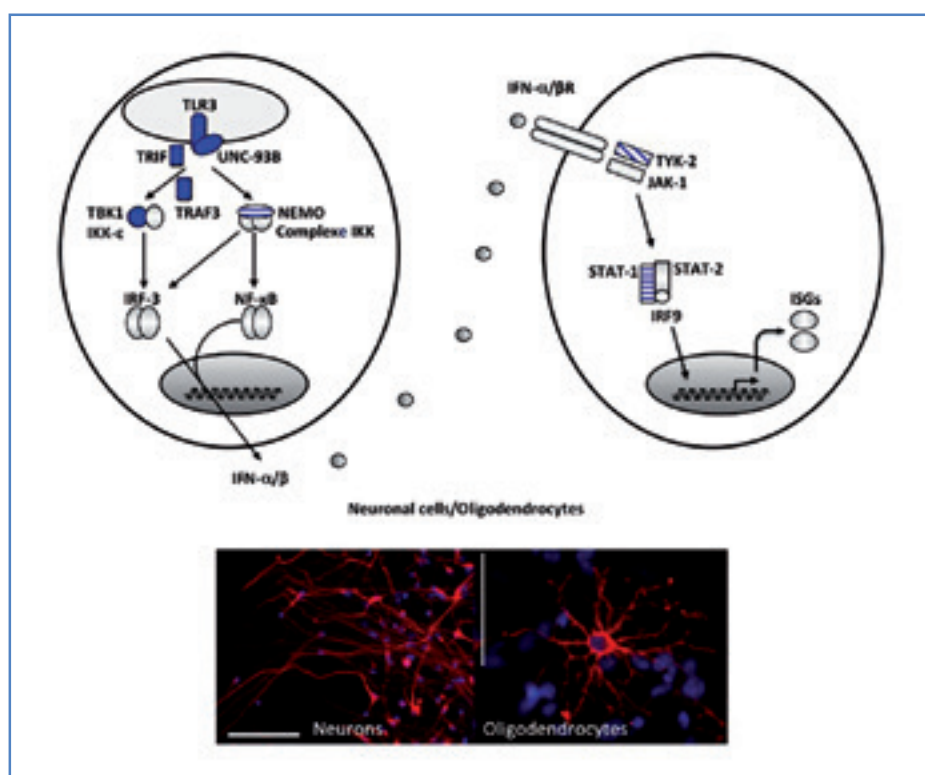
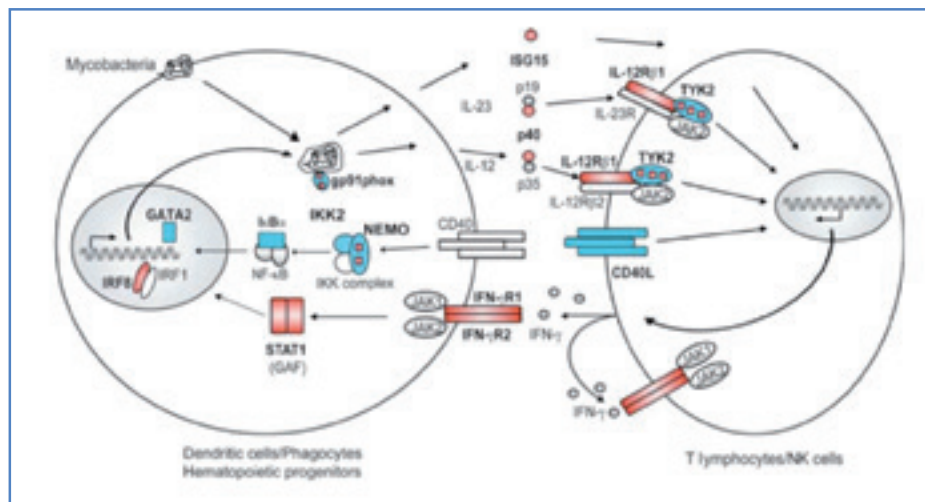
Invasive pneumococcal disease (IPD) due to mutations in the NF- κ B pathway. Following on our identification of NEMO, IRAK4, and MyD88 deficiencies, we identified the first patients with impaired linear ubiquitination, due to mutations in HOIL-1 or HOIP, two components of the LUBAC. These patients have auto-inflammation and bacterial infections. Linear ubiquitination via LUBAC is thus essential for the modulation of inflammation and the control of bacterial infections.

Life-threatening influenza due to IRF7 deficiency. The amplification of anti-viral IFNs is IRF7-dependent in both plasmacytoid dendritic cells (PDCs) and induced pluripotent stem cell (iPSC)-derived pulmonary epithelial cells. Herpes simplex encephalitis (HSE) due to inborn errors of TLR3 immunity. The pathogenesis of HSE involves the impairment of IFN production by neurons and oligodendrocytes in the central nervous system.

Epidermodysplasia verruciformis (EV), due to papillomaviruses, and Kaposi sarcoma (KS), due to human herpes virus 8. Both conditions can result from inborn errors of T cell immunity (mutations in RHOH and MST1 for EV, and mutations in STIM1 and OX40 for KS). Other acute viral conditions, such as fulminant viral hepatitis, are also being studied.

Fungal diseases, such as chronic mucocutaneous candidiasis disease (CMCD) and deep dermaphytosis disease (DDD). CMCD results from inborn errors of IL-17 immunity (loss-of-function mutations in IL17F, IL17RA and ACT1, and gain-of-function mutations in STAT1) and DDD from bi-allelic null mutations in CARD9. Invasive fungal diseases, such as cryptococcosis and aspergillosis, are also being studied.

These projects are based on a worldwide recruitment of patients, and a cutting-edge strategy combining genome-wide investigations, in particular using next-generation sequencing, with in-depth functional studies of leukocyte subsets or iPSC-derived non-hematopoietic cells. Overall, our work provides proof-of-principle that severe infectious diseases in otherwise healthy children and young adults, in the course of primary infection, may result from single-gene inborn errors of immunity that rarely display complete penetrance. This provides a model for the genetic architecture of severe infectious diseases. Our studies also showed that certain immunological pathways play a relatively narrow role in protective immunity to infections in natural conditions, at odds with the mouse model of experimental infections.





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HUMAN LYMPHOHEMATOPOIESIS

The common denominator of our project is the human lymphohaematopoietic system, characterized by cells with differing self-renewal and differentiation capacities as a function of the individual's age and clinical status (i.e. healthy or diseased). In adult mammals, haematopoiesis (i.e. the expansion and differentiation of haematopoietic stem cells into blood cells in the bone marrow) undergoes constant, tightly regulated renewal and undergoes profound changes over the lifespan.

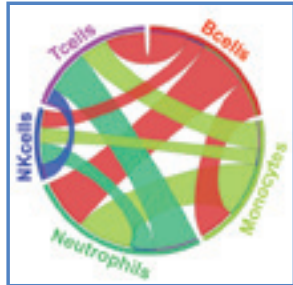
Understanding of the hierarchy of human haematopoiesis and the different steps in T and B cell differentiation in the healthy body and in very particular disease situations constitutes the most fundamental part of our research project. Overall, the knowledge generated by these studies will help us to actively implement new treatment protocols. Haematopoietic stem and progenitor cells (HSPCs) harvested from a healthy or diseased individual and ex vivo gene modifications constitute essential tools for curing most severe, cell-intrinsic, inherited defects of the lymphohaematopoietic system. Nevertheless, several issues still compromise the full success of these types of therapies.

Improvements in this HSPC-based strategy have resulted from progress and discoveries provided by the first part of our project and by other research groups. The most recent findings on the characteristics of human T cells (i.e. their long life, self-renewal capacity, homeostasis and functions) have prompted us and others to consider their in vivo use after ex vivo manipulation - paving the way for less toxic therapeutic approaches.

1. HSPC homeostasis and hematopoietic hierarchy

The follow-up of gene therapy trials performed in the Biotherapy Department give us the unique opportunity to track progenitor cells and their descendants through deep sequencing analysis of retroviral integration sites (RIS) (a collaboration with F. Bushman (University of Pennsylvania, Philadelphia, USA)). This extensive RIS analysis is conducted in the context of several immunodeficiencies (such as SCID-X1, WAS, and beta-thalassemia). The major advances in integrase knowledge provide unique information on human hematopoietic ontogeny that can be inferred by integration

sites tracking in fractionated blood cell populations. In the Wiskott-Aldrich Syndrome (WAS) patients, this clonal tracking highlights a diversity of hematopoietic differentiation programs with different levels of contribution to the myeloid and lymphoid lineages. These new findings provide unique data on human hematopoiesis.



Circos plot showing integration sites sharing between lineages. Sharing of integration site is depicted for one WAS patient 3 years after gene therapy treatment. The proportion of integration sites shared between myeloid (Neutrophils and Monocytes) and lymphoid (B cells, T cells and NK cells) lineages is represented by the ribbons connecting each combination of two lineages. Six Emmanuelle

2. STUDY OF PATHOLOGICAL T AND B CELL DIFFERENTIATION

We have a unique opportunity to study a cohort of patients presenting intrinsic cellular defects at different stages in the hematopoietic differentiation process. These “natural” models provide us with key information for implementing our knowledge of human hematopoietic development and homeostasis. Our cohort of primary immunodeficiency (PID) patients includes those with combined T and B cell defects. Some PIDs are related to a peripheral defect in the late phase of lymphoid differentiation or maturation, whereas others are related to a central defect with an early block in B and T differentiation. Two examples are presented here:

a. Moesin deficiency: a T-cell and B-cell defect compromising the migration/survival of the two lineages

We have been interested by the similar clinical features of 7 male patients. During childhood, most of them developed severe varicella, pneumopathies and recurrent pulmonary infections. All the patients have a severe peripheral leucopenia, hypogammaglobulinaemia and a poor response to vaccinal Ag. Despite the severe leucopenia, Igs and prophylactic treatment appeared sufficient to prevent severe infections. Among the T lymphocytes, the naïve compartment was particularly low and T cell proliferation in vitro decreased as compared to the controls. Using exome-sequencing analysis, we have identified in all patients the same missense mutation in the moesin gene, a member of the ERM protein family, which links plasma membrane proteins with actin-based cytoskeletons and is implicated in various cellular functions such as survival, adhesion, migration and activation.

b. B-cell defects: immunoglobulin switch recombination deficiencies

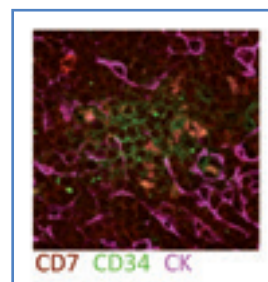
We have a unique opportunity to study a cohort of primary immunodeficiency (PID) patients including primary antibody deficiencies and combined T and B cell defects. Some PIDs are related to a peripheral defect in the late phase of lymphoid differentiation or maturation, whereas others are related to a central defect with an early block in B and T differentiation. Disturbed PI3K/AKT/mTOR signaling as disease causing mechanism for PIDs is one of our main focus of studies.

3. FROM BENCH TO BEDSIDE: THE CHALLENGE OF TRANSLATIONAL MEDICINE

The ideal treatment for a number of PIDs is replacement of the patient's HSPCs by allogeneic healthy or autologous gene modified ones. However, allogeneic or gene modified autologous hematopoietic stem cell transplantation (HSCT) faces common as well as specific obstacles. Common obstacles are related to the inflammatory cytokines present at the time of treatment, the need to obtain “empty niches” without inducing toxicity and the long time period needed to reconstitute the adoptive T-cell compartment. This last obstacle is responsible for 30% of deaths when the patient presents on-going, severe, opportunistic infections and the HSPC donor is only partially HLA-compatible. This obstacle could be solved through an acceleration of T-cell generation by ex vivo generated T-cell progenitors.

a. Acceleration of T cell generation by transplantation of ex vivo generated T-cell progenitors

We have developed a new culture system based on the immobilized Notch ligand DL-4. Culture of human HSPCs in this system enabled the in vitro generation of large amounts of T-cell progenitor cells and accelerated T-cell reconstitution after HSCT in NSG mice. This culture system thus provides a feeder-cell-free culture technique mimicking the thymic niche, with the potential for rapid, safe transfer to a clinical setting. In this context, the project aims at (i) translating the protocol into a clinical trial, (ii) further enriching this artificial thymic niche by identifying thymic factors implicated in the recruitment, growth and commitment of HSPCs, and (iii) understanding how ex vivo generated T-cell precursors migrate to the thymus and participate to the regeneration of the thymic stroma.



CD34+ lymphoid progenitors (green) seed the thymus (pink) and immediately engage in the process of thymopoiesis in specialized thymic niches (as illustrated by CD7 expression (red)). André-Schmutz Isabelle.

b. Gene therapy and hereditary disorders

With the Biotherapy Department and the fundamental research laboratory, gene therapy trials constitute a real challenge to not only cure patients with rare genetic diseases but also to better understand the clinical aspects of these disorders. Today, gene therapy is necessary as a means of treatment of extreme power and extraordinary efficiency.

The use of haematopoietic stem cells to correct genetic disorders is the main task in our laboratory and induces high expectations for paediatric patients enrolled into our clinical studies:

- Pre-clinical studies: Fanconi anemia, sickle cell disease, IPEX syndrome or severe combined immunodeficiency, familial hemophagocytic lymphohistiocytosis type 3, HIV.
- Clinical studies: Wiskott-Aldrich syndrome, sickle cell disease, beta-thalassemia, CGD, CD45RA.

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Publications:

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J., Cerf-Bensussan N Meresse, B. Interleukin 15-dependent T cell-like innate intraepithelial lymphocytes develop in the intestine and transform into lymphomas in celiac disease. *Immunity*. 2016 ; 45: 610-25.

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INTESTINAL IMMUNITY

With a 300m² surface, the intestine is the main body's interface. This wide surface is indispensable for efficient digestion and absorption. Yet, it is colonized after birth by a vast and complex community of microbes, which utilize host-derived resources, while reciprocally playing an increasingly recognized role in host metabolic and signalling pathways. To cope with the gut microbiota and preserve mutualistic interactions, the gastrointestinal tract has evolved into a highly dynamic and tightly regulated barrier, inside which epithelial cells cooperate with immune cells of hematopoietic origin to restrict body access to microbes and undigested food antigens while avoiding deleterious inflammation and tissue damage. Impairment of one of the many mechanisms, which sustain the gut barrier, can result in severe human diseases. By dissecting the genetic bases of severe intestinal diseases, we expect to delineate key effector and regulatory mechanisms of the human gut barrier and, simultaneously, to identify new diagnosis tools and rationale-based therapeutic strategies. In parallel, we intend to pursue our past work, which has identified Segmented Filamentous Bacterium as a key driver of the post-natal maturation of the mouse gut immune barrier in order to identify the mechanisms of its unique stimulatory properties and to translate results obtained in mice to humans.

Pathogenesis of severe human enteropathies

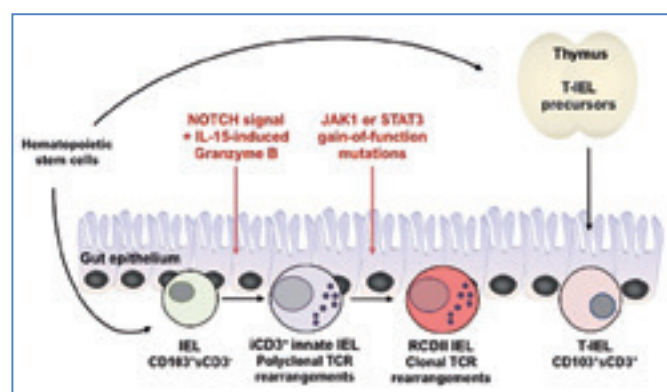
1- Coeliac disease (CD): is a long-standing axis of research for our team, which coordinates a National INCA network for diagnosis and treatment of complicated CD. This frequent autoimmune-like disease is driven by chronic ingestion of wheat-derived gluten in genetically predisposed individuals. CD is generally cured by a strict gluten-free diet, and past studies from several groups have shown how HLA-DQ2 molecules, the main genetic predisposing factor, can orchestrate the activation of gluten-specific CD4+ T cells. Yet, severe complications can develop, notably irreversible

autoimmune diseases and intestinal lymphomas. CD is thus a model disease to analyse the overlapping mechanisms that prevent autoimmunity and adverse responses to food proteins in humans as well as the links between chronic inflammation and lymphomagenesis. Based on the analysis of a large cohort of well-characterized patients, on in situ and ex vivo analyses of human intestinal lymphocytes and on mouse models, we investigate the mechanisms that drive intestinal tissue damage and lymphomagenesis. We have shown that interleukin 15 (IL-15) is a key player. This cytokine impairs local immunoregulation and cooperates with antigen-specific CD4+ T cells to activate cytotoxic lymphocytes and tissue damage. IL-15 can also promote the onset of lymphomas from an unusual subset of lymphocytes that we have identified in the gut epithelium. The latter lymphocytes differentiate locally from bone marrow-derived precursors in response to sequential NOTCH and IL-15 signals. NOTCH signals initiate T cell differentiation, revealed by expression of intracellular CD3 (iCD3+) and evidence of T cell receptor rearrangements. IL-15 induces Granzyme B, a protease that cleaves NOTCH into a peptide deprived of transcriptional activity. As a consequence, T cell differentiation is prematurely stopped. Cells are redirected by default toward the NK pathway and acquire NK markers and function. While innate-like iCD3+ lymphocytes form a minor polyclonal subset of lymphocytes in the normal adult gut epithelium, their massive clonal expansion is a diagnosis hallmark of CD-associated lymphomas. Strikingly, in many cases, malignant innate-like T cells display gain of function somatic mutations in JAK1 and/or STAT3, which confer a selective advantage in the cytokine (IL-15-) rich environment of the coeliac intestine. Our present work aims at further dissecting the mechanisms that drive malignant transformation and progression from low- to high-grade lymphomas and at using these results to improve diagnostic and therapeutic strategies.

Differentiation of innate ICD3⁺ intraepithelial lymphocytes (IEL) in the normal gut epithelium and role of somatic mutations in driving the their clonal expansion in type II refractory coeliac disease (RCDII), a low grade proliferation which often precedes the onset of overt lymphoma in CD (Reproduced from Ettersperger, Montcuquet et al, Immunity 2016)

2- Mendelian inherited intestinal disorders

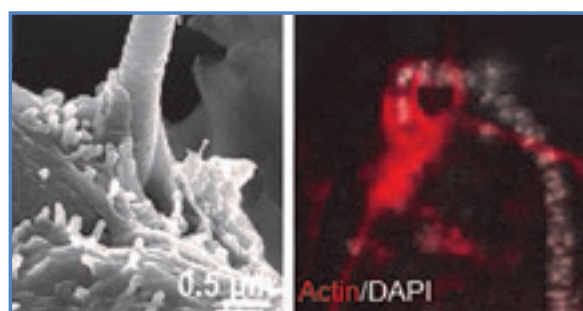
This more recent axis of research is currently supported by an Advanced ERC grant and has two complementary goals: - to take advantage of monogenic diseases to identify non redundant mechanisms indispensable to sustain the human gut barrier; 2- to set up a diagnosis platform and improve the care of these rare but life-threatening diseases. Patients are studied in collaboration with clinicians in France (Immunobiota protocol) and in Europe (GENIUS network). The molecular defect is searched for by combining phenotype-based functional analyses, custom made targeted gene panel sequencing and whole exome sequencing. A known Mendelian disease was identified in 32 % of the first 215 patients with early onset intestinal disorders already investigated and a diagnosis strategy has been proposed depending on the clinical phenotype. Novel mutations in the IL-10 receptor causing very early onset colitis have been found, including one with a founder effect as well as mutations in MALT1 as a cause of autoimmune enteropathy combined with severe immunodeficiency. Biallelic mutations in the epithelial NADPH oxidase DUOX2 have been identified as a novel monogenic cause of early onset colitis. Several novel candidate genes are under study and highlight the cooperative role of the epithelial or the hematopoietic components of the gut barrier in intestinal homeostasis. In parallel to this work, an H2020 program coordinated by F. Ruemmele aims at assessing and improving therapy of pediatric inflammatory bowel diseases.



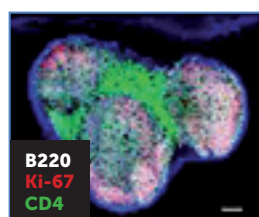
Differentiation of innate ICD3⁺ intraepithelial lymphocytes (IEL) in the normal gut epithelium and role of somatic mutations in driving the their clonal expansion in type II refractory coeliac disease (RCDII), a low grade proliferation which often precedes the onset of overt lymphoma in CD (Reproduced from Ettersperger, Montcuquet et al, Immunity 2016)

Host-microbiota cross-talk and development of the intestinal barrier

The gut microbiota has emerged as a key determinant in health and disease. One outstanding challenge is now to identify which members of the microbiota are indispensable to promote host fitness and to delineate their mechanisms of action. Based on analyses led in gnotobiotic mice, we have demonstrated that Segmented Filamentous Bacterium (SFB) is indispensable to drive the post-natal maturation of the mouse gut immune barrier. SFB is notably a potent inducer of secondary and tertiary gut lymphoid tissue. It strongly stimulates IgA secretion and intestinal T cells and, most strikingly, is indispensable to launch gut homeostatic TH17 responses. Unlike other commensals, which typically reside in the intestinal lumen and have limited access to the intestinal surface, SFB is unique in that it intimately attaches to ileal epithelial cells. This attachment is species-specific, suggesting a co-evolutionary symbiosis between SFB and its many vertebrate hosts. Based on the hypothesis that SFB growth requires direct contact with live epithelial cells, we have developed a method for in vitro culture of SFB, which allows to recapitulate its very characteristic life and to induce a transcriptomic epithelial response similar to that observed in vivo. Thus, attachment allows SFB access to host resources indispensable for its growth. Conversely, colonization of SFB does not lead to pathology but induces as yet poorly defined signals, which stimulate innate and adaptive immunity. Our goals are now to identify the mechanisms of SFB stimulation at the cellular and molecular levels, to define whether SFB is part of the human microbiota and if so, to define its impact on the intestinal immune barrier in health and diseases with the long term goal to develop SFB into a probiotic and or a vaccinal platform.



SEM and fluorescence analysis: in vitro culture of SFB reproduces characteristic attachment of SFB to eukaryotic epithelial cells (Schnupf et al. Nature 2015)



Immunohistochemistry: potent activation of Peyer's patches in response to mouse colonization by SFB (Lécuyer et al. Immunity 2014)



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Publications:

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LABORATORY OF DEVELOPMENTAL BRAIN DISORDERS

Developmental brain disorders (DBD) encompass a highly heterogeneous group of diseases characterised by impairments in cognition, communication, behaviour or motor functioning as a result of atypical brain development. This group of disease includes intellectual disability (ID), autism spectrum disorder (ASD), attention deficit hyperactivity disorder, specific learning disorder, and motor disorders. Neurodevelopmental disorders, also extends to conditions such as schizophrenia and epilepsy. Epidemiological studies show that co-occurrence of several neurological features is the rule. For example, up to 70% of individuals with ASD present with ID. Similarly, the prevalence of epilepsy in people with ID is 26%. Cerebellum developmental defects are recognized to be responsible of specific neuropsychological deficits and paediatric onset-ataxia presents often as developmental delay and intellectual disability. This phenotypic overlap is also mirrored at the genetic level. A number of studies have shown that CNVs (i.e. the 16p11.2 deletion) or genes (i.e. SHANK3, SCN2A genes) linked to ASD are also found in ID, epilepsy or schizophrenia. Taken together, these observations support the existence of common pathophysiological mechanisms for DBD which should be viewed as a continuum of developmental brain dysfunction.

Despite recent progresses, a large number of cases remain unexplained. With a combined prevalence of up to 3% of the population, DBD accounts for 10% of the total health care cost in most Western countries far more than cancer or cardiovascular diseases. Understanding the biological bases of these conditions is thus a major medical and socio-economical challenge. Our project aims to decipher the molecular defects underlying cognitive disorders and to

elucidate the pathophysiological mechanisms leading to cognitive impairment.

Decipher the genetic architecture of DBD

Over the last decade and using state-of-the-art genetic and genomics technologies, our group has characterized numerous chromosomal anomalies and disease-causing mutations responsible for DBD. To evaluate the functional impact of newly identified genomic variants several complementary approaches based on yeast models, CRISPR-Cas9 genome editing system in human neural stem cells and organisms like zebrafish or mouse are used.

Our most important scientific accomplishments over the recent years include (i) the identification of the MED23 gene, highlighting the key role of the Mediator in brain development and functioning and suggesting that altered immediate early genes expression might be a molecular hallmark of cognitive deficit; (ii) The demonstration that loss of function mutations in SNX14, coding for a protein involved in intracellular trafficking, impacts lysosome and autophagosome homeostasis with consequences on cerebellum development and neurons survival; (iii) the demonstration that members of the Drosophila Behaviour Human Splicing (DBHS) protein family play a key role in inhibitory synapse biology; (iv) The identification of biallelic mutations in FRRS1L as a new cause for severe ID and the demonstration of the key role of this gene in the priming step of AMPAR biogenesis and fast excitatory synaptic; (v) The characterization of a new mechanism of pontocerebellar hypoplasia (PCH) related to inositol phosphates metabolism.

Evaluate the role of epigenomic variations in the etiology of ASD

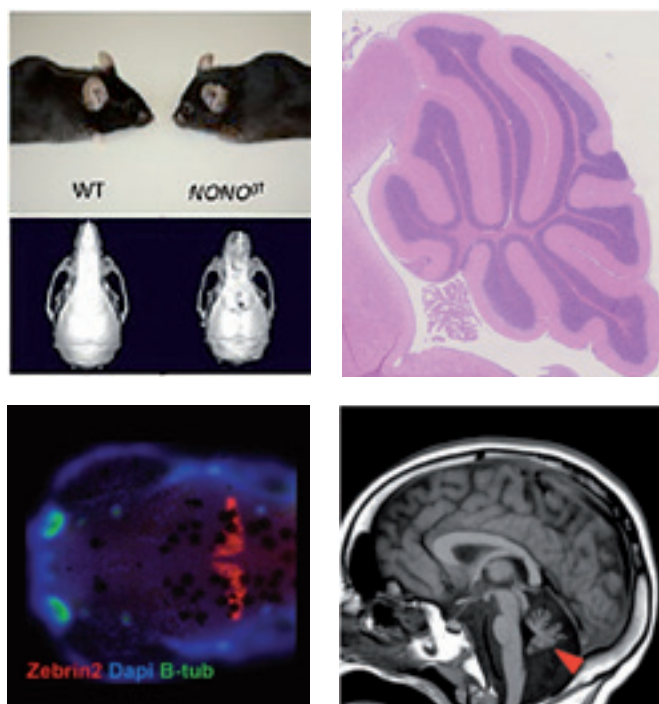
In parallel, we also addressed the issue of the role of microRNAs (miRNAs) dysfunction in the etiology of ASD. Autism spectrum disorder (ASD) is a neurodevelopmental disease caused by an interaction between genetic vulnerability and environmental factors. MicroRNAs (miRs) have emerged as key post-transcriptional regulators and are involved in multiple aspects of brain development and connectivity. Profiling miRNAs in olfactory mucosal stem cells (OMSC), we were able to identify a molecular signature of four microRNAs commonly deregulated in ASD. This signature is conserved in primary skin fibroblasts and allows discriminating between ASD and ID samples. In the mouse brain, these miRs display strong neuronal expression in regions important for high cognitive functions, and we demonstrated that reproducing abnormal miR expression in human neural stem cells leads to impaired neuronal differentiation. Mouse models are currently being developed to understand how miRNAs expression deregulation alters brain development and synaptic functions.

Identify the molecular causes of developmental cerebellar disorders with ID

Cerebellar defects are well known to cause imbalance and poor coordination. However, over the last decade, clinical and neuropsychological investigations highlighted the important role of the cerebellum in the acquisition of higher-order cognitive and affective skills. A better understanding of human cerebellum development should help to understand its role in cognition. We currently use exome sequencing in patients from Necker hospital or from the Middle East to identify new genes involved in these disorders and we study the effect of the identified variants using cell, fish or mouse models.

Characterize the physiopathological mechanisms involved in the neurological symptoms caused by a defect in protein N-glycosylation

The disruption of protein N-glycosylation is responsible of a group of genetic diseases frequently associated with ID and cerebellar atrophy/hypoplasia. The reason why the central nervous system and mostly the cerebellum are especially sensitive to this defect is totally unknown. This project aim is to identify the cellular and biochemical targets involved in these diseases using a conditional knockout mouse model for the *Srd5a3* gene.





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Publications:

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ORIGINS AND FUNCTIONS OF SKELETAL STEM CELLS IN BONE REGENERATION

Musculoskeletal disorders affect 1 in 7 people (10 million people in Europe) and are the second cause of disability worldwide. Fractures due to genetic diseases, osteoporosis or trauma have a prevalence of 1 in 50 people affected annually. Large bone defects caused by trauma, resection of bone tumors, osteonecrosis and severe skeletal dysplasia represent significant clinical challenges, as bone does not regenerate spontaneously in these situations. In order to enhance musculoskeletal regeneration, our research concentrates on the biology of skeletal stem cells that are the basis for the high regenerative capacities of skeletal tissues and that are potentially deficient in various musculoskeletal diseases and disorders. We aim to elucidate the mechanisms of stem cell activation in their complex tissue environment in development, disease and repair.

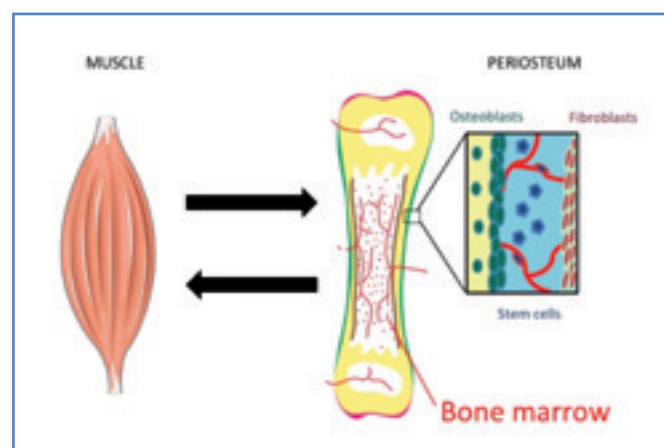
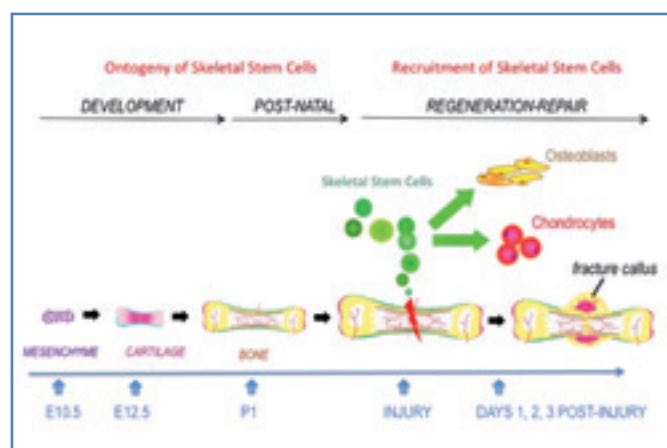
1-Role of skeletal stem cells

The process of bone formation begins during embryogenesis and continues throughout bone growth, homeostasis and aging, and during bone regeneration and repair. Many aspects of the developmental process are recapitulated during bone repair, including the differentiation of skeletal progenitors into osteoblasts and chondrocytes and the re-expression of genes involved in skeletal development and angiogenesis. We aim to understand the mechanisms of skeletal stem cell recruitment

from bone marrow and periosteum, the tissue that lies at the outer surface of bone, and that we showed is the major contributor to skeletal repair. We study the ontogeny of skeletal stem cells, how they are established during the development and growth of the skeleton in genetic mouse models and how they are affected in genetic diseases.

2-Role of muscle-bone interactions in musculoskeletal regeneration

The recruitment of skeletal stem cells in bone defects or injuries occurs in an inflammatory environment and is influenced by environmental mechanical signals and the surrounding tissues such as muscle. Bone and skeletal muscle are closely linked across development, growth and aging. Genetic disorders affecting muscle such as Duchenne Muscular Dystrophy (DMD) also impact bone and we have shown that bone regeneration is deficient in a mouse model of DMD. Similarly, loss of bone quality in osteoporosis is linked with sarcopenia. While it is generally recognized that muscle plays an important role in bone healing, the mechanisms of action remain poorly understood. In this project, we investigate the cellular and molecular contributions of muscle to bone repair, by identifying muscle-derived stem cells and growth factors involved in bone repair, and by assessing the impact of muscle injury on skeletal stem cell activation within periosteum.





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Publications:

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MOLECULAR AND PHYSIOPATHOLOGICAL BASES OF OSTEOCHONDRODYSPLASIA

Genetic disorders of the skeletal system may affect bone and/or cartilage formation from early embryo-fetal development up to childhood. Skeletal development is a temporally-regulated non-linear process orchestrated by a complex genetic network that proceeds via two distinct ossification mechanisms, namely membranous and endochondral. An impairment of these processes are responsible for a group of rare and often severe disorders: the osteochondrodysplasia.

Our research aims to contribute to the understanding of the ossification process by:

1. Identifying the molecular basis of osteochondrodysplasias, studying large cohort of patients clinically well characterized through the reference center for skeletal dysplasia.
2. Developing novel therapeutic approaches in bone fragility disorders using human osteoblasts and mouse models.
3. Deciphering proteoglycan synthesis impairment, in chondrodysplasia with multiple dislocations, using cellular and mouse models.

4. Understanding the link between of ADAMTS(L) proteins and the related microfibrillar network, TGF β signaling, and ossification processes, using cellular and mouse models with short and tall stature phenotypes.
5. Elucidating the molecular and cellular mechanisms involved in craniofacial development using Fgfr3 zebrafish lines.
6. Providing an in-depth understanding of FGFR3 signalling in axial skeleton formation
7. Evaluating the relationships between FGFR3 gain-of-function mutations and signalling pathways involved in primary cilia, autophagy and in cartilage and bone lineage cells
8. Conducting pre-clinical studies to test and identify drugs able to correct long bone growth plate, craniofacial and spine anomalies in achondroplasia and hypochondroplasia mouse models

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TGFβ signaling and growth

The diagram illustrates the TGFβ signaling pathway and its association with various syndromes. On the left, the FBN1 gene structure is shown, with mutations linked to Marfan syndrome and Tall stature/Short stature syndromes. The TGFβ signaling pathway is depicted on the right, showing the interaction between TGFβ and its receptors (TGFβRI, TGFβRII), leading to the activation of Smad proteins (Smad2, Smad3, Smad4) and downstream effectors like Myh9 and Myh10. The pathway ultimately leads to the activation of target genes in the nucleus.

Mouse model generated:
 1 Cre CMV Adamt2^{fl} (GD)
 2 flox Y1699C (GD)

The diagram illustrates the FGFR3-related osteochondrodysplasias signaling pathway. It shows the progression from Reserve chondrocytes to Proliferating chondrocytes and finally to Postproliferating and Hypertrophic chondrocytes. Key components include FGFR3, FGFR3-IG, and various signaling molecules like SHC, GRB2, SOS, RAS, RAF, MEK, ERK, and p38. The pathway leads to Chondrocyte proliferation, Chondrocyte differentiation, and Autophagy. The diagram also includes images of a human skeleton, a zebrafish embryo, and a zebrafish larva.



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Publications:
 1. Frémond, M.L. et al. Efficacy of the Janus kinase 1/2 inhibitor ruxitinib in the treatment of vasculopathy associated with TMEM173-activating mutations in 3 children. *J Allergy Clin Immunol* 138, 1752-1755 (2016)
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calcifications and cysts. *Nat Genet* 48, 1185-92 (2016).
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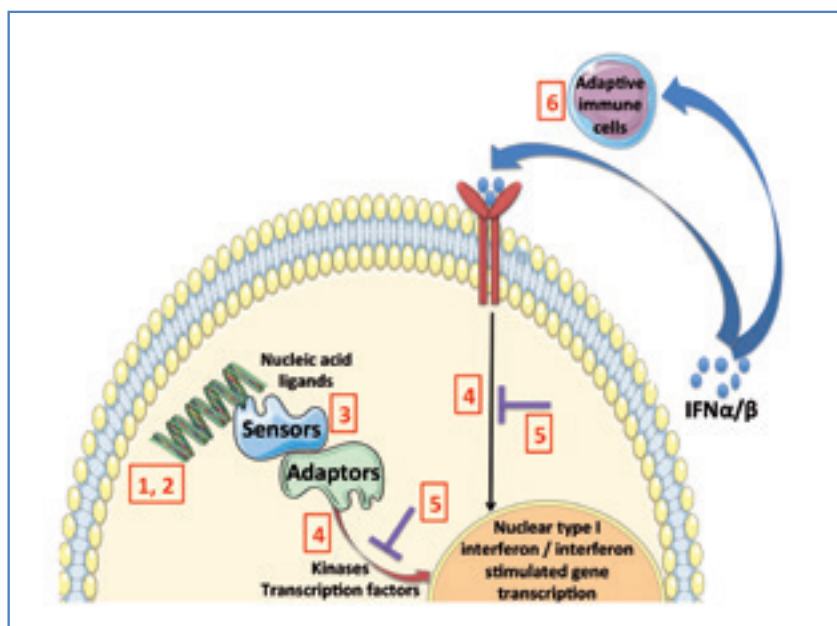
5. Rice GI et al. Assessment of interferon-related biomarkers in Aicardi-Goutières syndrome associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, and ADAR: a case-control study. *Lancet Neurology* 2013;12:1159-69.

LABORATORY OF NEUROGENETICS AND NEUROINFLAMMATION

Our work has concentrated on the Mendelian inflammatory disorder Aicardi-Goutières syndrome (AGS). Clinical and genetic studies of this severe disease have helped to define a cell-intrinsic mechanism for the initiation of autoinflammation / autoimmunity by interferon-stimulatory nucleic acids, and have further emphasised the importance of type I interferon metabolism in the pathogenesis of certain non-Mendelian disorders, particularly systemic lupus erythematosus. A combination of clinical, genetic and immunological perspectives have led us to suggest that monogenic disorders associated with an upregulation of type I interferons represent a novel set of inborn errors of immunity due to abnormal sensing, inappropriate stimulation, or defective negative regulation of the type I interferon system – the so-called type I interferonopathies (Figure). This concept immediately suggests the possibility of 'anti-interferon' / 'anti-inflammatory' therapies, and has important implications for fundamental research into mechanisms of self / non-self discrimination and viral immunity.

Possible mechanisms leading to a type I interferonopathy

1. Inappropriate stimulation of the type I interferon response machinery due to an abnormal accumulation of an endogenous nucleic acid ligand
2. Inappropriate stimulation of the type I interferon response machinery due to a change in the composition of an endogenous nucleic acid ligand
3. Enhanced sensitivity or ligand-independent (constitutive) activation of a nucleic acid receptor signalling to the type I interferon pathway
4. Enhanced sensitivity or ligand-independent (constitutive) activation of a non-nucleic acid receptor component (e.g. an adaptor molecule) of the interferon-signalling pathway
5. Defective negative regulation of a nucleic-acid dependent type I interferon response Mutations in other genes involved in non-nucleic acid related stimulation / regulation of the type I interferon pathway (including components of the adaptive immune response)





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Publications:

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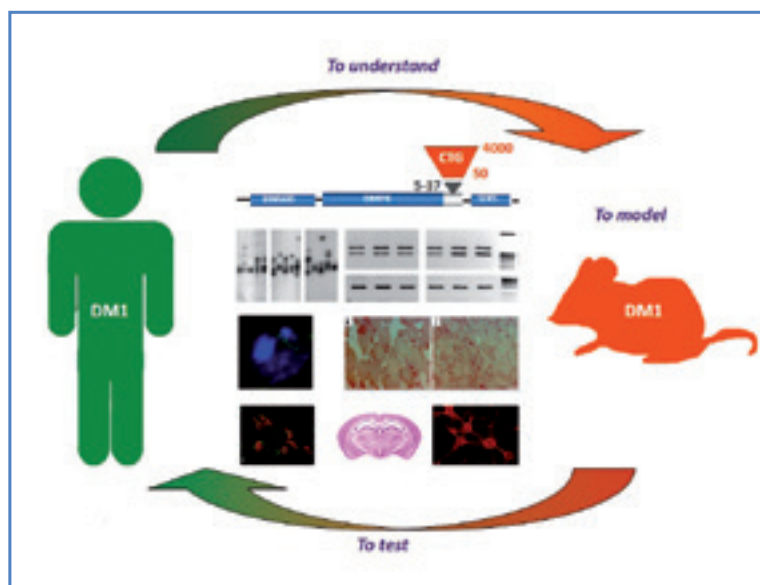
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CTG REPEAT INSTABILITY AND MYOTONIC DYSTROPHY

Myotonic dystrophy type I (DM1) is dominantly inherited, clinically highly variable and is caused by the unstable expansion of a CTG repeat in the 3'UTR of the *DMPK* on chromosome 19. The normal *DMPK* gene contains 5-37 CTG repeats in the 3'UTR, while all DM1 patients have repeats expanded from 50 to several thousand CTG trinucleotides. The size of the CTG repeat increases from generation to generation, is generally correlated with clinical severity and age at onset, providing a molecular basis for the anticipation phenomenon observed in DM1 families. Furthermore, the repeat increases with age in several tissues, possibly in relation with the progression of the disease with time. Mutant *DMPK* mRNAs accumulate in nuclear inclusions, interfering with the activity, localization and/or steady-state levels of RNA-interacting proteins. These toxic RNA deregulates the splicing program of a subset of developmentally regulated genes in multiple tissues, resulting

in a multi-systemic condition. However, recent findings suggest that DM1 molecular pathogenesis is vastly more complex, going beyond spliceopathy, involving changes in gene expression and translation efficiency, antisense transcripts, non-conventional translation and micro-RNA (miRNA) deregulation. A better understanding of the disease pathophysiology is crucial for the rational development of effective therapies targeting the molecular defects that underlie the multi-systemic symptoms that characterize myotonic dystrophy.

Several years ago, we created a transgenic mouse model carrying very large human genomic sequences containing the *DMPK* gene and the largest CTG repeat introduced in mice so far. These mice show a very high level of CTG repeat instability and reproduce the trans-dominant effect of the mutant *DMPK* gene. Our research follows three main axes:



Characterization of the mechanisms involved in trinucleotide repeat instability

Analysis of the CTG repeat length in transgenic mouse tissues and over generations showed that the CTG repeat instability, in our mice, is very similar to the CTG repeat instability observed in DM1 patients. Furthermore it revealed that the CTG surrounding genomic sequences and the human chromatin environment are necessary to recreate the features and the characteristic dynamics of the trinucleotide repeat instability in mice. We have also demonstrated that MMR proteins are the main actor in the formations of CTG expansions. We pursue our studies towards a better characterization of the dynamics of repeat instability. In collaboration with the Necker hospital diagnostic center and the French DM registry DMScope, we have identified very unusual families showing stabilization or contraction of the repeat through successive generations; identification of the mechanisms involved will give new hints for the development of new therapeutics approaches.

Molecular and physiopathological consequences of CTG repeat expansions

The *DMPK* transgene carrying the expansion is expressed in different mouse tissues and during development, contributing to the development of a variety of symptoms in multiple tissues and organ systems. In the laboratory, we decided to focused on the consequences of the mutation:

1) in the central nervous system.

We are using various tools to understand the molecular, cellular and behavioral mechanisms behind the neuropsychological impairment and brain abnormalities observed in DM1 patients.

2) in neonates.

The congenital form of the disease (CDM) is extremely severe at birth and in young children. Using our mouse model showing high mortality in the neonatal period, we intend to identify mechanisms behind very characteristic CDM symptoms such as mental retardation and respiratory failure.

Preclinical gene therapy in DM1 mice

Different groups working on DM1 have dedicated their efforts to the development of gene therapy strategies aiming to reduce the CTG repeat expansion at the DNA level, to destroy the toxic mutant RNA, to correct DM1 splicing defects or to restore the function of the proteins affected by the CUG expansion. Using our transgenic mouse model, we are collaborating with different industrial and academic research groups world-wide in the assessment of therapeutic tools recently developed (pharmacological, antisense oligonucleotides, CRISPR/Cas9, TALEN, AAV).

OLIVIER HERMINE



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Publications:

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MOLECULAR MECHANISMS OF HEMATOLOGIC DISORDERS AND THERAPEUTIC IMPLICATIONS

The Department belongs to INSERM U 1163/ CNRS ERL 8254 research units and is associated to the Necker Hospital clinical hematological department of hematology as well as to national reference centers for mastocytosis (CEREMAST), immunodeficiencies (CEREDIH), hemoglobinopathies and belongs to the Labex GR-ex (coordinator O. Hermine).

Our group has as major objectives:

1. the characterization of mechanisms governing the physiopathology of hematological disorders.
2. the development of therapeutic strategies to treat these diseases
3. the development of clinical research and technology transfer

Erythropoiesis regulation and its clinical applications

Our research group has been working from the last years in erythropoiesis and erythropoietic disorders. We have shown that caspases activation is critical for erythroid differentiation. Our current aims are: (i) to decipher the mechanisms triggering caspase activation and parameters that control caspase activity, particularly HSP70; (ii) to characterize the role of the TGF- β family in erythropoiesis and erythroid disorders, including thalassemia, sickle cell disease and congenital anemia; (iii) to identify new genetic defects in congenital anemia; (iv) to decipher mechanisms involved in the interactions between red blood cells and their environment (immune cells and iron metabolism), including TGF- β members and serotonin ; (v) to understand the physiology of red cell survival and its

application on blood transfusion ; (vi) translate our findings on the erythroid cell regulation to other diseases, including degenerative and malignant diseases.

Transferrin receptor (TfR1/CD71) is overexpressed in cancer cells compared to their non-malignant counterparts and several studies have suggested the therapeutic potential of targeting this receptor in cancer and immune response. Our objectives are: (i) identify the molecular partners of TfR1 involved in cell signaling; (ii) develop, in collaboration with the startup Inatherys (Ivan Moura and Olivier Hermine cofounders) an antibody directed against TfR1 to treat malignant diseases, erythroid disorders and immune complications of bone marrow transplantation.

The physiopathology and treatment of virus-related lymphoproliferation and lymphoproliferation occurring in patients with immunodeficiencies

Our group is also interested in the development of novel targeted therapies for virus-associated lymphoproliferation in general and lymphoproliferation associated with human T-lymphotropic virus type 1, hepatitis C virus and Epstein Bar virus infections in particular. Our aims are: (i) identify the molecular mechanisms involved in the physiopathology of these diseases; (ii) develop strategies to take advantage of pathways involved in virus infection to kill tumor cells to avoid the need of chemotherapy treatment; (iv) understand the physiopathology of lymphoma associated with immune-inflammatory diseases; (v) in collaboration with Theravectys we are developing a vaccine strategy to treat HTLV-1 related lymphoproliferation.

Mastocytosis and role of mast cells in disease

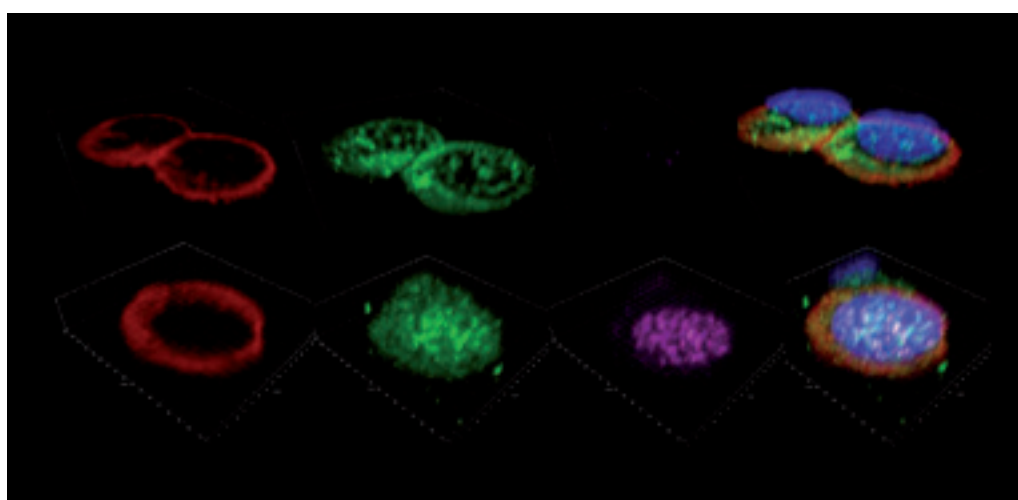
Mastocytosis is a rare disease caused by the accumulation of mast cells in various tissues. Our aims are: (i) understand the development of normal and malignant mast cells; (ii) understand how c-KIT mutations may explain the disease phenotype and outcome; (iii) identifying genes involved in familial cases; (iv) define new therapeutic strategies; (v) in collaboration with a pharmaceutical company (AB Science, Oliver Hermine cofounder) we are developing kinases inhibitors to treat this disease and mast cells-related disorders in human and animals.

Physiopathology of graft versus host disease in allogeneic bone marrow transplantation

Following the immune reconstitution after bone marrow transplantation in human, we have shown that complement and cells of innate immunity including natural killer T cells, myeloid regulatory cells and basophils are important determinants of graft versus host disease (GVHD). Our aims are: (i) develop murine and humanized murine models of allogeneic bone marrow transplantation to understand the physiopathology of on GVHD and graft versus leukemia (GVL); (ii) develop predictors of bone marrow transplantation complication; (iii) develop strategies to inhibit GVH and increase GVL and anti-tumor response.

Role of coagulation factors in hemophilia complications.

Hemophilic patients are suffering of arthropathies. Our aims are to decipher the mechanisms of hemophilia-associated arthropathy, focusing on immune regulation by blood cells and coagulation factors.



hematological
disorders

Basic
science

Diagnosis and
targeted therapies

ALAIN HOVNANIAN



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Publications:

1. de Veer SJ, Furio L, Swedberg JE, Munro CA, Brattsand M, Clements JA, Hovnanian A, Harris JM. Selective Substrates and Inhibitors for Kallikrein-Related Peptidase 7 (KLK7) Shed Light on KLK Proteolytic Activity in the Stratum Corneum. *J Invest Dermatol.* 2017 Feb;137(2):430-439

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GENETIC SKIN DISEASES: FROM DISEASE MECHANISMS TO THERAPIES

The skin forms a mechanical and immune barrier which is essential for body survival. Our team investigates several severe genetic skin diseases of children and adults in which these protective functions are drastically altered. These include rare, monogenic and orphan diseases, whose genes have been identified by our group: dystrophic epidermolysis bullosa, Netherton syndrome, Darier disease, Hailey-Hailey disease, but also frequent and polygenic diseases such as Hidradenitis suppurativa atopic dermatitis. Our projects aim at better understanding the molecular mechanisms involved in these diseases, at identifying factors responsible for their phenotypic variability in order to develop new therapeutic strategies using gene and cell therapy, protein replacement, small molecules and/or pharmacological approaches.

Biotherapies, modifiers genes and mouse models for dystrophic epidermolysis bullosa (DEB)

We have implemented a first Phase I/II ex vivo gene therapy trial for recessive DEB as part of the GENEGRAFT European project (coordinated by Alain Hovnanian). This trial uses reconstructed autologous grafts genetically corrected with a secure, self-inactivating (SIN) retroviral vector expressing type VII collagen (orphan drug). Other approaches developed by the team include exon skipping for which we have generated a COL7A1 humanised mouse, nonsense reading through and cell therapy using genetically modified fibroblasts. New strategies using bone marrow derived mesenchymal stem cells are also being developed in a xenograft model using human RDEB skin equivalents grafts. A viable knock in murine model for RDEB carrying a homozygous hypomorphic Col7a1 mutation has been generated and extensively studied. This model has brought further insights into the development of fibrosis and provides a new in vivo model for therapeutic approaches. Transcriptomic and proteomic approaches aiming

at identifying modifier genes and biological pathways involved in disease severity and in the development of squamous cell carcinomas in DEB are being pursued.

Netherton syndrome (NS): allergy by epidermal proteases dysregulation

We have characterized the biological cascade leading to skin inflammation, allergy and abnormal desquamation in NS. The cascade involves unopposed kallikrein (KLK) 5 (KLK5), KLK7 and KLK14 activities as a result of defective inhibition by LEKTI, leading to protease-activated receptor 2 (PAR2) activation and thymic stromal lymphopoietin (TSLP) production. KLK5 is a major therapeutic target, which activates pro-KLK7 and pro-KLK14, and we are currently involved in the development of KLK5, KLK7 and/or KLK14 specific inhibitors using different strategies. Other biotherapy approaches aiming at blocking pro-inflammatory cytokines overexpressed in NS are also being considered and tested in clinical trials. The team has developed several murine models, including a transgenic mouse overexpressing human KLK5, a conditional Spink5^{-/-} and a double-knock out (Spink5^{-/-}-xKLK5^{-/-}) model, which have confirmed the roles of klk5 and klk7 in NS pathogenesis and are useful models for drug testing.

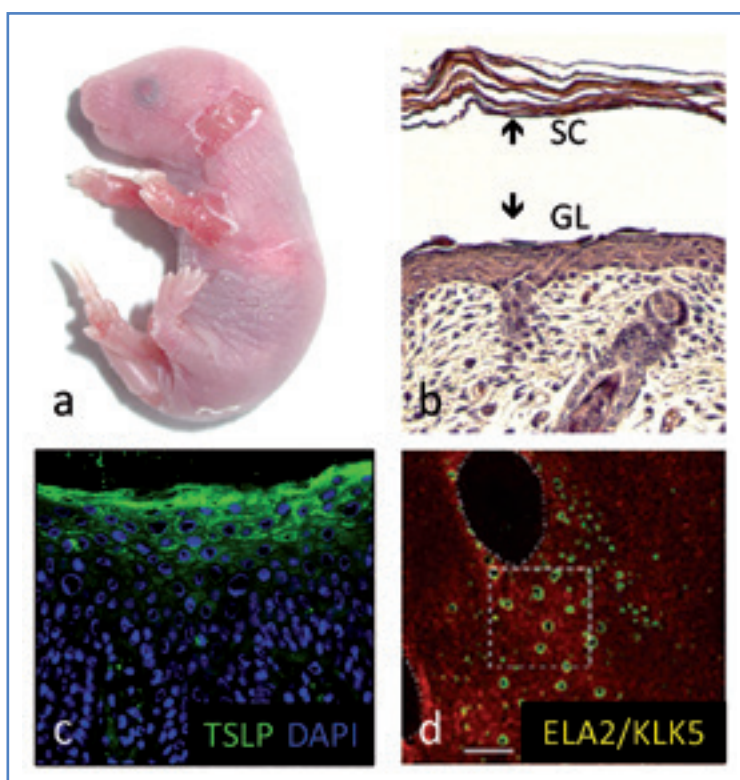
Darier disease (DD), a disease model of abnormal calcium homeostasis

We previously identified ATP2A2 (encoding SERCA2, a calcium pump of the endoplasmic reticulum (ER)) as the defective gene in Darier disease. We have recently shown that loss of calcium transport leads to ER stress and abnormal trafficking of intercellular adhesion molecules. We have further shown that inhibition of ER stress with pharmacological agents leads to relocalization of E-cadherin and desmosomal components to the plasma membrane, indicating that these agents have a

therapeutic potential. We have also recently identified different biological cascades involved in abnormal differentiation and skin inflammation which could guide new therapeutic approaches.

The team develops linkage or association studies and exome sequencing approaches to identify new genes for severe monogenic or polygenic skin diseases. These include rare keratinizing and inflammatory disorders such as Olmsted

syndrome and severe ichthyosiform erythroderma, and frequent diseases such as atopic dermatitis and hidradenitis suppurativa. Functional studies of identified genes are being developed in order to better understand the pathogenesis of these disorders, to disclose biological cascades involved and to identify therapeutic targets.



Netherton syndrome (NS): from skin barrier defect to severe allergy a and b, Spink5 knock-out mice show stratum corneum (CC) detachment resulting from desmosomal cleavage secondary to unopposed kallikrein 5 (KLK5) activity. C. Patient skin shows strong TSLP expression, a major pro-Th2 cytokine which promotes naive T cell differentiation into Th2 lymphocytes leading to allergy. d. Elastase 2 (ELA2) is a new epidermal protease which is hyperactive in NS. ELA2 co-localises with KLK5 in granular keratinocytes. ELA2 contributes to epidermal barrier defects seen in NS. CG: granular layer



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Publications:

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LYMPHOCYTE ACTIVATION AND SUSCEPTIBILITY TO EBV

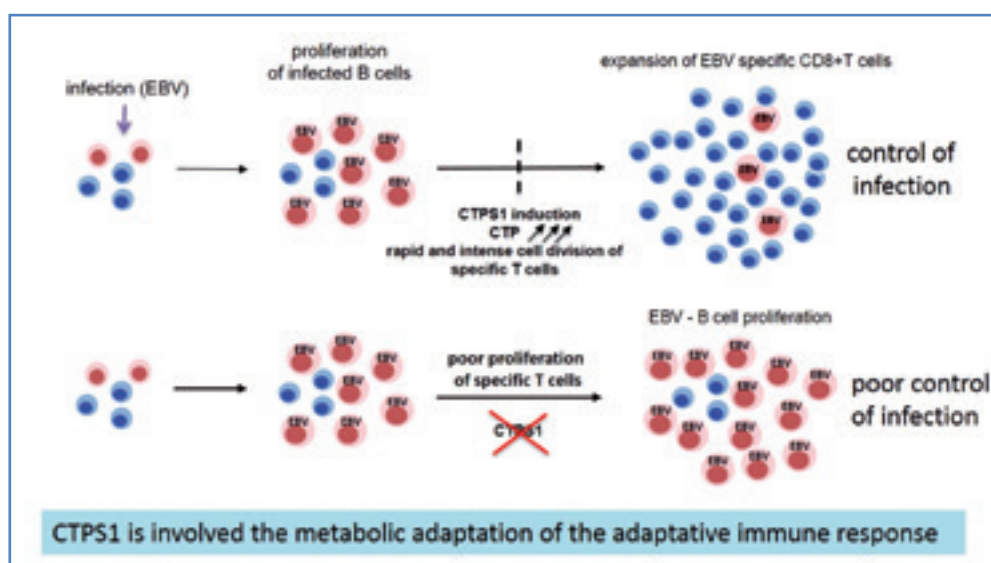
The efficiency and the homeostasis of the adaptive immune response are dependent of a variety of mechanisms that tightly regulated the production, the proliferation, the function and the death of lymphocytes, the main cells involved in this response. During the immune response to a pathogen, T lymphocytes are activated, proliferate and differentiate to acquire effector functions allowing the clearance of the pathogen, and finally die once the pathogen is eliminated. Numerous pathological conditions are caused by disequilibrium in these different processes. The team is focused on the study these mechanisms and pathological conditions resulting from genetic defects in these mechanisms, in particular during Epstein Barr virus (EBV) infection, which is one of the most potent trigger of the immune system in humans. One aim of the team is to decipher the genetic basis of the susceptibility of EBV infection in humans, which is responsible of several severe lymphoproliferative and inflammatory disorders including lymphoma and haemophagocytic lymphohistiocytosis. The team is also interested in primary immunodeficiencies associated with defects affecting T-lymphocyte development

and functions. Recently, the team identified several key factors involved in the immunity to EBV: CTPS1 (CTP Synthetase 1) an enzyme responsible of the de novo synthesis of the nucleotide CTP and CD70 a surface molecule highly expressed on B cells upon EBV infection. We showed that these factors are required for the proliferation and the expansion of activated T lymphocytes during the immune response.

At present the research project of the team is mainly focused on:

- identification and characterization of novel gene defects associated with an abnormal immune response to EBV and/or T-cell defects in patients with unknown genetic diagnosis;
- biochemical, molecular and cellular characterization of activation and regulation pathways involved in the immune response to EBV, with a particular interest in cell division/expansion processes in activated T lymphocytes;

These studies include the development of genetically modified mice models.





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Publications:

1. Gordon CT, Weaver KN, Zechi-Ceide RM, Madsen EC, Tavares ALP, Oufadem M, Kurihara Y, Adameyko I, Picard A, Breton S, Pierrot S, Biosse-Duplan M, Voisin N, Masson C, Bole-Feysot C, Nitschké P, Delrue MA, Guion-Almeida ML, Padilha Moura P, Gamba Garib D, Munnich A, Ernfor S, Kurihara H, Hufnagel RB, Saal HM, Weaver DD, Katsanis N, Lyonnet S, Golzio C, Clouthier DE, Amiel J. Mutations in the Endothelin Receptor Type A Cause Mandibulofacial Dysostosis with Alopecia. *Am J Hum Genet* 2015;96:519-31
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Cause Lethal Ciliopathies Ranging from a Hydroletharus Phenotype to Short-Rib Polydactyly Syndrome. *Am J Hum Genet* 2015;97:311-8.

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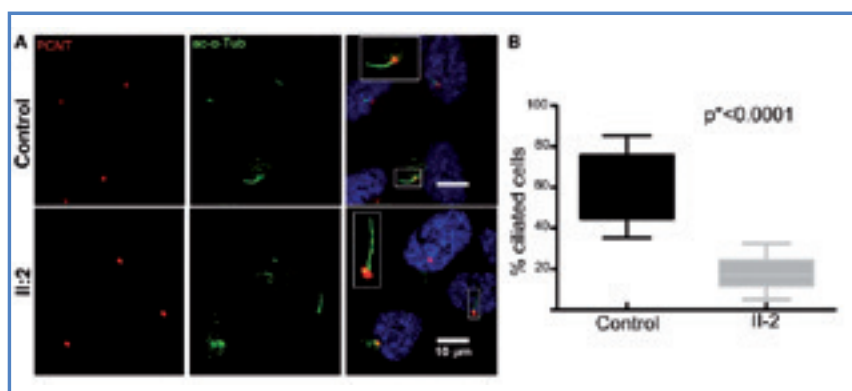
EMBRYOLOGY AND GENETICS OF MALFORMATIONS

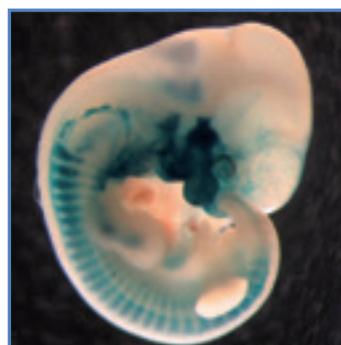
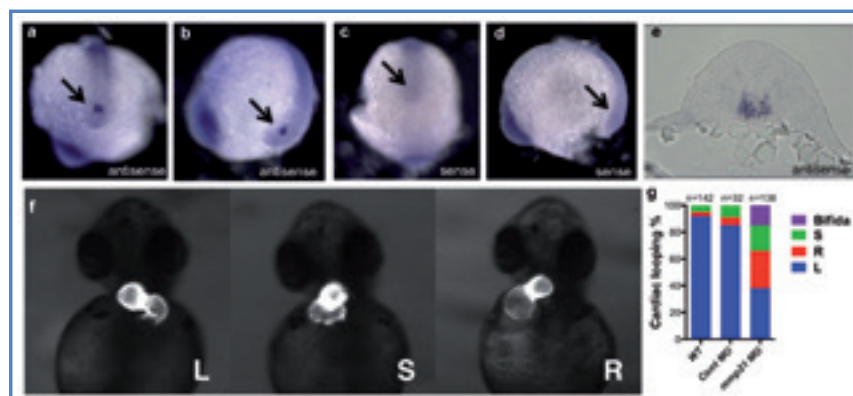
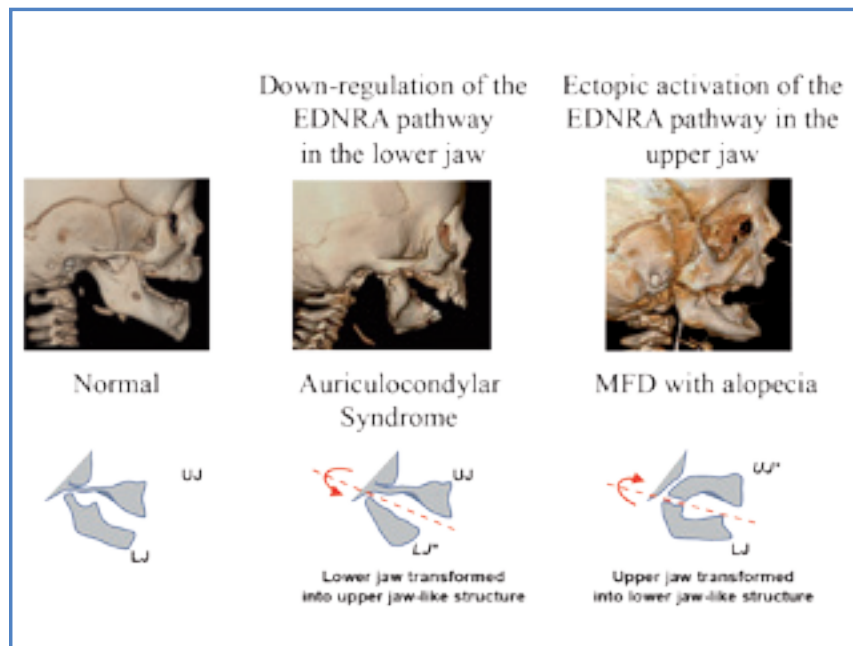
Our research program is aiming to identify genes or non-coding genomic alterations responsible for congenital malformations and answer important questions in clinics, biology and developmental genetics. We have a special interest for tissues derived from the neural crest (neurocristopathies), and ciliopathies.

The neural crest is a transitory embryonic structure that participates to the development of many structures. We have a long lasting interest on the development of the enteric nervous systems and Hirschsprung disease, a model for complex oligogenic and sex-dependent inheritance. In collaboration with many reference centers for rare diseases on the Necker

Hospital campus we also developed research projects on craniofacial (especially mandibulofacial dysostoses), syndromic deafness and cardiac malformations through NGS, in vitro and in vivo analysis in zebra fish and mice.

Ciliopathies are a fast growing group of diseases that are the consequence of an abnormal genesis or functioning of the motile and/or primary cilia. Our work on ciliopathies contributes to the understanding of primary cilium formation and links extreme lethal phenotypes with viable syndromes. A recent focus has been made on corpus callosum agenesis, the most frequent brain malformation, as well as brain neuronal migration defect.







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Publications:
 1. Ragni CV, Diguët N, Le Garrec JF, Novotova M, Resende TP, Pop S, Charon N, Guillemot L, Kitasato L, Badouel C, Dufour A, Olivo-Marín JC, Trouvé A, McNeill H and Meilhac SM. Amotl1 mediates sequestration of the Hippo effector Yap1 downstream of Fat4 to restrict heart growth. Nat Commun. 2017 Feb 27;8:14582.
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cells. Methods Cell Biol. 2015;127:55-73.
 3. Meilhac SM, Lescroart F, Blanpain C and Buckingham ME. Cardiac cell lineages that form the heart. Cold Spring Harb Perspect Med. 2014 Sep 2;4(9):a013888.
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mouse heart. Bioinformatics 2013 Mar 15; 29(6):772-9.
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HEART MORPHOGENESIS

The acquisition of a specific shape is key for organ function. With advances in molecular biology and microscopy, gene networks involved in morphogenesis have been reconstituted and cell behaviour can be traced. However, local cell behaviour mainly impacts morphogenesis when it is coordinated. Thus, the *Imagine*-Institut Pasteur group of Heart Morphogenesis studies how cells are coordinated at the level of the tissue and how their local behaviour generates shape changes in 3 dimensions.

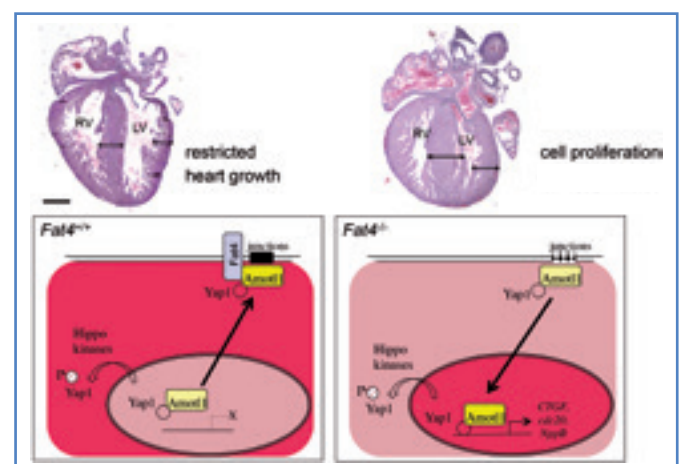
We use the developing mouse heart as a striking model of morphogenesis, in which the size and alignment of cardiac chambers are essential for the function of driving blood circulation. Our study faces novel challenges which require interdisciplinary efforts, to quantify biological processes and shape changes or examine the clinical impact of the work. We use a combination of approaches, including mouse genetics, transcriptomics, embryology, primary cultures of cells, 3D imaging, quantitative image analyses and computer simulations.

We have previously characterized the lineages and behaviour of myocardial cells during heart morphogenesis. We have also developed interdisciplinary tools for the quantification of orientations in 3D tissues (Pop et al., 2013 ; Le Garrec et al., 2013) and revealed that myocardial cells coordinate locally their orientation of division during cardiac chamber expansion.

Recently, we have studied the atypical cadherin Fat4, which is involved in cell-cell interactions. It was initially discovered in the fly as a major regulator of organ size, upstream of the Hippo pathway. However, whether this function of the Fat pathway was conserved in mammals had remained poorly understood. We have shown that Fat4 is required to restrict heart growth at birth, by repressing cell proliferation (Ragni et al. 2017). This is mediated by an up-regulation of the transcriptional activity of Yap1, an effector of the Hippo pathway. This occurs without variation in the level of phosphorylation of Yap1 or the Hippo kinases, indicating a non-canonical modulation of the pathway. We show instead that Fat4 is required to sequester out of the nucleus a partner of Yap1, the scaffold protein angiomin-1-like

1 (Amotl1), which is not present in flies . This novel signalling of cardiomyocyte proliferation has potential applications in the field of cardiac regenerative medicine. Further research is ongoing to identify novel regulators of myocardial growth.

Another objective of our research is to address cell coordination at a larger scale, by dissecting how left-right patterning of the embryo drives heart morphogenesis, resulting in the correct alignment of cardiac chambers. The rightward looping of the embryonic heart tube provides an example of how left-right patterning is sensed by organ precursors to generate asymmetric morphogenesis. We have set up High Resolution Episcopic Microscopy (HREM) at the *Imagine* Institute and developed tools to quantify in 3D the process of heart looping. The relevance of our work in the mouse to congenital heart defects, such as malposition of the ventricles or the great vessels, is explored in collaboration with our colleagues of the Hospital Necker.



Fat4 mutant hearts (right panels) show an excessive growth of the myocardium. We show that this results from increased cell proliferation (Ragni et al., 2017) . Fat4 (blue) acts upstream of the Hippo pathway, and by sequestering Amotl1 (yellow), prevents the nuclear translocation of Yap1, independently of Hippo kinases. Higher Yap1 levels are shown in dark red.



Team:
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Publications:

1. Ménager MM, et al. Ménasché G, Romao M, Knapnougél P, Ho CH, Garfa M, Raposo G, Feldmann J, Fischer A, de Saint Basile G. Secretory cytotoxic granule maturation and exocytosis require the effector protein hMunc13-4. *Nat Immunol.* (2007) Mar;8(3):257-67. Epub 2007 Jan 21. PMID: 17237785

2. Côte M*, Ménager MM*, Burgess A, Mahlaoui N,

Picard C, Schaffner C, Al-Manjomi F, Al-Harbi M, Alangari A, Le Deist F, Gennery AR, Prince N, Cariou A, Nitschke P, Blank U, El-Ghazali G, Ménasché G, Latour S, Fischer A, de Saint Basile G., Munc18-2 deficiency causes familial hemophagocytic lymphohistiocytosis type 5 and impairs cytotoxic granule exocytosis in patient NK cells, *J Clin Invest.* (2009) Dec;119(12):3765-

73. doi: 10.1172/JCI40732. Epub 2009 Nov 2. PMID: 19884660 (* Co-first-authors).

3. Ménager MM, Littman DR., Littman DR., Actin Dynamics Regulates Dendritic Cell-Mediated Transfer of HIV-1 to T Cells, *Cell*, (2016) Jan 27. pii: S0092-8674(15)01700-6. doi: 10.1016/j.cell.2015.12.036. PMID:26830877

INFLAMMATORY RESPONSES AND TRANSCRIPTOMIC NETWORKS IN DISEASES

NETWORK INFERENCE AS A NEW APPROACH TO BETTER CHARACTERIZE AUTOINFLAMMATORY DISEASES

At the Inflammatory responses and transcriptomic networks in diseases lab, we are proposing to combine state of the art single-cell transcriptomic and chromatin accessibility experiments with new powerful computational biology tools, as a novel and an unbiased way to explore the complexity of innate immune response and autoinflammation. The idea is to use the emerging field of **transcriptome-based network inference analysis** to get a deeper and unbiased understanding of the diversity of the **molecular mechanisms behind autoinflammatory diseases**.

The fine-tuned analysis and detailed characterization of regulatory networks controlling inflammation will be a major step forward to replace costly life-long immunosuppressive treatments by more definite cures, with hopefully less side effects. Given the scale of the human genome and the corresponding large scale and complexity of regulatory networks, unbiased approaches to **network inference enable comparisons not always possible with single-gene experimental design**. It is providing the molecular biology field with a weighted map of potential interactions that can be **used to select precisely and prioritize factors to further characterize and decipher the complexity of a particular process, in our case dysregulation of inflammation**

Major Goals:

- In particular we are interested in **studying the transcriptomic changes leading to an excess of IFN production in**

pathologies. SAMHD1, is of particular interest to our lab by being both mutated in Aicardi-Goutières Syndrome (AGS) and also known as being a restriction factor of HIV-1 in human dendritic cells (DCs). Interestingly, in both cases, an increase of type I IFN secretion can be observed.

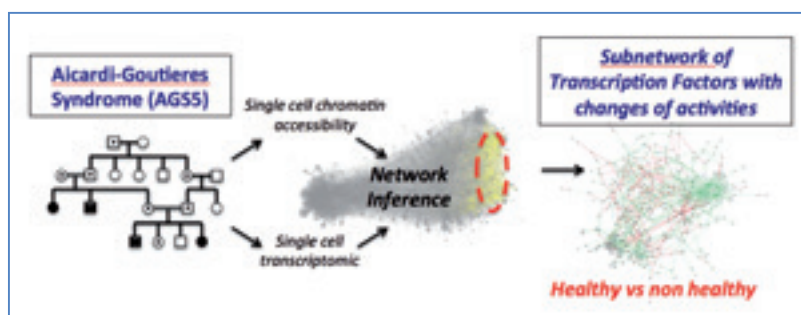
- With a single cell approach, we hope to **better characterize the sub-cell type responsible for an excess of IFN production** and by using Network inference we are looking forward to **identify pathways responsible for IFN induction in absence of any pathogen infection**.

INTERACTIONS BETWEEN HUMAN DENDRITIC CELLS AND HIV-1

1) HIV-1 sensing and priming of an adaptive immune response.

A cell-intrinsic sensor for HIV-1, cGAS, has the potential to **activate the type I interferon response to reverse-transcribed viral DNA in DCs, but is not typically engaged owing to a block in reverse transcription** mediated by the host dNTP hydrolase **SAMHD1**. It has been found that HIV-1 infects DCs, if the cells are first exposed to virus-like particles (VLPs) that deliver the protein Vpx (absent in HIV-1 but encoded by SIV and HIV-2). **By promoting degradation of SAMHD1, Vpx enables HIV replication in DCs, sensing by cGAS and subsequent type I IFN production**.

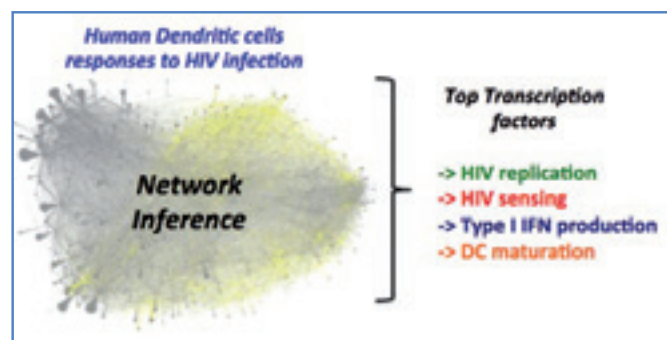
To **characterize the regulatory network controlling host transcriptional responses to HIV-1**, we carried out a large-scale genomic interrogation of a subset of dendritic cells stimulated by different means including HIV-1 infection. For each type of stimulation, we have measured transcription



via RNA-seq coupled to methods for measuring chromatin accessibility (ATAC-seq). **In collaboration, with members of Richard Bonneau's laboratory at the Simons foundation, we have analyzed this large integrated data-set and inferred a dynamic computational model that describes the molecular-level regulation of transcriptional responses following HIV-1 infection in human dendritic cells.** This project is now a very intense international collaborative effort between my lab and four different laboratories: **Nicolas Manel (Curie Institute), Alan Aderem (Seattle), Dan Littman (New York) and Richard Bonneau (New York).**

Major Goals:

With this dynamic modelization of Transcription factors-genes interaction, we have now a great tool to generate new hypotheses that will then need to be experimentally validated to **better understand HIV replication, sensing, type I IFN production and Dendritic cell maturation in response to HIV infection.**



2) Molecular mechanisms leading to HIV-1 transfer from DC to T cells

DCs express cell surface receptors for HIV-1 entry, but are **relatively resistant to productive viral replication**. They do, however, **capture the virus and transfer it to co-cultured T-helper cells, without first being infected**, in a process called **trans-infection**. Taking advantage of this DC to T-cell transfer mechanism, the virus could evade, at least in part, the first line of defense of the immune system in mucosal tissues and establish and amplify infection of CD4+ T cells in lymph nodes, with minimal detection by the immune system.

To better understand this cellular biological process, we have **set up and performed an shRNA screen in primary human monocytes derived dendritic cells (MDDCs)** to individually knockdown close to 500 genes involved in membrane and vesicular trafficking and compare their efficiency of HIV-1 transfer. We identified several genes and pathways, **among which TSPAN7 and DNM2. These two proteins control actin nucleation and stabilization, a process required to maintain HIV-1 on actin-rich dendrites in order to be efficiently transferred toward CD4+ T cells.** Beyond these two molecules, this work showed the **key role played by actin nucleation in dendritic cells in limiting internalization of HIV-1 and membrane protrusion formation.** We also discovered as reported in other biological systems, e.g. the neuronal

growth cone, that in MDDCs, opposing forces control the formation and rapid switch between actin-rich dendrites (Actin-nucleation-driven) and blebs (Actomyosin contraction-driven).

Our genetic approach was a first step toward a better understanding of the molecular and cell biological aspects of HIV-1 transmission between DCs and T lymphocytes, which is needed to evaluate the importance of this process in animal models and, eventually, in infected individuals.

Major Goals:

- > HIV-1 as model of study for transfer of pathogens from DCs to T lymphocytes
- Better understanding of **molecular mechanisms linking Actin nucleation/stabilization, dendrites formation and control of endocytic mechanisms.**
- **Identification of other mechanisms of HIV-1 transfer.** In our shRNA screen, 84 hits are left with potentially no direct connections with actin nucleation, membrane protrusions and positive regulation of endocytosis.
- Investigation of the **physiological relevance of the mechanisms identified for HIV-1 transfer**, their impact on other key cellular functions and potential applications to other pathogens.

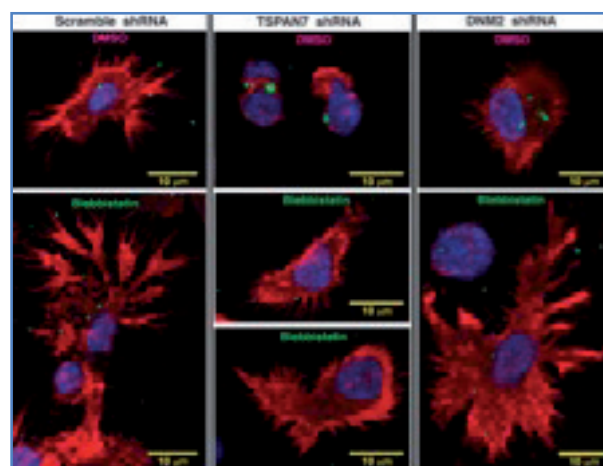


Fig 1: Effect of inhibition of actin nucleation or actomyosin contraction on HIV-1 transfer.

Confocal microscopy images of MDDCs stained for filamentous actin with phalloidin (red) and for nuclei with Dapi (blue), 4 days after transduction with either scrambled, TSPAN7 or DNM2 shRNAs. Incoming HIV-1 particles are detected in green, based on the GFP expression. One Z-stack of 400nm is displayed. TSPAN7 knockdown (upper panel, middle image) leads to the loss of actin-rich dendrites and accumulation of HIV-1 (Green) in macropinocytic vesicles, which results in a decrease of HIV-1 transfer. Actomyosin inhibition (Blebbistatin) can increase (in a context of intact actin nucleation, bottom panel image on the left) or rescue (in absence of actin nucleation, bottom panel middle image) actin-rich dendrites formation, prevent HIV-1 macropinocytosis and increase HIV-1 transfer. DNM2 function (right panel) is not required for dendrites formation but is involved in cortical actin stabilization, to prevent an excess of HIV internalization through macropinocytic events.



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Publications:

1. Miccio A, Cesari R, Lotti F, Rossi C, Sanvito F, Ponzoni M, Routledge SJ, Chow CM, Antoniou MN, Ferrari G. In vivo selection of genetically modified erythroblastic progenitors leads to long-term correction of beta-thalassemia. *Proc Natl Acad Sci U S A*. 2008 Jul 29;105(30):10547-52
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4. Romano O., Peano C., Tagliazucchi G.M., Petiti L., Poletti V., Cocchiarella F., Rizzi E., Severgnini M., Cavazza

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5. Cavazzana M., Antoniani C., Miccio A. Gene Therapy for β -Hemoglobinopathies. *Molecular Therapy*, 2017, Apr 1. pii: S1525-0016(17)30123-5. doi:10.1016/j.ymthe.2017.03.024.

LABORATORY OF CHROMATIN AND GENE REGULATION DURING DEVELOPMENT

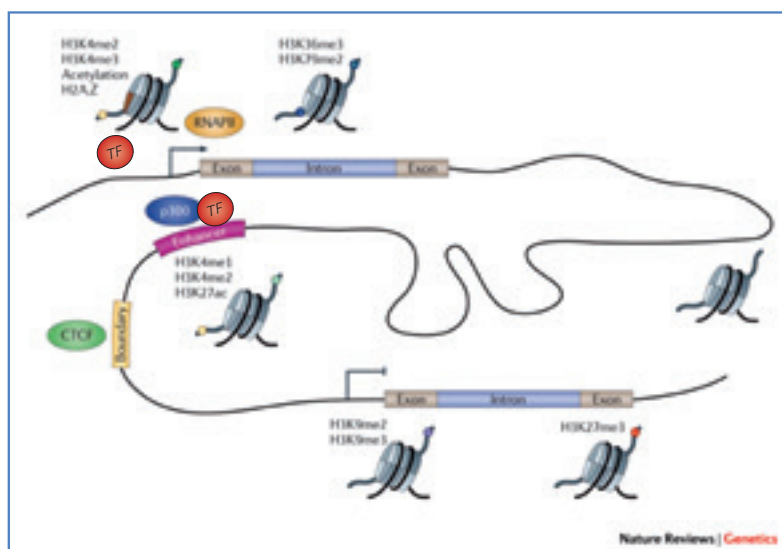
The laboratory of Chromatin and gene regulation during development studies two main areas:

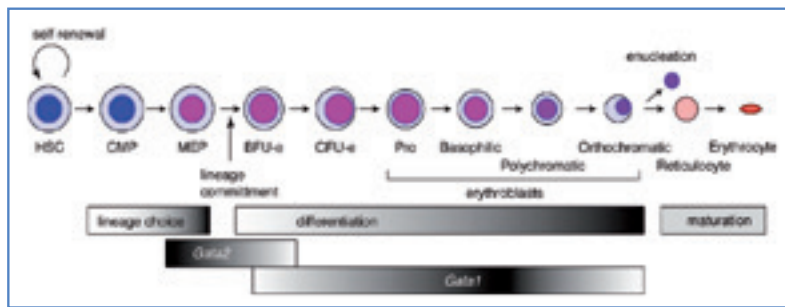
1) Dynamics of transcriptional and epigenetic networks during stem cell development

The definition of regulatory regions controlling the gene expression programs is fundamental for understanding the molecular mechanisms underlying many diseases and for the development of novel therapeutic approaches (Romano, Antoniani and Miccio, *Stem Cells Translational Medicine*, accepted). As an example, numerous disease-associated sequence variations occur in cis regulatory elements, which represent in some cases potential therapeutic targets. The aim of our projects is the genome-wide definition of the entire set of regulatory sequences used by human stem/progenitor cells and their lineage-restricted progeny at different stages of development. The definition of the genetic and epigenetic programs is achieved through the use of a

number of genomic and bioinformatic tools, including RNA-seq, deepCAGE, Retroviral scanning and ChIP-Seq. The outcome of this research is a better understanding of the molecular basis of stemness and lineage commitment of clinically relevant stem cells, which provides a knowledge basis for safer and more efficient usage of stem cells in cell and gene therapy (Cavazza A., et al., *Stem Cell Reports*. 2016; Romano O. et al., *Scientific Reports*, 2016).

Currently, we are analyzing genome-wide the occupancy of hematopoietic transcription factors (e.g., GATA1 and GATA2) and their co-factors, and the epigenetic histone modifications associated to transcription or silencing to define regulatory regions involved in hematopoietic stem cell biology and in erythroid commitment and differentiation. Validation of putative regulatory regions is performed by CRISPR-Cas9 targeted disruption and chromatic conformation capture assays (Romano et al., in preparation).



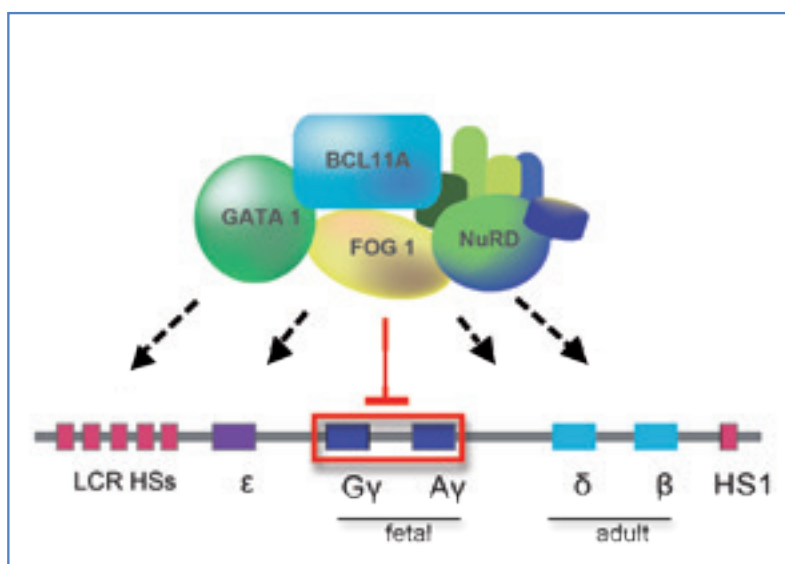


2) Molecular-based approaches for the treatment of β -Hemoglobinopathies

Sickle cell disease (SCD) and β -thalassemias are genetic diseases caused by mutations in the gene coding for the adult hemoglobin β -chain. They represent the most common monogenic disorders worldwide, affecting thousands of newborns annually. In β -thalassemia, the reduced production of adult β -chains causes α -globin precipitation and red blood cell death. In SCD, a single aminoacid substitution in the β -globin chain leads to polymerization of the sickle hemoglobin (HbS) and red blood cell deformation. β -globin disorders may lead to a severe clinical phenotype characterized by anemia, pain crises, and organ damage. So far, the only curative treatment is represented by bone marrow transplantation from a compatible donor, which, however, is available to less than 30% of the patients. Experimental treatments include gene therapy and pharmacological intervention. In the latter approach, efforts are underway to identify compounds that raise the expression of the fetal γ -globin genes. The rationale for this treatment is based on the long-standing observation that patients harboring mutations that trigger elevated γ -globin expression, experience a more benign clinical course of the disease (Cavazzana, Antoniani and Miccio, Molecular Therapy, 2017). However, pharmacological treatments are not equally effective for all

patients, are associated with a considerable toxicity and do not represent a definitive treatment. Several nuclear factors, such as the erythroid master regulator GATA1, its cofactors FOG1 and BCL11A and the NuRD repressor complex, are implicated in the silencing of γ -globin expression. However, their role in erythroid development and hemoglobin switching has yet to be completely elucidated.

The goal of our research is to provide the basic scientific knowledge for developing safe therapies for SCD and β -thalassemias based on lentiviral and genome editing approaches aimed at increasing γ -globin expression. We aim at characterizing the transcription factors and the regulatory genomic elements that control the switch from fetal to adult globin gene expression. The fine mapping of regulatory elements involved in hemoglobin switching provides potential targets for therapeutic induction of fetal hemoglobin. Our studies are focused on the molecular mechanisms underlying the β -to- γ -globin switching, as well as on the evaluation of the efficacy and safety of these therapeutic approaches. We apply established and novel molecular techniques (e.g. genome-wide genomic analyses, lentiviral and CRISPR/Cas9 technologies) by using different cellular models, including clinically relevant hematopoietic stem cells (Antoniani, Meneghini et al., under revision; Lattanzi et al., in preparation; Weber et al., in preparation).



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Publications:

1. Ledonne F, Orduz D, Mercier J, Vigier L, Grove E.A., Tissir F, Angulo M.C., Pierani A. and Coppola E. Targeted inactivation of Bax reveals subtype-specific mechanism of Cajal-Retzius neuron death in the postnatal cerebral cortex. *Cell Reports* (2016), 17, 3133–3141.

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4. Griveau A., Borello U., Causeret F., Tissir F., Boggetto N., Karaz S. and Pierani A. A Novel Role for Dbx1-derived Cajal-Retzius Cells in Early Regionalization of the Cerebral Cortical Neuroepithelium. *PLoS Biol.* (2010), 8, e1000440.

5. Bielle F., Griveau A., Narboux-Nême N., Vigneau S., Sigrist M., Arber S., Wassef M. and Pierani A. Multiple origins of Cajal-Retzius cells at the borders in of the developing pallium. *Nature Neuroscience* (2005), 8, 1002–1012.

GENETICS AND DEVELOPMENT OF THE CEREBRAL CORTEX

Cognitive functions depend on the precise construction of complex neural circuits which begins during early embryonic development. Studies in the past decades have revealed that abnormal brain development participates to the aetiology of multiple neurological and psychiatric disorders including epilepsy, schizophrenia, autism spectrum disorders, obsessive-compulsive behaviors and bipolar disorders.

Our work has shown that proper cortical development also depends on the action of different cell types that are transiently present during the construction of neural circuits. These transient signalling neurons express at high levels genes whose mutations have been associated with neurological and psychiatric disorders. At the earliest stages of corticogenesis in mice, long before any functional synapses are formed in the cerebral cortex, these neurons express genes that are involved in neurotransmission and are thought to be exclusively present at mature synapses. We have published and unpublished data showing that “synaptic” genes, whose mutations have been associated with pathological conditions, control neuronal migration during embryogenesis. Our recent results in primates also suggest that an increase in both number and diversity of migrating transient signalling neurons could be an evolutionary addition to wire higher-order cortical areas in the cerebral cortex and to increase vertebrate brain complexity and cognitive function.

Our data show that transient variations in the kinetics of arrival of these migrating signalling neurons during early development, or of their death at the end of corticogenesis have profound consequences on the construction of

normal and pathological neural circuits. We have shown that changes in neuronal migration during embryonic life lead to dysfunctional cortical circuits spanning from severe neonatal cortical malformations to subtle and transient defects, which mimics diseases with onset at puberty/adolescence. By coupling studies on the function and dysfunction of transient neuron development in mice and primates, our future projects aim at linking developmental neuroscience with evolution and pathology in humans.

Our projects span from early onset cortical malformations to susceptibility to later-onset diseases characteristic of psychiatric illnesses. They are now reaching the stage where we wish to, and can, ask questions relevant to human health. Thus, we have decided to join the Institute *Imagine (Institut des Maladies Génétiques, Hôpital Necker Enfants malades, Paris)* and the Institute of Psychiatry and Neurosciences of Paris (IPNP, *Hôpital St Anne, Paris*) to be able to develop this translational project in collaboration with neuroscientists, human geneticists and clinicians. Our Team moved in September 2017 and is reinforced by 4 people holding permanent positions (two researchers, one Engineer and one MD). This allows closer interactions with human geneticists and clinical experts in rare diseases, brain imaging and malformations. Our team’s strong expertise in cortical development will introduce a novel dimension fostering synergistic interactions across disciplinary boundaries. Our future projects should provide new genetic tools to develop mouse models for cortical abnormalities and contribute to the understanding and diagnosis of neurodevelopmental diseases in humans.

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Publications:

1. Fischer A, Rausell A. Primary immunodeficiencies suggest redundancy within the human immune system. *Science immunology* (2016) Vol. 1, Issue 6, doi: 10.1126/sciimmunol.aah5861

2. Rausell A, Muñoz M, Martínez R, Roger T, Telenti A, Ciuffi A. Innate immune defects in HIV permissive cell lines. *Retrovirology* (2016) 13:43.

3. Juliá M, Telenti A, Rausell A. Sincell: an R/Bioconductor package for statistical assessment of cell-state hierarchies from single-cell RNA-seq. *Bioinformatics* (2015), 31 (20) 3380–3382.

4. Bartha I*, Rausell A*, McLaren P, Tardaguila M, Mohammadi P, Fellay J, Telenti A. Heterozygous gene truncation delineates the human haploinsufficient

genome. *Plos Computational Biology* (2015), 11(12) e1004647. *Cofirst authorship.

5. Rausell A, Mohammadi P, McLaren PJ, Bartha I, Xenarios I, Fellay J, Telenti A. Analysis of stop-gain and frameshift variants in human innate immunity genes. *Plos Computational Biology* (2014), 10 (7), e1003757.

THE CLINICAL BIOINFORMATICS LAB

At the Clinical Bioinformatics lab we are interested in understanding the genetic and transcriptional basis of human health and disease, focusing on rare diseases associated to the immune system. In such context, Rausell's recent findings have contributed to better characterizing two main paradigms arising from large-scale genome and transcriptome sequencing projects: i) the widespread potential to cause disease of rare loss-of-function variants occurring in heterozygosis through haploinsufficiency or negative dominance; and ii) the transcriptional basis of the heterogeneity in permissiveness to infection across single cells within individuals, despite sharing the same genetic background.

The ultimate goal of our research is to provide computational tools and biomarkers to help decision-making on the diagnosis and treatment in a clinical set up. To this aim, we perform large-scale integrative studies of genomic (full exome/genome sequencing), transcriptomics (bulk and single-cell RNA-seq), phenotyping and clinical data generated at the *Imagine* Institute and by international collaborators. Additionally, we further interpret this data by mining publicly available bioinformatics resources. Notably, we develop bioinformatics methods and software making use of biostatistics and machine-learning approaches to extract relevant information from such high-dimensional and heterogeneous data sets (see below our Software list). We are also developing know-how on Big Data Analysis by adapting data-mining techniques to the challenges posed by the Personalized Medicine era, where the monitoring of patients through multi-omics technologies and personal devices is expected to generate overwhelming amounts of valuable data.

The laboratory currently has the following main research lines:

- 1) Bioinformatics software development for the functional assessment of human genetic variants detected by full exome/genome sequencing to predict/prioritize disease-causing variants. Methods under development include protein truncating variants (stop-gains, frameshifts and splice-disrupting variants potentially leading to a loss of function), missense variants (producing a change in the amino-acid that could affect a functional residue of the protein) and non-coding variants with potential regulatory consequences.
- 2) Phenotype-driven identification of causal variants in a multi-cohort study of immune diseases integrating

genomic and clinical datasets. The study will include Genome- and Phenome-Wide Association Studies (GWAS & PheWAS). Here we aim at exploring the genetic and clinical heterogeneity within different cohorts of patients, the pleiotropy of genes and pathways, and the comorbidities of the clinical phenotypes.

- 3) High-dimensional single-cell data analyses in functional genomics studies, addressing intra-individual cell heterogeneity and how it relates to immune disorders and susceptibility to infectious diseases. These analyses are performed in collaboration with *Imagine*'s experimental research groups and with international partnerships. The final aim is the identification of biomarkers with a clinical value.

Bioinformatics Methods & Software:

MCXpress: R package for the identification of rare subpopulation of cells and their gene signatures from single-cell RNA-seq data.

<https://github.com/cbl-imagine/MCXpress>

NCboost: python/R package of the pathogenicity assessment of non-coding variants from Whole Exome/Genome Sequencing (soon to be released as open-source software in github)

Sincell: R/Bioconductor package for the statistical assessment of cell state hierarchies from single-cell RNA-seq data.

<http://bioconductor.org/packages/sincell>

NUTVAR: Null and Truncating variant analysis. Sequence-based functional annotation of truncating variants from genome and exome data.

<https://git.io/Nutvar2.cbl.fr>

S3det - MCdet: C++ software for the prediction of functional specificity residues and protein subfamilies from multiple sequence alignments using Multiple Correspondence Analysis. Software integrated in TreeDet server
<http://treedet.bioinfo.cnio.es> and distributed within **JDet package**

JDet: interactive calculation and visualization of function-related conservation patterns in multiple sequence alignments and structures.

<http://csbg.cnb.csic.es/JDet>



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Publications:

1. Jeremiah N, Neven B, Gentili M, Callebaut I, Maschalidi S, Stolzenberg MC, Goudin N, Fremont ML, Nitschke P, Molina TJ, et al. Inherited STING-activating mutation underlies a familial inflammatory syndrome with lupus-like manifestations. *The Journal of clinical investigation*. 2014;124(12):5516-20.

2. Lanzarotti N, Bruneau J, Trinquand A, Stolzenberg MC, Neven B, Fregeac J, Levy E, Jeremiah N, Suarez F, Mahlaoui N, et al. RAS-associated lymphoproliferative disease evolves into severe juvenile myelo-monocytic leukemia. *Blood*. 2014;123(12):1960-3.

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4. Magerus-Chatinet A, Neven B, Stolzenberg MC, Daussy C, Arkwright PD, Lanzarotti N, Schaffner C, Cluet-Dennetiere S, Haerynck F, Michel G, et al. Onset of autoimmune lymphoproliferative syndrome (ALPS) in humans as a consequence

of genetic defect accumulation. *The Journal of clinical investigation*. 2011;121(1):106-12.

5. Holzelova E, Vonarbourg C, Stolzenberg MC, Arkwright PD, Selz F, Prieur AM, Blanche S, Bartunkova J, Vilmer E, Fischer A, et al. Autoimmune lymphoproliferative syndrome with somatic Fas mutations. *The New England journal of medicine*. 2004;351(14):1409-18.

IMMUNOGENETICS OF PEDIATRIC AUTOIMMUNE DISEASES

Our project focuses on the mechanisms involved in the control of self-tolerance in primary human immunodeficiencies and in hyper immune syndromes. The autoimmune lymphoproliferative syndrome (ALPS), characterized by a benign tumoral syndrome along with autoimmune cytopenia, is associated with heterozygous dominant mutations of the FAS gene and apoptosis deficiencies. This condition thus represents a key model to study some aspects predisposing to autoimmune diseases in the context of apoptosis deficiency. Moreover, we discovered that the apparent non-penetrance of the germline FAS mutations is explained by additional somatic events affecting the second allele of FAS in patients. We believe that such somatic events may account for the onset of other pediatric autoimmune diseases.

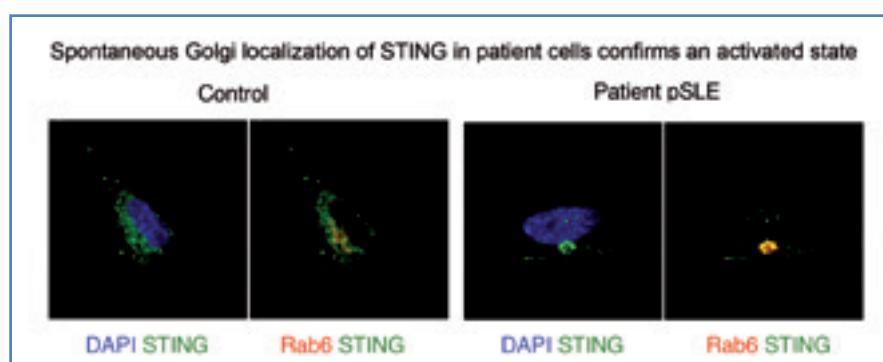
Based on our preliminary findings we are now studying three groups of patients presenting with:

1- ALPS and related diseases: the recent identification of KRAS mutations in this group of patients extent the group of apoptosis-related diseases and is prolonged by the study of Juvenile Myelo-Monocytic Leukemia. We are searching for modifiers by combining apoptosis functional assays and a genetic screen.

2- Evan's syndrome: This disease is defined by an early-onset severe cytopenia. It can be variably accompanied with other autoimmune manifestations such as autoimmune enteropathy or endocrinopathy. Following a whole-exome-sequencing (WES) approach we are currently validating gene mutations affecting the immune regulation.

3- Pediatric lupus (pSLE): a WES approach performed on a cohort of pSLE patients allowed us to identify an activating mutations of TMEM173/STING, encoding an adaptor of the cytosolic DNA sensing, in a familial case of autoinflammation and lupus features. The study of additional mutations of genes related to nucleotide sensing is currently under progress and should decipher the genetic as well as the pathophysiological bases of the pSLE.

This project is based on the availability of the patients' blood samples, as well as on the development of animal or cellular models. This work should provide a better understanding of the molecular and cellular bases of the mechanisms involved in T cells homeostasis and self-tolerance, and should allow the identification of susceptibility factors to human auto-immune diseases.



Spontaneous Golgi localization of STING in patient cells confirms an activated state



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Publications:

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GENETICS OF MITOCHONDRIAL DISEASES

Mitochondrial diseases are characterized by a huge clinical and genetic heterogeneity and the mitochondrial and nuclear disease causing genes have been identified in only 20% of cases. Moreover, there is almost no therapy for these devastating diseases.

Therefore our objectives are:

1. to identify new nuclear genes responsible for mitochondrial dysfunction in human for a better understanding of its heterogeneity
2. to improve our understanding on the replication of mitochondrial DNA during embryo-fetal development with the aim to propose prenatal procedures for mtDNA disorders
3. to test on patients fibroblasts drugs previously identified in yeast to restore deficient mitochondrial functions

Gene identification by next generation sequencing

The number of disease-causing mutations in mitochondrial diseases is constantly growing but it should be borne in mind that no mutation has been identified in 70% of the patients. The clinical and genetic heterogeneity of these diseases as well as the large number of candidate genes (1000-2000) make the identification of these genes more and more difficult. Indeed, we are now facing a large number of sporadic cases. Therefore, next generation sequencing has been

proved to be the best approach to identify new disease genes. We have already performed and will keep on doing exome sequencing for our patients. Nevertheless, our experience has taught us that exome sequencing is particularly successful i) when performed on two or more affected sibs or on clinically homogenous patients and ii) when guided by a specific biochemical phenotype. Therefore, we shall now combine various biochemical approaches (RC assembly, mitochondrial translation) with the aim of better characterizing the abnormal mitochondrial function and/ or defining the best candidate genes. Depending on the function of the mutant genes, various approaches will be developed with the aim of validating the pathogenicity of the mutations.

Mitochondrial DNA replication during embryo-fetal development

Eukaryotic cells contain a large number of copies of maternally inherited mtDNA. Very few data are available with respect to mtDNA replication during human oogenesis and embryogenesis, both in wild-type individuals and carriers of mtDNA mutations. Most of the data were obtained in animals and are sometimes contradictory. The lack of data on mtDNA replication during embryo-fetal development hampers to propose fully reliable pregestational and prenatal diagnosis to couples at risk to transmit mtDNA mutation. Our project aims at studying when and how normal and mutant mtDNA

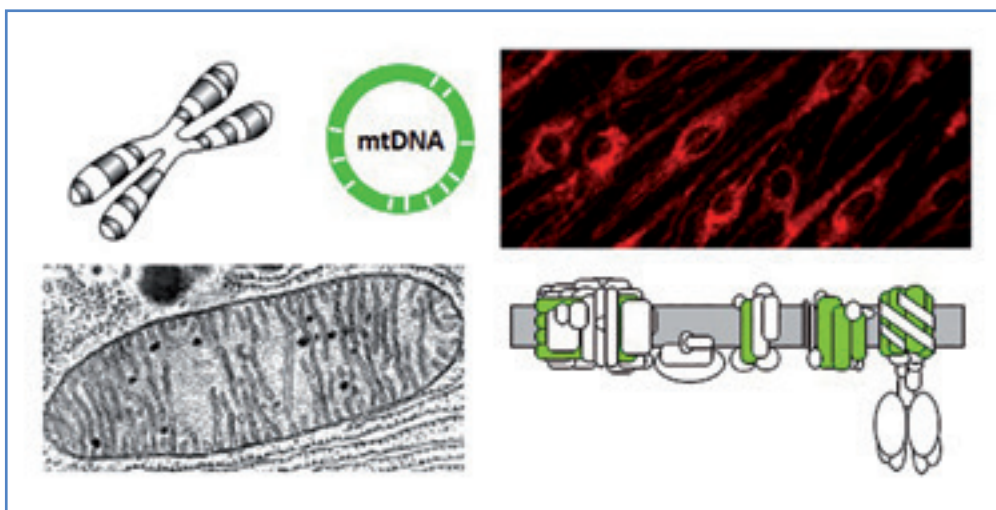
replicates throughout embryofetal development in human. In order to get an insight into these questions, we have collected a large number of human samples from control and mutant adult females (gametes and somatic cells), control and mutated embryos, fetuses and placentas. Using these samples, we shall assess the mtDNA copy number and mutation rate, the mtDNA replication, and the expression level of both mitochondrial genes and nuclear genes involved in replication and transcription of mtDNA, at the single cell level.

Neurodegeneration with brain iron accumulation (NBIA)

NBIA encompasses a group of rare neurodegenerative disorders transmitted as an autosomal recessive trait¹. We are interested by NBIA because (i) mitochondrial dysfunction is often suspected as a differential diagnosis of NBIA, (ii) it is related to Friedreich ataxia due to mutations of frataxin, a mitochondrial protein involved in iron metabolism and (iii) our local recruitment via Neuroradiology Unit of our Hospital. By exome sequencing we have identified a novel NBIA gene. This gene is involved in endocytosis and further work is underway to determine its involvement in iron metabolism.

Therapeutic approach of mitochondrial diseases

No efficient treatment of mitochondrial diseases is presently available. The use of human cells for testing a large number of drugs is relatively difficult as the only available cells are patient's fibroblasts that grow relatively slowly and as the study of mitochondrial functions require a relatively high amount of cells and is time consuming. We have initiated a consortium project aiming at using simple organisms such as *Saccharomyces cerevisiae* and *Caenorhabditis elegans* as tools for the first screen of drug libraries capable to modulate and/or restore deficient mitochondrial functions. This consortium includes four groups that are experts of mitochondrial functions in yeast and worm, chemists, and two groups involved in human genetics mainly involved in adult patients and our group in Necker hospital involved in pediatric patients. Yeasts or worms carrying nuclear or mitochondrial mutations corresponding to human disease mutations have been used for rapid screening of drug libraries that allowed to identify a small number of possible therapeutic molecules that will be tested on patient's fibroblasts.





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1. Gerber S, et al. Mutations in DNMI1/DRP1, as OPA1, result in dominant optic atrophy despite opposite effects on mitochondrial fusion and fission. *Brain* 2017, in press.

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GENETICS IN OPHTHALMOLOGY

In industrialized countries, hereditary eye diseases are leading causes of blindness in childhood. The goal of our laboratory is to improve knowledge about the natural history and molecular etiology of the most severe of these conditions, with the purpose of improving patient and family care, and of developing therapeutic means.

Over the last two decades, we have developed large cohorts of affected families, the clinical, genetic and molecular analysis of which has allowed:

- Mapping and/or identifying major genes for early-onset severe retinal dystrophies (Usher syndrome type 1, Stargardt disease, Leber congenital amaurosis, pseudo-dominant X-linked retinitis pigmentosa), non-syndromic hereditary optic neuropathies and eye dysgenesis (microanophthalmia, congenital microcoria, Gillespie syndrome), and
- Refining or modifying disease definitions and patient care.

In parallel, we have made proof-of-concept of intravitreal-antisense-oligonucleotide (AON)-mediated manipulation of splicing in retinal cells as a means to treat retinal diseases.

Our ongoing work aims at:

- Further characterizing the clinical, molecular and physiopathological bases of Leber congenital amaurosis, optic neuropathies, and inborn errors of eye development in families excluding known genetic causes. Our strategy combines family- and trio-based genome-wide next generation sequencing and OMICs analyses in patients' biological samples, cellular models and/or animal models. In corollary, extensive gene-directed clinical explorations are associated with these studies with the aim of detailing the ophthalmologic and systemic expression of gene defects.
- Characterizing the regulatory landscape of the 13q32.1 chromosomal region which deletion cause abnormal development of the iris.
- Bringing intravitreal oligotherapy (IVOT) to bedside by demonstrating the safety and efficacy of this strategy in transgenic mouse lines we produced at *Imagine* using CRISPR/Cas9 to model alterations of the major LCA gene, CEP290.

Brief Disease Definitions and Main Achievements

1. Inherited retinal dystrophies. Vast and heterogeneous group of eye diseases characterized by the gradual loss of photoreceptor cells and hence of light sensitivity of the retina (frequency 1:3,000).

- Stargardt disease. Juvenile macular dystrophy. Irreversible loss of central, high acuity vision (10 % of IRDs). Primary mapping and identification of the disease gene (STGD1/ABCA4); Evidence for allelism between juvenile and late-onset macular dystrophies; Evidence for a contribution of ABCA4 to age-related macular degeneration.

- Leber congenital amaurosis. Earliest and most severe IRD responsible for congenital or neonatal blindness. Occurs as a monosymptomatic disease or the presenting symptom of several systemic ciliopathies. 10 % of IRDs. Primary mapping and identification of LCA1/GUCY2D, AIPL1, RPGRIP1, TULP1, RDH12, NMNAT1, IFT140 (syndromic LCA), IFT81 (syndromic LCA); Evidence for an overlooked variability of the visual outcome, delineating a continuum with childhood-onset severe RDs known as EOSRD; Correlation between patient genotypes and disease outcome (visual outcome and systemic involvement); Evidence for highly restricted genetic overlap between monosymptomatic and syndromic LCA forms.

2. Hereditary optic neuropathies. Blinding diseases characterized by the gradual loss of retinal ganglion cells and atrophy of the optic nerve (frequency > 1:50,000). Primary mapping and identification of the major gene for autosomal dominant monosymptomatic HONs (Kjer disease, OPA1); Evidence for monosymptomatic autosomal recessive HON and identification of a first disease gene (OPA7/TMEM126A); Evidence for mitochondrial

dysfunction as a hallmark of monosymptomatic HON and for consistent silent to severe expression of HON mutations in high-energy demanding organs; Evidence for a genetic overlap between monosymptomatic HON and mitochondrial diseases with optic nerve involvement (SPG7, ACO2, RT4NIP1, NDUFS2, DNMI1 mutations in syndromic and nonsyndromic HON).

3. Inborn errors of eye development. A broad group developmental diseases and a frequent cause of severe visual deficiency in children.

- Anophthalmia and microphthalmia (A/M). Clinically and genetically heterogeneous group of early-eye-development anomalies resulting in absent or small ocular globes, respectively (frequency 3-30:100,00). Primary mapping and identification of a major gene for microanophthalmia, ALDH1A3; Very first genetic evidence of a direct link between retinoic acid synthesis dysfunction and early-eye development anomalies in humans.

- Congenital microcoria (MCOR). Very rare autosomal-dominant disorder of iris development with absence of dilator pupillae muscle and iridocorneal angle dysgenesis conferring high risk to glaucoma. Identification of 13q32.1 submicroscopic deletions as the unique cause of MCOR.

- Gillespie syndrome (GS). Very rare variant form of aniridia with cerebellar ataxia. Identification of ITPR1 mutations as the cause of autosomal recessive and dominant GS.

4. Therapeutic developments. Proof-of concept of AON-mediated correction of the most common LCA-causing CEP290 mutation (c.2991+1655A>G, 10% of all LCA cases) in cells from affected patients; proof-of-concept of AON-mediated splicing alteration in retinal cells using the intravitreal delivery route in the mouse.

GENEVIÈVE DE SAINT BASILE



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Publications:

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NORMAL AND PATHOLOGICAL HOMEOSTASIS OF THE IMMUNE SYSTEM

The mechanisms controlling immune homeostasis and inflammation are many and complex. Rare inherited conditions offer unique opportunities for describing complex mechanisms and gaining insight into key physiological processes. In addition, understanding the pathophysiology of primary immune diseases allows developing new diagnostic and therapeutic tools.

We have undertaken a research program aiming at the characterization of the molecular and functional bases responsible for inherited conditions associated with severe disturbance of immune homeostasis.

One of these conditions, the Haemophagocytic lymphohistiocytosis (HLH), is a unique immunopathological phenotype characterized by uncontrolled expansion and activation of polyclonal T lymphocytes and hyperinflammation. The condition may develop in a variety of disease contexts. Through the study of human natural mutants causing this condition, we have evidenced the involvement of the lymphocyte's cytotoxic function in this process and have identified critical effectors of the granule dependent cytotoxic activity. Several murine models that recapitulate the human disorder have been generated and have helped understanding the molecular and cellular bases of the development of primary and some "acquired" forms of HLH.

The mechanisms that regulate cytotoxic granule secretion are partially shared by other immune cells. We are currently characterizing protein complexes associated with kinesin-1

that regulate vesicle transport and function of Mast cell, platelets, and dendritic cells, beyond cytotoxic granules of lymphocytes.

Two major objectives will be pursued:

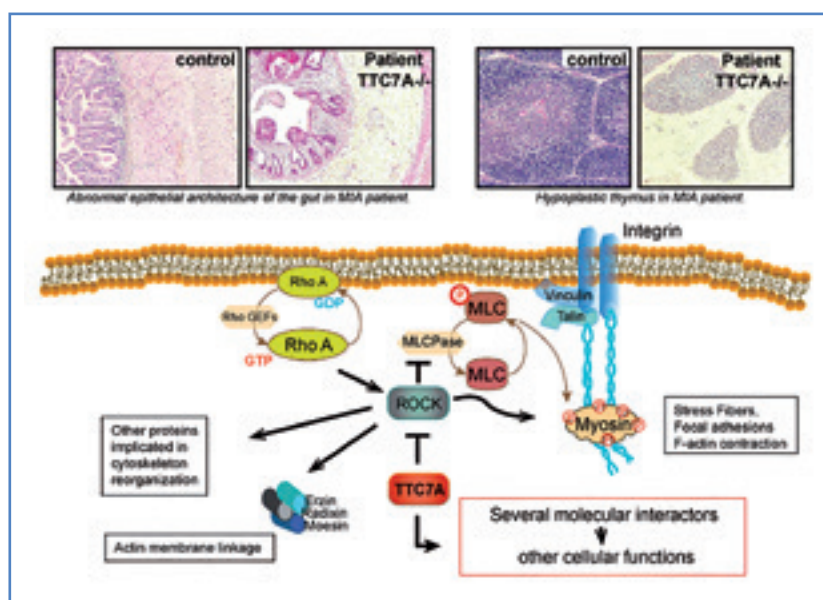
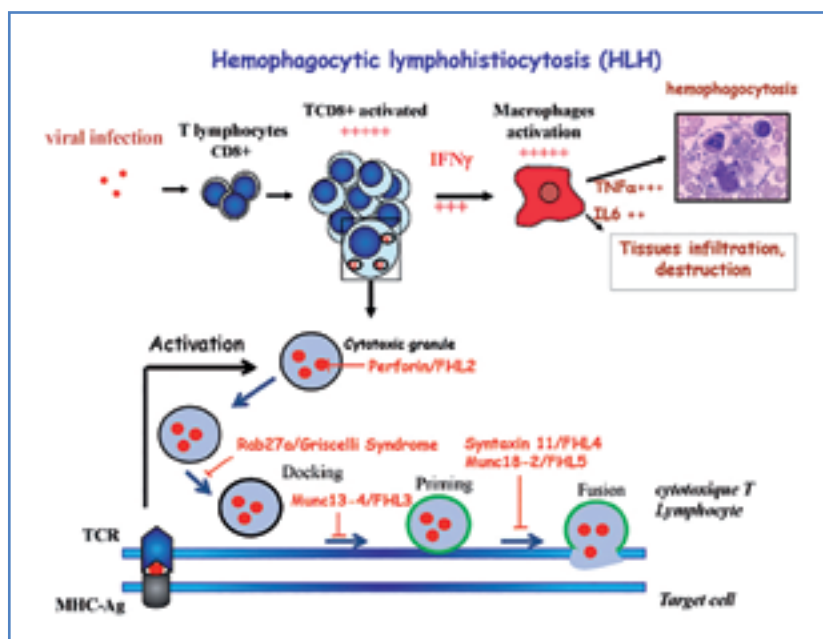
- A search for factors that account for the development of other primary and "acquired" forms of HLH, beyond cytotoxic-dependent defects, via a survey of pathological conditions in humans and the development of in vivo murine models.
- A search for effectors of Mast cell degranulation that can represent therapeutic targets and a search for genetic causes of severe allergic disorders via the study of "extreme" phenotypes.

A second condition results in a dysfunction of the immune system and changes in the epithelial architecture along the entire gastrointestinal tract. Severity of the disease varies from multiple intestinal atresia (MIA) to inflammatory bowel disease (IBD). Recently, we showed that the tetratricopeptide-repeat-domain-7A (TTC7A) responsible of these phenotypes leads to constitutive activation of Rho Kinase activity and impairs cell polarity. Although the function of TTC7A has yet to be defined, it is likely a key factor that bridges the process of both immune system and digestive tract homeostasis.

The goal of our research is to shed light on the molecular pathway and cellular function involving TTC7A in health and disease.

Two major objectives will be pursued:

- As a tetratricopeptide repeat-containing protein, TTC7A might act in a plurality of function through multiple protein complexes interactions that will be determined by a quantitative proteomic analysis followed by functional approaches.
- The natural murine Ttc7 mutant, the flaky skin (fsn) mouse, will be used to better analyse in vivo the precise underlying mechanisms leading to the complex phenotype observed and to test innovative therapeutic approaches of this condition and potentially of other IBD-like disorders.





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Publications:

1. Heidet L, Morinière V, Henry C, De Tomasi L, Reilly ML, Humbert C, Alibeu O, Fourrage C, Bole-Feysot C, Nitschké P, Tores F, Bras M, Jeanpierre M, Pietrement C, Gaillard D, Gonzales M, Novo R, Schaefer E, Roume J, Martinovic J, Malan V, Salomon R, Saunier S, Antignac C, Jeanpierre C. Targeted Exome Sequencing Identifies PBX1 as Involved in Monogenic Congenital Anomalies of the Kidney and Urinary Tract. *J Am Soc Nephrol*. 2017 May 31. pii: ASN.2017010043. doi: 10.1681/ASN.2017010043.

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MOLECULAR BASES OF HEREDITARY KIDNEY DISEASES: NEPHRONOPHTHISIS AND HYPODYSPLASIA

Our research aims at unraveling the pathogenesis of nephronophthisis (NPH) and renal hypodysplasia (RHD), two major genetic causes of renal insufficiency in children, using high throughput sequencing approaches and functional studies.

Nephronophthisis (NPH) is an autosomal recessive nephropathy, characterized by interstitial fibrosis and formation of tubular cysts, which represents the most common genetic cause of end-stage renal disease in children. NPH can be isolated or associated with extra-renal anomalies including retinal dystrophy, cerebellar vermis hypoplasia, skeletal dysmorphisms and/or situs inversus. The specific association of these anomalies defines complex syndromes called "ciliopathies". Based on large patient cohorts (>1000 NPH families) collected through a multicentric clinical network and thanks to the development of innovative NGS-based approaches, our group identified 14 of the 22 NPH causative genes known to date (NPHP1-20) as underlying NPH and associated syndromes. Most of the NPHP proteins localize at the primary cilium, an organelle which controls key signaling pathways during development and tissue homeostasis.

Over the past 5 years, we identified several new NPHP genes including two genes encoding IFTB components (IFT172 (Halbritter et al, 2013); IFT54 (Bizet et al, Nat. Comm., 2015)) and CEP83 (Failler et al, 2014) encoding a component of the centrosome required for ciliogenesis. Based on the use of in vitro kidney epithelial cell models, patient fibroblasts and in vivo models including mouse and zebrafish, we demonstrated that the NPHP and IFT proteins are indeed critical for ciliary function and also for cell polarity and epithelial morphogenesis

through extraciliary functions related to regulation of cytoplasmic microtubules dynamics (IFT54; Bizet et al., 2015). Through national and international collaborations which have been implicated in the identification of mutations in several other ciliopathy genes, DCDC2 in neonatal sclerosing cholangitis (Girard et al., 2016), KIAA0586 in Joubert syndrome (Albi et al., 2015), C2CD3, TMEM231 and TMEM107 involved in OFD syndromes (Thauvin et al., 2015; Roberson et al, 2015; Lambacher et al, 2016), and GAS8 (Lewis et al, 2016). These approaches have improved the molecular diagnosis of renal ciliopathies and broaden the spectrum phenotype associated with mutations of ciliary genes. Moreover, beside ciliary genes, using exosome sequencing, we identified mutations in MAPKBP1, a gene encoding a JNK scaffolding protein not involved in ciliary function, and showed that these mutations are associated with constitutive DNA Damage Response (DDR) signaling (Macia et al, 2017), a signaling pathway previously involved in renal ciliopathies (Chaki et al, 2012).

Renal hypodysplasia (RHD) is a phenotypically heterogeneous disorder that encompasses a spectrum of kidney development defects including renal agenesis, hypoplasia and dysplasia with or without cysts and belongs to the spectrum of CAKUT (Congenital Anomalies of the Kidney and Urinary Tract). It is also one of the most frequent causes of end-stage renal disease in children and the most severe forms (bilateral renal agenesis and multicystic dysplasia) are diagnosed in utero and justify medical termination of pregnancy. Although most RHD cases are isolated forms, familial and syndromic cases also exist and cystic kidney dysplasia can be associated with ciliopathy-like anomalies (situs inversus, skeletal and retinal defects, liver



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EPITHELIAL BIOLOGY AND DISEASE

Lysosomal signaling in proximal tubular cells of the kidney

Specialized epithelial cells constitute the dominant executors of tissue-specific physiological functions. In the kidney, our main organ of interest, there are a number of different epithelial cells organized in segments along the nephron, and we are particularly interested in the proximal tubules. Epithelial cells of the proximal tubules have a very active endolysosomal system, and this is because its main task is to reabsorb virtually all the proteins that are filtered by the glomerulus. For this, the apical brush borders are equipped with a dedicated protein uptake pathway, involving the multiligand receptors Megalin and Cubilin. Failure of this pathway results in low-molecular-weight proteinuria, which is a hallmark of proximal tubulopathies (e.g. cystinosis and Dent's disease). Our recent research in *Drosophila* has introduced a novel mechanism for the control of apical protein uptake with strong implications for proximal tubular cells (Gleixner et al., 2014). Our findings propose that lysosomal mTOR signaling - a major nutrient sensing pathway that controls metabolic decisions from the lysosomal surface - regulates the expression of Megalin as well as the morphogenesis of the apical surface. Therefore, we are studying how protein and lipid ligands from the tubular lumen can amplify a cycle of endocytosis and lysosome-to-nucleus signaling to satisfy the high metabolic needs of proximal tubular cells. Our main experimental model is the *Drosophila* nephrocyte that shares strong similarities with mammalian podocyte and proximal tubular cells.

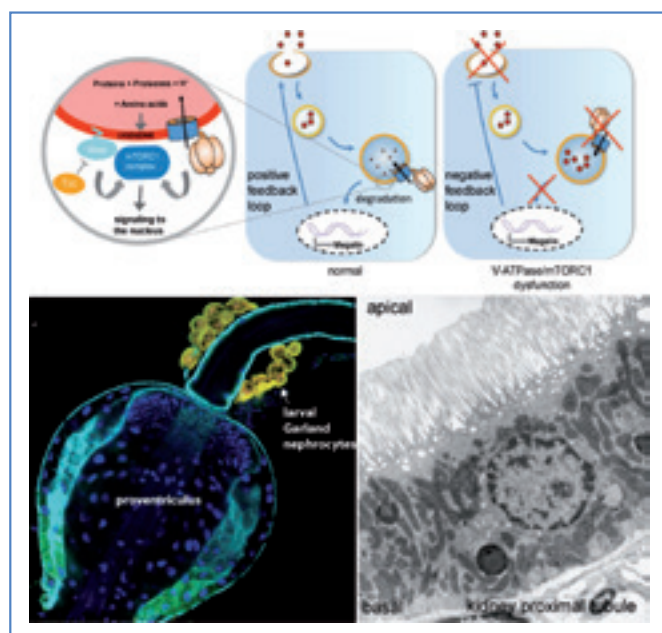
Phenotypic consequences of proton pump dysfunction

Another line of research deals with the functional characterization of the accessory V-ATPase subunit, ATP6AP2 (also known as the (pro)renin receptor). Our results suggest that this protein participates in the assembly of the V-ATPase complex in the endoplasmic reticulum (Rujano, Cannata Serio et al., in press). We are addressing the role of ATP6AP2 and the V-ATPase in autophagy, various signaling pathways (PCP, Wnt, Notch, mTOR etc.) as well as human genetic diseases

(Hermle et al, 2013; Trepiccione et al, 2016; Rujano, Cannata Serio et al., in press).

Drosophila as a tool in human genetics

The understanding of human genetic diseases has been greatly improved by novel techniques, such as next generation sequencing, allowing the complete genotyping of vast numbers of affected individuals and their relatives. Moreover, novel genome editing methods and reprogramming of patient-derived cells have enhanced the possibilities for functional follow-up studies. However, the evaluation of the pathogenicity of genetic variants remains a major bottleneck, because the human genome still lacks important functional gene information. An important goal of the lab is to employ the *Drosophila* model as an innovative toolkit for the rapid identification of novel genes for hereditary diseases, particularly in the area of kidney disease.





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Publications:

1. Elodie Bal, Hyun-Sook Park, Zakia Belaid-Choucair*, Hülya Kayserili*, Magali Naville**, Marine Madrange**, Elena Chiticariu, Smail Hadj-Rabia, Nicolas Cagnard, Francois Kuonen, Daniel Bachmann, Marcel Huber, Cindy Le Gall, Francine Côté, Sylvain Hanein, Rasim Özgür Rosti, Ayca Dilruba Aslanger, Quinten Waisfisz, Christine Bodemer, Olivier Hermine, Fanny Morice-Picard, Bruno Labeille, Frédéric Caux, Juliette Mazereeuw-Hautier, Nicole Philip, Nicolas Levy, Alain Taieb, Marie-Françoise Avril, Denis Headon, Gabor Gyapay, Thierry Magnaldo, Sylvie Fraitag, Hugues Roest Crolius, Pierre Vabres, Daniel Hohl, Arnold Munnich, Asma Smahi. Mutations in ACTRT1 gene and its enhancer RNA elements lead to aberrant activation of the Hedgehog signaling pathway in inherited and

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THE GENETICS OF MONOGENIC AUTO-INFLAMMATORY DISEASES

In recent years, we have characterized the molecular mechanisms underlying incontinentia pigmenti (IP, an inflammatory disease that mostly targets the skin and central nervous system) and demonstrated that it results from major inhibition of the NF-κB signaling pathway related to genetic defects in its NEMO regulatory subunit. We have also characterized the molecular mechanisms of rhabdomyolysis related to fever.

1. We are continuing to identify novel NEMO mutants and characterize their respective impacts at different steps in the NF-κB pathway. This process is important for better understanding severe forms of IP and thus defining the best drug targets in this orphan disorder. Linear ubiquitination has been recently emerged as a canonical pathway to activate NF-κB signaling via the linear ubiquitination of NEMO and RIP1. It is catalyzed by an enzymatic complex formed by HOIP, HOIL-1L and SHARPIN. We have identified a splice mutation in NEMO gene which arise in a central frame deletion resulting in a protein of 32kDa. The deleted domain is known in mice to be involved in linear ubiquitination. We demonstrate a total impairing of NF-κB activation in fibroblasts derived from IP male aborted and carrying the splice mutation. We have demonstrated an impairing in linear ubiquitination due to the fact that the truncated form doesn't interact specifically with SHARPIN (manuscript in revision JACI). With respect to the role of the NF-κB pathway in inflammation and epidermal homeostasis, we hypothesized that elucidating the genetic and molecular abnormalities involved in generalized pustular

psoriasis (GPP, an inflammatory skin disease displaying a Mendelian mode of inheritance) might unveil the key contribution of dysregulated inflammatory circuits. This latter strategy allowed us to characterize the molecular defects underlying GPP for the first time, which consist of deficiency of the IL-36 receptor antagonist activity and enhanced skin and systemic inflammatory responses. These genetically inherited abnormalities of the innate immune response have prompted reclassification of GPP as an auto-inflammatory disease. In another hand, In collaboration with the team of F. Capon, we have contributed to the identification of AP1S3, a gene which encodes a protein that promotes vesicular trafficking involved in endosomal translocation of the TLR-3 receptor involved in viral infection, consistent with the fact that viral infection is a major trigger of GPP flares. AP1S3 deficiency causes an abnormal accumulation of p62 impairing keratinocytes autophagy which arise in final to enhanced NF-κB signalling. Finally, gain-of-function mutations in CARD14 gene encoding a positive regulator of NF-κB signaling have been identified in various forms of psoriasis. Consequently, the three genetic conditions described above display enhancing NF-κB signaling pathway as a common defect. In the same line, we have identified via linkage and exomes analyses in a multiplex family with a complex auto-inflammatory disease with predominant cutaneous manifestations homozygous mutations in a novel gene encoding for a negative regulator of both two canonical pathways, NF-κB and Beta-Catenin, both involved in epidermal homeostasis. We demonstrated an hyperactivation of the two

signalling pathways in keratinocytes and monocytes upon Lipopolysaccharide stimulation. We have also been able to decipher a novel pathophysiological mechanism underlying a complex genodermatosis with high inflammatory phenotype which resulted from mutation in desmosomal protein and have linked the barrier function defect to inflammation via the NF- κ B signalling pathway. The candidate protein is an unexpected inhibitor of epithelial inflammation via the inhibition of NF- κ B signaling pathway (manuscript in revision).

Our main objectives are thus to:

- identify new gene defects associated with GPP by using homozygosity mapping in several multiplex consanguineous families showing a Mendelian segregation of the GPP trait and by leveraging recent advances in the high-throughput sequencing of large genomic regions to screen for targeted loci.
- investigate the effector mechanisms responsible for the exacerbated inflammatory reaction, in view of our recent findings in support of a key role of significantly dysregulated skin and systemic innate immune responses depending on IL-1 family members. We shall focus on the range of inflammatory and regulatory cytokines released during the flares and will address the cellular response in vitro in keratinocytes, macrophages and dendritic cells (i.e. the main cell types putatively involved in systemic and skin inflammation in GPP).
- decipher the molecular mechanisms involved in the inflammatory cascade leading to cytokine release. We shall focus mainly on the NF- κ B signaling pathway which, in inflammatory macrophage populations, has been shown to be a key pathway downstream of the activation of many receptors by their respective ligands, including IL-1 and TNF.
- identify cellular and molecular interactions of the inflammatory cascade by using existing genetically engineered mouse models of the IL-36/IL-36Ra pathway. These studies should allow the identification of new targets for the design of innovative therapeutic strategies for not only GPP but also systemic diseases with excessive inflammatory responses that frequently involve the skin and locomotor system (bones and joints), as is usually observed in severe forms of pustular psoriasis.
- to identify new genes responsible for uncharacterized auto-inflammatory diseases with skin involvement, in view of the recent classification of GPP as an autoinflammatory group disease, the known involvement of a misregulated

immune innate response in GPP and our ability to recruit patients presenting with complex inflammatory syndromes. This applies to severe forms of febrile neutrophilic dermatosis with major systemic inflammation, such as PASH syndrome (pyoderma gangrenosum, acne and suppurative hidradenitis - a new auto-inflammatory disease that is distinct from PAPA syndrome with pyogenic arthritis, pyoderma gangrenosum and acne) or other unclassified, systemic, pyoderma gangrenosum syndromes which might have an early onset in childhood or in young adults.

2. Concerning rhabdomyolysis, our working hypothesis is that fever-related rhabdomyolysis may be triggered and/or worsened by a dysregulation in innate immunity and/or inflammatory response, and by protein thermolability as showed in aldolase A deficiency. Moreover, irrespective of the cause of rhabdomyolysis, the pathophysiologic events follow a common pathway, the increased intracellular calcium concentration by either direct injury to the sarcolemma or failure of energy production. To test our hypotheses we will mainly focus on severe inherited rhabdomyolysis triggered by fever and due to i) a primary Fatty acid Beta-oxidation deficiency (FAO), as any pathogenic role of inflammation, thermolability and calcium release in FAO disorders has barely been studied, ii) and mutations in new genes discovered by exome sequencing. Five questions will be addressed:

- Is inflammation associated with rhabdomyolysis caused by FAO deficiencies and by mutations in new genes found by Exome sequencing? We will determine the spectrum of serum inflammatory and innate immune mediators released during flares for each causes of rhabdomyolysis described above, and identify immune and non-immune cellular actors responsible for hyper-inflammation in myoblasts cultured under innate immune stimuli.
- Is protein thermolability associated with rhabdomyolysis from all causes?
- Is there any toxicity for identified inflammatory mediators on skeletal muscle cells in vitro as assessed by calcium release and metabolic functions?
- Are there other consequences of gene defects at the cellular and the molecular levels in the context of severe rhabdomyolysis related to inflammation (cellular compartment composition and/or trafficking, biochemical evidences)?
- Are candidate drug therapies able to restore i) defective vesicular dynamic or inflammatory signaling pathways identified, ii) thermolability, iii) abnormal calcium flux?

JEAN-PIERRE DE VILLARTAY & PATRICK REYV



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Publications:

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Hoyeraal-Hreidarsson Syndrome Patient Highlight the Importance of the ARCH Domain. *Hum Mutat* 2016;37(5):469-72.

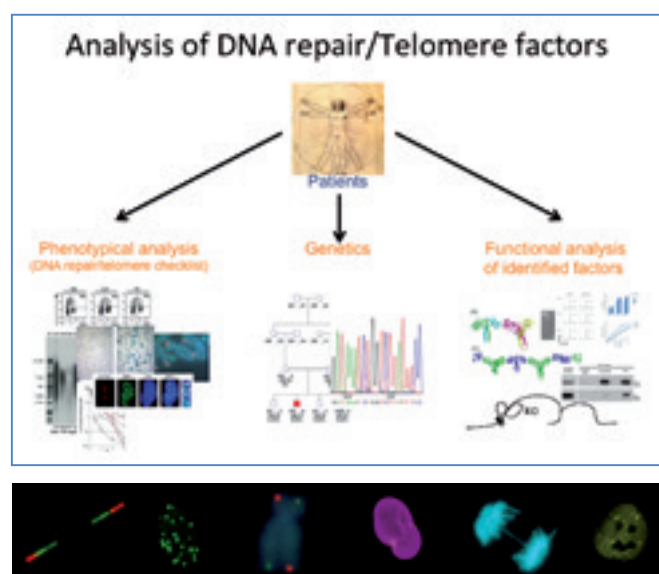
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GENOME DYNAMICS IN THE IMMUNE SYSTEM

The DNA (nuclear and mitochondrial), vector of the genetic information, is constantly subject to DNA lesions and/or modifications by endogenous sources or exogenous DNA damaging agents. DNA modifications are nevertheless essential for insuring the diversity of living organisms through intended germline recombination events in gametes during meiosis or somatic DNA recombination during the development of the adaptive immune system (V(D)J recombination). Recently, a new type of programmed DNA damage during neuronal activity has been identified. The cellular response to DNA damage (DDR) involves several stepwise reactions initiated by DNA damage sensing and cell cycle arrest (DNA damage checkpoint). These two initial events are followed by the recruitment of DNA repair machineries at the lesion. The inability to cope with DNA lesions can translate into a wide variety of pathological conditions in humans. Perhaps the most devastating consequence of DNA repair deficiency is the resulting genomic instability and generation of mutations, a port of entry to developing cancers. Although DNA repair pathways have long been considered as highly dedicated to specific types of lesions, they are now considered as an **intricated cobweb of factors, which can accommodate all types of DNA lesions**. Several questions remain unanswered:

- What are the rules that govern the combinatorial associations of DNA repair factors to insure their specialized intended functions as genome guardians and in the maintenance of telomeres?
- How are the various DNA repair pathways regulated, especially during programmed DNA modification mechanisms?
- What are the specificities of mitochondrial DNA repair and the consequences of its defect in pathology?
- How do they "speak to each other" (crosstalk)?
- What are the consequences of DNA repair defects, in particular in the context of cancer development or premature ageing diseases?

The overall objective of our research is to tackle these questions through the integration of several experimental strategies, which associate patient-driven studies to the development of innovative in vivo and in vitro animal and cellular experimental models for in-depth pathophysiological analyses. In addition to the purely cognitive interest of DDR studies, work in this field has direct clinical implications. For example, it is known that most anti-cancer treatments and many conditioning regimen necessary for hemopoietic stem cell transplantation, are based on the use of genotoxic agents that induce damage of DNA. We try to translate as much as possible the knowledge we gain at the bench for the direct benefit of the patients either for diagnosis or during treatments.



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NATHALIE BODDAERT



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Publications:

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5. Bricout M et al. Brain imaging in mitochondrial respiratory chain deficiency: combination of brain MRI features as a useful tool for genotype/phenotype correlations. J Med Genet. 2014.

IMAGE AT IMAGINE

Our research team's goal is to implement innovative anatomical and functional multimodal brain imaging methods for studying brain diseases in children and teenagers.

During the last decade, our team has identified brain abnormalities in autism and recognized brain imaging patterns leading to discovery of new mutations responsible for several neurogenetic diseases and metabolic encephalopathies. We are also engaged in the research of mastocytosis, childhood epilepsy, and pediatric brain tumors.

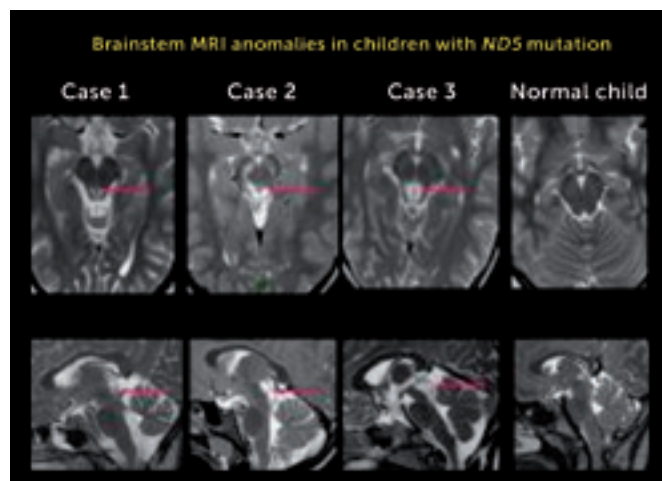
BRIEF OUTLINE OF THE PROJECTS:

- Characterization of radiological phenotype of pediatric genetic diseases using multimodal brain mapping
- Correlation of the radiological phenotypes with genotypes
- Investigation of the pathophysiology and natural history of selected diseases
- Application of brain imaging techniques to the monitoring of new treatments in clinical trials
- Optimization of candidate gene studies using an in-house multimodal database of clinically and radiologically homogeneous sub-groups of patients with encephalopathy and or mental retardation
- Radiogenomic of cerebral tumor.

1. Brain Imaging in neurometabolic and genetic developmental disorders

We have investigated phenotype/genotype correlations between well-known genetic entities and brain imaging patterns such as mitochondrial diseases (ND5, SENDA, Pla2G6),

encephalopathies (NBIA), epilepsies (KCNT1), cerebellar diseases (Joubert syndrome [RPGRIP1L], ponto-cerebellar hypoplasia [CASK], cerebellar dysplasia [OPHN1]), and in abnormal brain gyration (TUBA1A, TUBB2B). Using multimodal brain imaging, we've contributed to the delineation of novel clinical entities such as: defective fatty acid 2 hydroxylase (Fa2H) a neurodegenerative disorders with brain iron accumulation (NBIA), mitochondrial disorders (NUBPL), Ravine syndrome (non coding RNA). We have contributed to unravel the natural history of genetic diseases and to the monitoring of the first clinical trials using brain imaging (Freidreich ataxia and deferiprone). Finally, we have constructed algorithms using neuroimaging features to direct molecular genetic analyses (eg, brain iron accumulation and cerebellar ataxia).



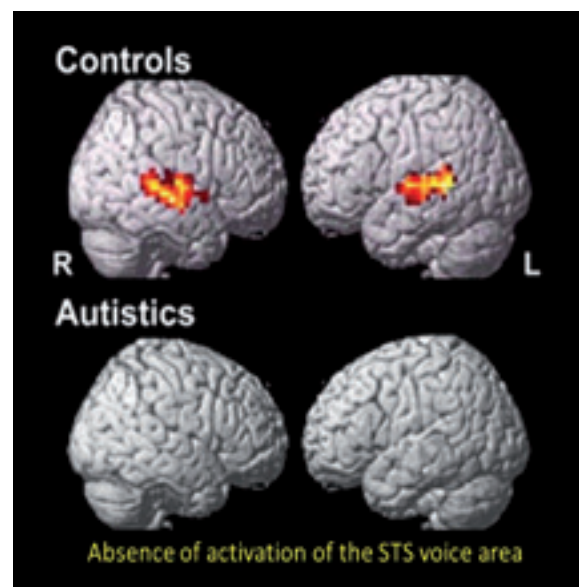
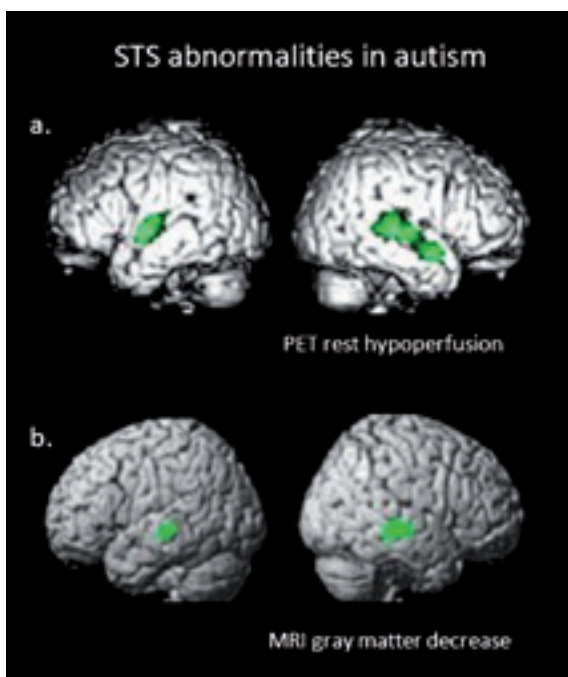
2. Brain Imaging in Autism

Identifying anatomo-functional brain anomalies is key to the great challenge of understanding autism. With multimodal brain imaging, we showed the existence of anatomical and functional abnormalities of the superior temporal sulcus (STS) in autistic patients. The STS is now known to be a critical region for social cognition. In the past decade we've shown:

i) Localized cortical anomaly of the STS correlated to autism severity, using PET (positron emission tomography) and MRI at rest (see figure); ii) the absence of activation of the STS voice area using fMRI (see figure); iii) an unexpectedly high rate (40%) of MRI abnormalities, mainly localized in the temporal area, illustrating the importance of including MRI studies in clinical evaluation of autism; iv) that it is possible to identify images of autistic children (sensitivity of 88%, specificity of 75%, correct classification rate of 86%) using multivariate classification of PET images. This suggests that rest cerebral blood flow (CBF) images may be a biomarker of autism.

Based on our previous results showing STS anomalies in autism, our research project are:

- To use MRI-ASL in order to measure the cerebral blood flow images and to find a biomarker of autism.
- To use eye tracking (a non-invasive method giving accurate information about how the subject has access to visual stimuli in a given social situation) to perform quantitative evaluation of social cognition in children with autism and correlate with multimodal MRI data.
- To document the involvement of the STS in social perception with rTMS (repetitive transcranial magnetic stimulation). rTMS is a non-invasive and painless technique that modifies the activity of neurons within the target area. This will be done by exciting or inhibiting the STS in autistic and healthy subjects.





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Publications:

1. Carré A, Stoupa A, Kariyawasam D, Gueriouz M, Ramond C, Monus T, Léger J, Gaujoux S, Sebag F, Glaser N, Zenaty D, Nitschke P, Bole-Feysot C, Hubert L, Lyonnet S, Scharfmann R, Munnich A, Besmond C, Taylor W, Polak M. Mutations in Borealin cause Thyroid Dysgenesis. *Human Molecular Genetics*. 2017 Feb 1;26(3):599-610.

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MOLECULAR BASIS OF SEVERAL CONGENITAL OR NEONATAL ENDOCRINE DISORDERS AND ESTABLISHMENT OF NEW THERAPEUTIC STRATEGIES

The main objective of the group is to understand the molecular basis of several congenital or neonatal endocrine disorders and to establish new therapeutic strategies.

The first goal of our team is to understand the causes of thyroid dysgenesis, a group of malformations of the thyroid gland leading to congenital hypothyroidism. This is done for the genetic part within the *Imagine* translational genomic laboratory in cooperation with Claude Besmond and within the INSERM U1016 unit. Normal thyroid function is essential for development, growth, and metabolic homeostasis. In utero and post-natally, thyroid hormones are key player in the normal development of the brain. Thyroid is an endodermal-derived organ. Understanding how such endocrine organs develop is important both to increase our knowledge of developmental processes and also as a basis to unravel the cause of specific pathologies of abnormal development and function of this organ. We identified, Borealin, normally implicated in mitosis as a factor involved in the adhesion and migration of thyrocytes. We showed that germ-line mutations in specific domain of this gene are responsible for thyroid dysgenesis, opening new avenues in the genetics of TD in humans.

Our second goal is to study some rare forms of congenital disorders of the endocrine pancreas. In the last fifteen years, we have focused our research on some specific forms of neonatal diabetes in Human. We have been able to define innovative treatments for children with neonatal diabetes, a rare genetic form of dysfunction of the insulin-secreting cell.

In a powerful translational approach, back to the patient with neonatal diabetes due to potassium channel mutation, we

were able to demonstrate that glibenclamide, a sulfonylureas, that enable to stop insulin injection in those children is a specific treatment of the condition, as its use led to a measurable cognitive and neuropsychological improvement in those children. We are advising AMMTek, a biotech company founded with the aim of providing repositioning of a sulfonylurea for newborns and children affected with neonatal diabetes, which is on the edge of obtaining a EU market authorization for this drug, under an orphan drug designation.

During those years we have gained a considerable experience in the study of the molecular control of the thyroid and islet cell development and we have also been able to establish a network with clinicians from France, Europe and several other countries in particular from Maghreb and Middle east; through this collaboration a depository of rare disorders of the thyroid and the endocrine pancreas has been established with a precise description of cases and DNA from index cases. This is a very helpful biological resource to continue our work.

Our team intends to pursue this « translational » research through further clinical trials, in link with our pediatric endocrinology and diabetology department at Necker Enfants Malades University hospital and the clinical investigation center within the *Imagine* institute.

We believe that, through our discovery of new molecular anomalies of thyroid or endocrine pancreas development we have and will: 1/ better understand some aspects of the development of those glands 2/ find new treatment strategy both pre- and post-natally in the affected children.

SABINE SARNACKI & ISABELLE BLOCH



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IMAG2 - COMPUTATIONAL ANATOMY FOR IMAGE-GUIDED MINIMALLY INVASIVE SURGERY IN PEDIATRIC TUMORAL AND DEVELOPMENTAL DISEASES

IMAG2 is a unique rising project at *Imagine* Institute in Necker Hospital gathering skills of surgeons dedicated to mini-invasive approaches, biomedical engineers specialized in 3D modeling with MRI images and radiologists experts in nerve tractography. The aim of this multidisciplinary team is to improve preoperative planning of pediatric tumors and malformations, leading to a higher level of security, efficacy and less morbidity. This project focuses for now on pelvic tumors and malformations, but aims at a spread to all pediatric surgical specialties that are represented in Necker Hospital.

Primary goals:

- Segmentation and 3D modeling of tumors. Abdominal and pelvic 3T MRI images will be used to develop segmentation models and build an executable file that will lead to semi-automatization of the process. This technology will be available for surgeons in routine to enhance the surgical strategy and will lead to the set up of a 3D radiologic database of patient with pediatric tumors and malformations.

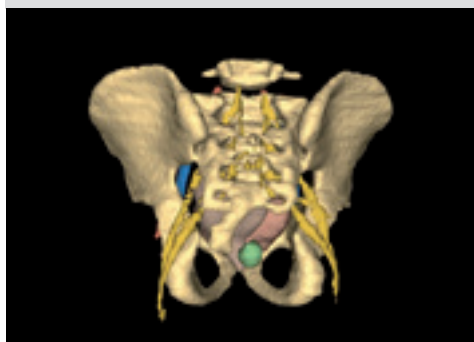
- Tractography of the pelvis. Pelvic 3T MRI images in DTI (diffusion tensor imaging) will be used to develop nerve tractography data, which will be associated to the results of 3D modeling. Computational analysis of images will be performed to optimize the representation of pelvic nerves network for preoperative workup of abdominal and pelvic tumors and malformations.

Secondary goal / Perspectives:

- Computer-assisted surgery through image overlay. Vizua3D platform will host the patient database provided by the primary goals and a morphing software. It will be connected to laparoscopic and robotic devices in the operating rooms in order to permit imaged guided surgery.

IMAG2 combines the best aspects of imaging and minimally invasive techniques to create optimal hybrid approaches for improving surgery in pediatric oncology and malformations. Pre-operative 3D modeling and nerve tracking will allow surgeons to plan and perform optimal hybrid procedures that leverage computer assistance and robotic augmentation to reproduce tasks that human surgeons alone cannot perform and improve pediatric surgical care.

Exemple of 3D modeling of a patient presenting a sacro-coccygeal teratoma, in the context of Currarino Syndrom



RHUC'IL-LICO

Imagine synergies to cure ciliopathies

On July 27th 2017, the French National Research Agency released the names of the 10 laureates out of 52 proposals of the 3d Call for proposals RHU. Hence the *Imagine C'IL-LICO* project is to benefit from the state Investments for the future Program (PIA - Programme Investissements d'Avenir).

C'IL-LICO aims at developing innovative, groundbreaking, and transformative diagnostic, prognostic and tailored therapeutic approaches in ciliopathies associated with renal failure, using cutting-edge artificial intelligence (AI)-based technologies, a unique combination of experimental and clinical data, and results already available within the consortium of the project.

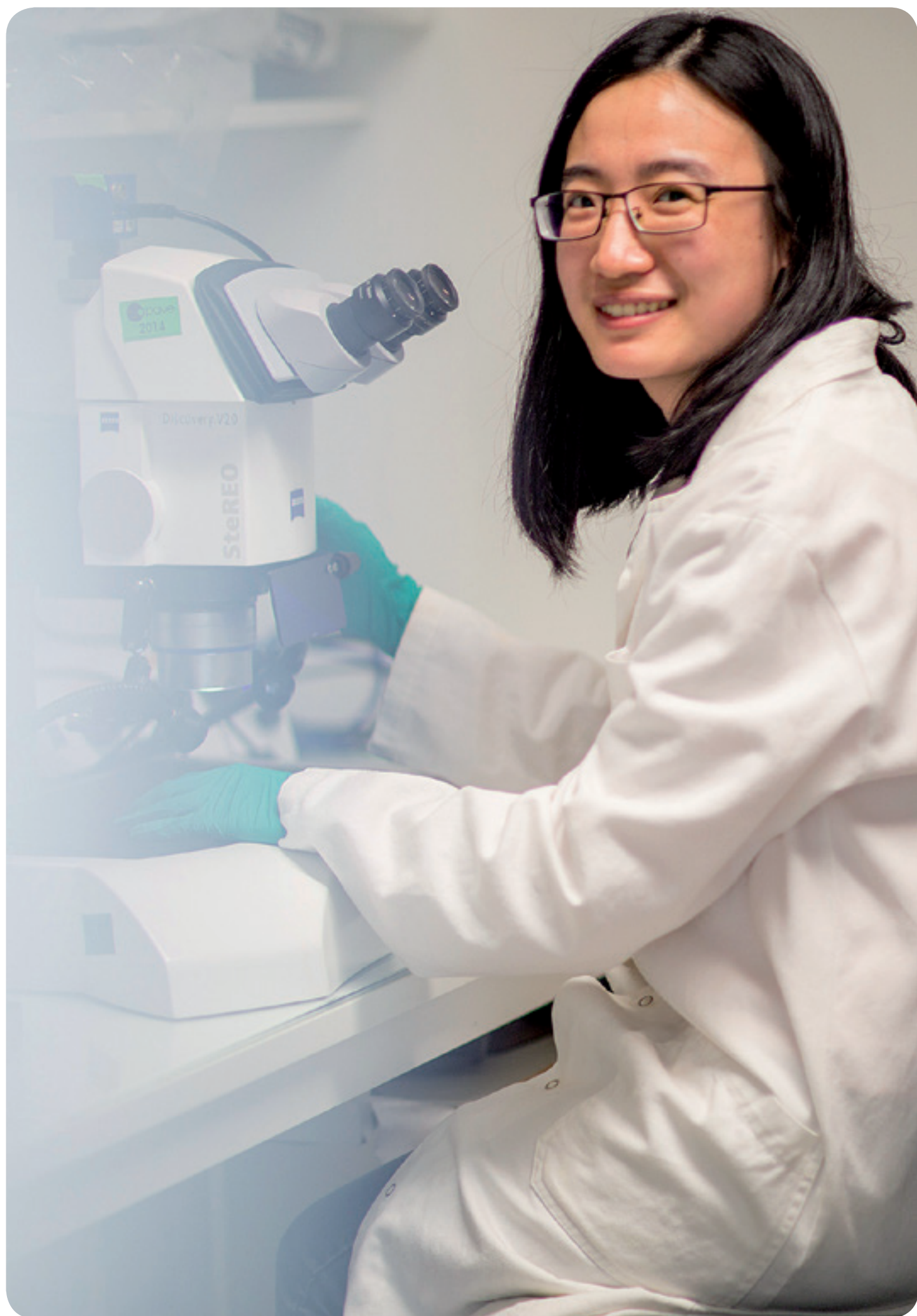
It brings together experts working in synergies at various laboratories of *Imagine* Institute, INSERM, APHP, Strasbourg University Hospital, and École Polytechnique, as well as Alexion, a major industrial partner internationally recognized in rare diseases. The project will be launched in 2017 and last 60 months. The PIA will contribute to the overall € 20.4 million budget with a € 5.9 million funding.

Ciliopathies are a large group of rare and severe genetic diseases caused by ciliary dysfunction. In spite of being individually rare, collectively they concern up to one per 2000 individuals. Despite their broad spectrum of clinical manifestations, a common cause of morbidity and mortality across several ciliopathies is the degradation of the renal function leading to end stage renal disease, for which the available standard of care is based on dialysis and transplantation only. However, the clinical and genetic heterogeneity as well as the lack of knowledge on patients' natural history limit the development of novel targeted therapies that could improve patients' care.

In this context, the C'IL-LICO project aims at developing innovative, groundbreaking, and transformative diagnostic, prognostic and tailored therapeutic approaches for patients suffering from ciliopathies leading to renal failure.

- First, the project proposes to construct a mechanistic stratification of ciliopathies (Cil-Smart), using artificial intelligence (AI), in order to regroup suspected and already diagnosed ciliopathies in a treatment-orientated classification (Cil-Biom) rather than the usual genetic-based classifications.
- Second, it allows building ready-to-use bio-kits for assessing both the diagnosis (Cil-Diag2), and the prognosis of developing renal alteration, in ciliopathy patients, and in particular undiagnosed cases.
- Third, it offers the opportunity to develop tailored first-class therapeutic approaches ready to enter clinical development.

The deliverables of the project will be highly beneficial to the patients affected by ciliopathies. They will also serve the partners involved in the consortium and every stakeholder interested in research and care through the use and exploitation of the tools, methods and products developed by the consortium. With its new paradigm and scientific approaches, addressing rare diseases as a group or groups rather than separate entities, the project will pave the way of next generation medicine enabled by AI and will have major consequences on personalized treatment of renal ciliopathies and eventually other complex disorders.



The core facilities

Core facilities are developed and supported together with the “Structure fédérative de recherche” (SFR), and the Necker-Enfants malades Research Institute (INEM) on the Broussais campus.



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NECKER DNA BIOBANK

The Necker DNA biobank is a core facility of the Federative Research Structure of Necker (SFR), with a large participation of Necker Hospital to its funding. It is located at the 1st floor of the *Imagine* building, for a total area of 500 sq.m.

The Necker DNA Biobank has been certified since December 2012 according to the French Standard of the Biological Resource Centers (NF S 96-900) and this certification has been renewed on December 2015, for 3 years.

Currently, the Necker DNA Biobank is an structure opened to the medical and scientific community and performs the establishment, storage, maintenance and enrichment of human biological collections.

Two types of samples are stored in the Necker DNA biobank:

1. samples from patients (almost only children) and their family with rare genetic disorders who are attending the various specialized departments of the Necker hospital;
2. samples that are part of collections generated through a defined research project.

For all the patients, the Necker DNA Biobank receives biological samples of various types:

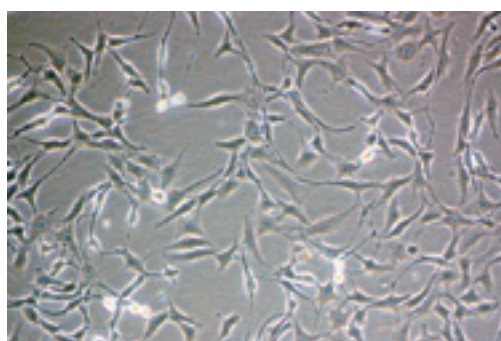
Blood samples are processed as follows:

- Obtention of pelleted white blood cells for genomic DNA extraction.
- Isolation of lymphocytes for future lineages, or for the immediate establishment of a lymphoblastic lineage.

Skin biopsies: fibroblasts cell lines are expanded and stored.

Other types of biological samples may be processed, depending on the research projects, after acceptance by the Necker DNA Biobank.

The total number of samples stored in the Necker DNA Biobank is currently more than 100000, with essentially 45660 leukocyte pellets, 9428 lymphoblastoid cell lines, 8693 lymphocytes, 286 fibroblasts cell lines, 37918 DNA from 50797 patients and their affected or unaffected relatives.



SOPHIE BERISSI



Team:
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Scientific manager:
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Members of the team:
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Noémie Gadessaud

Publications:

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HISTOLOGY PLATFORM



The Histology core facility was created in 2007 as a service of animal anatomopathology and a training service to various techniques of histology and protein localization.

In this aim, it will support your samples depending on your request: paraffin embedding, paraffin or cryo-sections, staining, scanning, and helpful for immunohistochemistry development. It may also form a team member who will have access autonomously to the different work stations to conduct her/his studies benefiting from the experience and technology of the core facility's team members.

The facility currently has all the equipment needed to carry out routine histological techniques and immunohistochemical techniques on fixed and frozen samples.

Available Equipments and services

The histology platform is equipped with:

- An ASP300 (paraffin impregnation system) and a table for inclusion EC 350,
- A SlideMate Slide Printer to reduce identification errors and eliminate the need for handwriting,
- Three semi-automatic microtomes for sectioning of paraffin-embedded samples, (2 HM340E Microm and 1 RM2145 Leica for the training),
- One cryostat LEICA (CM3050S) for sectioning of frozen tissues,
- Storage at -80°C for frozen sample pending,
- One Stainer Integrated Workstation Leica (ST5020-CV5030) to perform various colorations,
- A laser microdissector PALM MicroBeam (Zeiss) for the separation of two distinct structures included into the same tissue and subsequent differential studies on DNA, RNA or proteins,
- A Nanozoomer (Hamamatsu) that converts glass slides into digital slides by scanning them quickly at high resolutions

(bright or fluorescence),

- Two computer with Calopix software for analysis and quantification
- And a microscope, essential for training to have a permanent control of section quality.
- An OHREM (Optical High Resolution Episcopic Microscope, Indigo Scientific) to achieve imaging for 3D reconstruction purposes. Whole samples/embryos embedded in a resin and high resolution imaging of each cut surface lends itself to 3D reconstruction of the whole sample and accurate measurement.

Services provided

The core facility provides:

- Advice for sample preparation,
- Tissue processing for paraffin,
- Sectioning of paraffin/frozen samples,
- Classical histological stains (HE, Periodic Acid Schiff, Masson trichrome, Picro-sirius, Toluidine blue)
- Immunohistochemistry: Training and advice,
- Digital slides,
- Training to use Calopix,
- Collaboration, training and advice to the development of microdissection Laser projects,
- Mouse tissue bank,
- Training and advice in tissue processing, sectioning and staining.

Proposed applications:

- Inflammation detection,
- Glycoprotein detection (glycogen),
- Fibrosis detection (collagen I or collagen I and III),
- Staining conservation or quantification in bright or fluorescence,
- DNA, RNA or protein analysis of distinct structure,
- Tissue control (+/-) for staining,
- 3D reconstruction.

CLAUDE BESMOND



Team:

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Marie Faoucher
Erwan Mercier

Publications:

1. Poirier K, Hubert L, Viot G, Rio M, Billuart P, Besmond C, Bienvenu T. CSNK2B splice site mutations in patients cause intellectual disability with or without myoclonic epilepsy. *Hum Mutat.* 2017 Aug;38(8):932-941.

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TRANSLATIONAL GENETICS CORE FACILITY

Rare genetic diseases are the main reason for consultations and hospital stays at the Necker-Enfants malades hospital. The majority of these genetic diseases are investigated by the research teams at the *Imagine* Institute. However, a significant number of "genetic cases" remain orphan diseases. These are patients with a complex clinical presentation which does not fit with an identified research priority and is therefore not covered by a research team. Orphan cases are also patients with a clinical presentation for which the usual or plausible genetic defects have already been sought by the research teams, without success.

The role of the Translational Genetics core facility is to identify the gene at the root of these as-yet unnamed genetic conditions. The majority of cases we receive are unique and often present a complex array of symptoms, which, taken together, cannot be linked to an identified genetic defect or development abnormality. Our strategy is based on high-throughput methods, such as the exome (NGS), as targeted chip sequencing (TNGS) is a prerequisite for exome analysis or genome sequencing conducted in our Genomics core facility in the *Imagine* Institute. Exome sequencing is carried out in the Institute's Genomics core facility. Data are then analyzed in cooperation with the bioinformatics facility on the basis of algorithms developed by the facility. Genome profiles produced by exome analysis are stored in a special database with access provided to the clinical departments and research teams. The Translational Genetics core facility is at the interface between a large number of departments and centers: i) the *Imagine* university hospital, the ii) 32 rare disease reference centers at Necker-Enfants Malades hospital, iii) the clinical research centers, iv) the INSERM research teams at the campus, v) the Rare Diseases Foundation, and iv) the clinical departments or research teams we may collaborate with for the

cases we study. Decisions to refer patients to the Translational Genetics Team are made during multi-disciplinary meetings in the Genetics Department.

In 2016, we investigated 56 families with unknown genetic causes. Our research strategies allowed us to identify the genes involved in more than 50% of these families. Of these, we assigned three "new" genes for conditions that had been classified as orphan diseases. Since our group started working in 2012, we have discovered the genetic causes of 36 rare genetic diseases.

Since our work focuses on neurological conditions, the majority of the genes identified concerned the ion channels, neuronal growth and chromatin remodeling. In conclusion, we have demonstrated that the trials conducted at the Translational Genetics core facility i) improve the characterization of the complexity of rare genetic diseases, ii) give us a deeper understanding of very early human development, and iii) afford clinicians the opportunity to perform more detailed clinical diagnoses of patients and provide their entourage with a wider range of services.



CHRISTINE BOLE-FEYSOT



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Publications:

1. Gordon CT, Xue S, Yigit G, Filali H, Chen K, Rosin N, Yoshiura KI, Oufadem M, Beck TJ, McGowan R, Magee AC, Altmüller J, Dion C, Thiele H, Gurzau AD, Nürnberg P, Meschede D, Mühlbauer W, Okamoto N, Varghese V, Irving R, Sigaudy S, Williams D, Ahmed SF, Bonnard C, Kong MK, Ratbi I, Fejjal N, Fikri M, Elalaoui SC, Reigstad H, Bole-Feysot C, Nitschke P, Ragge N, Lévy N, Tuncbilek G, Teo AS, Cunningham ML, Sefiani A, Kayserili H, Murphy JM, Chatdokmaiprai C, Hillmer AM, Wattanasirichaigoon D, Lyonnet S, Magdinier F, Javed A, Blewitt ME, Amiel J, Wollnik B, Reversade B. De novo mutations in SMCHD1 cause Bosma arhinia microphthalmia syndrome and abrogate nasal development. *Nat Genet.* 2017 Feb;49(2):249-255. doi: 10.1038/ng.3765. Epub 2017 Jan 9.
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GENOMIC PLATFORM

Imagine's genomic core facility was created in 2008 to provide high-throughput sequencing and gene expression services to the Necker research community on a fee-for-service basis. The facility performs all the molecular biology steps required to produce raw data from the DNA and RNA samples provided by the users. The Experimental design and the analysis and interpretation of results are performed on an interactive basis with investigators and the bioinformatics facility (*Imagine* Foundation/Paris Descartes University).

Equipment

Imagine's genomic core facility has acquired its first next generation sequencer in 2010 and has increased its sequencing capabilities over the time.

The genomic platform is equipped with:

- Two high throughput next generation sequencers HiSeq2500 (Illumina) since 2013
- One next generation sequencer Ion Torrent PGM (Personal Genome Machine, Life Technologies) since 2011
- One next generation sequencer MiSeq (Illumina) since 2013
- Other equipment:
 - DNA shearing: Covaris E220
 - Capillary electrophoresis: Fragment analyzer (Proteogene), Tape Station 2200 (Agilent Technologies)

- Nucleic acids measurement: Xpose spectrophotometer (Trinean), QuBit fluorimeter (Invitrogen), real time PCR StepOnePlus (Life Technologies)

Services

The core facility provides:

- A help to the experimental design
- The quality check of DNAs and RNAs samples
- The library construction, clonal amplification and sequencing with next generation sequencers
- The primary data analysis and transfer to the bioinformatics facility for further data analysis

Proposed applications:

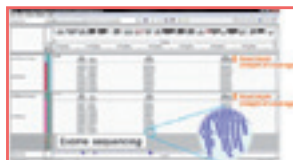
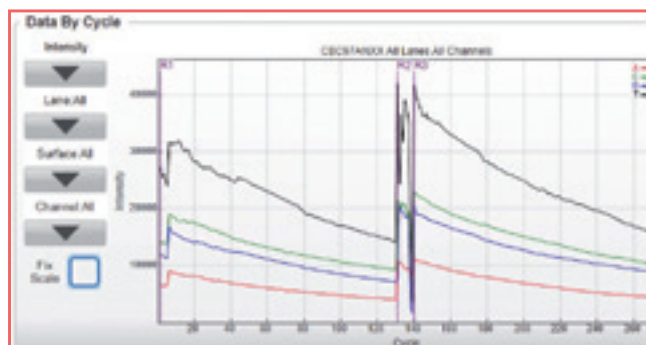
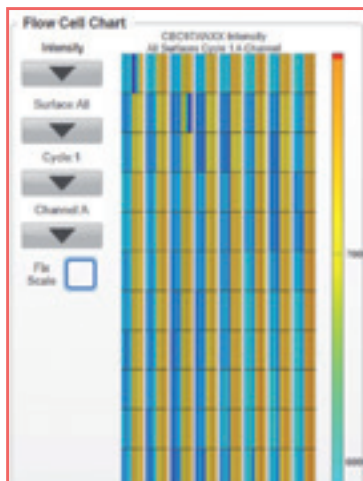
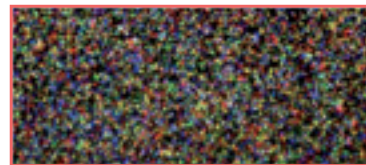
- Exome sequencing
- Targeted re-sequencing using panels of genes of interest
- Transcriptomic analysis by RNA sequencing
- Other applications of next generation sequencing on demand:
 - whole genome sequencing
 - sequencing of amplicons for various applications
 - ChIP-Seq (sequencing of immunoprecipitated chromatin),...

Recent Highlights

- The facility completed in 2016 the analysis of 4759 samples in total (3948 samples in 2015) for targeted resequencing applications by NGS mainly:
 - 1477 samples were analyzed by whole exome sequencing (targeted resequencing of ~58 Mb corresponding to the coding regions of virtually all the exons of the human genome).
 - 2742 samples were analyzed by targeted resequencing using various panels of genes that have been customized by various *Imagine*'s team for research and/or diagnosis purposes.
- Two new applications were introduced in 2016:
 - transcriptomic analysis by RNAseq: 204 samples analyzed (15 projects)
 - human whole genome sequencing: 18 samples analyzed (4 projects)

- Since 2014, the facility transmits its technological expertise to Necker's hospital labs devoted to the molecular diagnosis of genetic diseases: staff training and transmission of optimized capture protocols used for hybridization based targeted resequencing of genes panels.

These optimized protocols leads to a significant reduction of the cost (~650 000 € saved from 2013 to the end of 2016), hands-on-time and samples throughput for this type of application.



CORINNE CORDIER



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**Scientific
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Emmanuelle Six

Publications:

1. Gagnerault, M. C., O. Lanvin, V. Pasquier, C. Garcia, D. Damotte, B. Lucas, and F. Lepault Autoimmunity during Thymectomy-Induced Lymphopenia: Role of Thymus Ablation and Initial Effector T Cell Activation Timing in Nonobese Diabetic Mice J. Immunol. 183, 4913-4920 (2009)
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CYTOMETRY PLATFORM

Cytometry is a very powerful technique that identifies and quantifies populations of cells in a heterogeneous sample. The cell subsets are measured by labelling population-specific proteins with a fluorochrome on the cell surface or in the intracellular compartment. The main advantage of the cytometry is the speed of acquisition of the data for one very large number of cells, allowing the analysis of complex and/or rare cellular sub-populations. The cell sorter cytometers have the ability to physically isolate the cell sub-populations of interest. The collects can be done in bulk (tubes) or by cloning in multiwell plates.

Missions:

- Put equipment at the disposal of the scientific community
- Assist the users in the optimisation and the development of their project in cytometry
- Train and help the users for using the cytometers, for the interpretation of the results and the use of different analysis softwares
- Propose new technical developments

Equipment:

- Becton Dickinson LSR Fortessa SORP analyser with 355nm, 405nm, 488nm 561nm and 632nm Lasers, permits to analyse up to 18 parameters.
- Sony SP6800 Spectral analyser with 488nm, 405nm et 633nm Lasers able to collect photons from 420 to 800nm
- Becton Dickinson FACS Aria IIIu sorter with 407nm, 488nm, 561nm and 633nm, permits to analyse up to 16 parameters and to sort 4 different populations simultaneously.
- Becton Dickinson FACS Aria II SORP sorter with 355nm, 405nm, 488nm 561nm and 632nm Lasers, permits to analyse up to 18 parameters and to sort 4 different populations simultaneously.

- Sony SH800 sorter with 2 Laser 488nm and 561nm, permits to analyse 8 parameters and to sort up to 2 populations simultaneously.
- Amnis ImageStreamX Mark II, imager flow cytometer, combines classical flow cytometry with the detailed imagery and functional insights of microscopy. With 375nm, 405nm, 488nm, 560nm and 642nm Lasers.

Applications:

- Detection of surface or intracellular molecules, Immunophenotyping, Phosphorylated proteins
- DNA content analysis, cell cycle analysis, apoptosis
- RNA content analysis
- Cell viability analysis
- Cellular functions analysis (Calcium flux, intracellular pH, cytoplasmic and mitochondrial membrane potential, oxidative stress, cell proliferation analysis)
- Cytokines detection (CBA technology)
- Fluorescent proteins (as markers for gene) detection
- Rare events analysis (Dendritic cells, Stem cell/progenitor cells)

The work of the Cytometry core facility of the SFR Necker is involved in many scientific domains: immunology, hematology, immunogenetics, human genetic, genetics of human diseases and infectious diseases, study of the bone regeneration, study of the renal and intestinal diseases, cellular biology of the growth and the signaling, cancer research, microbiology, neurobiology.



Team:
Pierre David

TRANSGENESIS PLATFORM

Forming part of the LEAT (animal experimentation and transgenesis laboratory), the transgenesis platform was set up in 2015 to provide research teams with easier access to the transgenic mouse model.

The mouse genome is completely understood and various transgenic techniques enable it to be modified. The transgenic mouse model is thus particularly interesting because it offers numerous possibilities such as the study of gene function, modeling of human diseases and testing of different therapies, etc.

The production of such models has recently become much easier through use of the Crispr/Cas9 system which considerably reduces the time and cost of transgenesis.

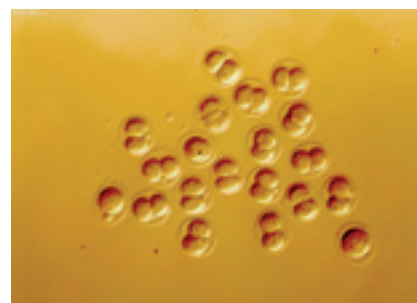
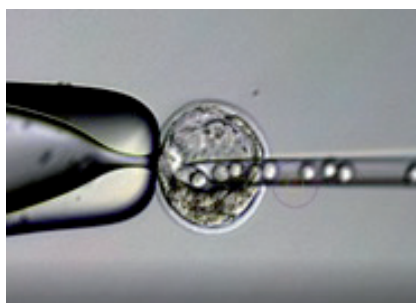
Missions :

- Generation of transgenic mouse lines with the Crispr/Cas9 approach. That includes help for the Crispr production, zygote production, micro-injection with Crispr/Cas9 reagents, embryo transfer into pseudo-pregnant females
- Generation of transgenic mouse lines with ES cell injections in blastocysts embryos
- Cryorecovery of mouse lines from cryopreserved embryos

Equipment:

- CO2 incubator
- -80°C freezer
- Leica DMI-8 inverted microscope
- Eppendorf NK2 micromanipulators
- Eppendorf Femtojet micro-injector
- 2 stereomicroscopes
- Horizontal laminar airflow cabinet

In 2016, ten "knock-out" lines (simple frameshift or major deletion) and one "knock-in" line (single-base mutation) have been established, mostly on the C57BL/6J genetic background. This technology was optimized by using ribonucleoproteins (protein Cas9 associated in vitro with the guide RNA). Currently, ssODN modified with phosphorothioate are being used in the aim of increasing the knock-in event.



SYLVIE FABREGA



Manager:
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Team:
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Sofiane Hadj Hamou

Scientific direction:
Sébastien Storck

Publications:

1. Ivan Nemazanyy et al. EMBO Mol Med. 2013
2. Emmanuel Martin et al. Nature 510, 288–292, 12, June 2014

3. Lam Son Nguyen et al. Molecular Autism, jan 8 2016
4. Elias A. El-Habr et al. Acta Neuropathol DOI 10.1007/s00401-016-1659-5. 2017.

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GENE TRANSFER VECTOR CORE

As part of the *Imagine* and INEM project and in association with Inserm and the Paris Descartes University, we have set up the VVTG core facility for gene transfer technologies. The VVTG platform offers production and purification of recombinant Lentiviruses, Retroviruses and Adenoviruses for research use.

Gene transfer vector core

Gene transfer is an essential component of functional genomic studies and therapeutic target identification, and it is widely used to modify cultured cells and laboratory animals, both for basic research gene therapy and vaccines. Virus-based vectors are the most efficient way to introduce foreign sequences into cells and are commonly used in vitro and in vivo.

Proposed gene transfert applications:

- cDNA, fluorescent reporter expression
- gene inactivation: shRNA, miRNA, cre
- gene selection with drugs,
- gene immortalisation,
- genome editing tools: CRISPR-Cas9 system

Expertise and service provided:

1. Production of viral batches for in vitro and in vivo gene transfer applications;
2. Maintenance of available vectors database and assistance in submitting protocols and files to the regulatory agencies (Haut Conseil des Biotechnologies, HCB);
3. Provides information and advices for the use of viral vectors, including manipulation in L2 and L3 laboratories;
4. Contacts with outside vector core facilities for the production of pre-clinical grade vectors.

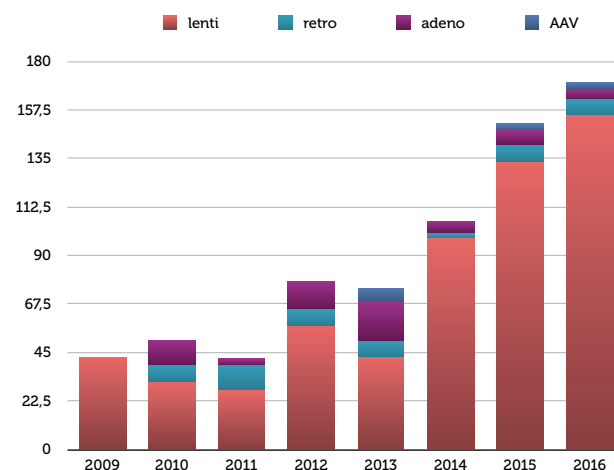
The facility has been recognized as an emerging structure in 2009 by the GIS IBISA. It is accessible from the SFR-Necker website <http://www.necker.fr/sfr-necker>

2016 Highlights

170 viral productions: 155 lentiviruses, 7 retroviruses, 5 adenovirus and 3 rAAV. (50% increase over 2014).

65% for Necker, 72% for University Paris Descartes (UPD) laboratories, and 28% except off UPD laboratories.

We are engaged in a quality management process for a certification in 2018.



	2009	2010	2011	2012	2013	2014	2015	2016
lenti	43	31	27	57	43	98	133	155
retro		8	12	8	7	2	8	7
adeno		12	3	13	18	6	7	5
AAV					7	0	3	3

2016, a progress of the coverages of the viral productions: 170 viral productions, 28 scientific Projects, 20 viral productions more with regard to 2014.

A validation of the quality of the services by tests of production.

Available Equipment

The gene transfert core as L1 and L2 premises on the site of the Faculty of Medecine of Paris Descartes University, Broussais site (75 014 Paris).

NICOLAS GARCELON



Team:
Nicolas Garcelon
Vincent Benoit
Hassan Faour

Publications:

1. Garcelon, N., Neuraz, A., Benoit, V., Salomon, R., Kracker, S., Suarez, F., Bahi-Buisson, N., Hadj-Rabia, S., Fischer, A., Munnich, A., Burgun, A., 2017. Finding patients using similarity measures in a rare diseases-oriented clinical data warehouse: Dr. Warehouse and the needle in the needle stack. *Journal of Biomedical Informatics* 73, 51–61. doi:10.1016/j.jbi.2017.07.016
2. Garcelon, N., Neuraz, A., Benoit, V., Salomon, R., Burgun, A., 2016. Improving a full-text search engine: the importance of negation detection and family history context to

identify cases in a biomedical data warehouse. *J Am Med Inform Assoc.* doi:10.1093/jamia/ocw144

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France. *Stud Health Technol Inform* 192, 572–575.

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DATA SCIENCE

The "data science" support team was created at the *Imagine* Institute in 2012, and has been labeled data science platform in 2017. The platform is made up of three IT engineers. The platform develops methods to accelerate translational research between doctors and researchers, between the hospital and the institute. We create software allowing the storage and analysis of patients' phenotypic data.

Phenotypic and genetic databases

The aim is to help researchers and clinicians to collect, pool, structure, sustain and secure patient data for local, national or international studies. We developed the "eCohorte" software to quickly set up a database containing all the necessary tools for data entry and retrieval. We now manage 82 databases with a total of 131,000 patients. Much of this work also involves the automated retrieval and load of retrospective data.

The transversal tools

We have developed several tools for researchers, clinicians and managers: *BioPancarte* for personalized visualization of laboratory results, *Auxo* for the creation of growth curves, *Gecko* for the management of clinical studies and inclusions of Patient, *Gene2CT* for automatic monitoring of clinical trials associated with genetic mutations etc. These software are deposited to the Agency of Protection of the Programs.

Biomedical data warehouse

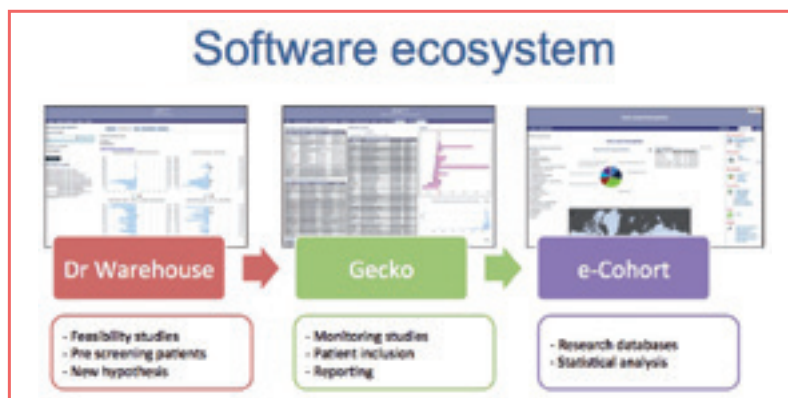
We developed Dr. Warehouse, a biomedical data warehouse that integrates free text data (hospitalization, consultation, prescription reports, etc.) as well as coded data (biological results).

Dr Warehouse is implemented in Necker-*Enfants Malades* hospital. We loaded 4 million documents from 20 different sources (EHR, Biomedical databases) from 1996 to 2017 for 480,000 patients. It also contains 36 million biological results.

The main functionalities are to be able to search patients using a 'Google like' search engine, to be able to carry out automatic phenotypic descriptions, and to propose tools to help diagnosis by similarity calculation between patients. Dr. Warehouse's interface provides physicians with ergonomic tools to explore medical records to accelerate the recruitment of patients into clinical studies.

Dr Warehouse is now also released under the GNU GPL (open source License).

	2012	2013	2014	2015	2016	2017
#Created research databases	13	12	11	17	18	11



MERIEM GARFA-TRAORÉ



Team:
Head of the platform:
Meriem Garfa-Traoré

Team:
Nicolas Goudin

Scientific referents:
Gaël Ménasché
Geneviève de Saint Basile

Publications:

1. Habarou F, Hamel Y, Haack TB, Feichtinger RG, Lebigot E, Marquardt I, Busiah K, Laroche C, Madrange M, Grisel C, Pontoizeau C, Eisermann M, Boutron A, Chrétien D, Chadeaux-Vekemans B, Barouki R, Bole-Feysot C, Nitschke P, Goudin N, Boddaert N, Nemazanyy I, Delahodde A, Kölker S, Rodenburg RJ, Korenke GC, Meitinger T, Strom TM, Prokisch H, Rotig A, Ottolenghi C, Mayr JA, de Lonlay P. Biallelic Mutations in LIPT2 Cause a Mitochondrial Lipoylation Defect Associated with Severe Neonatal Encephalopathy. *Am J Hum Genet.* 2017 Aug.
2. Joel Babbior, Delphyne Descamps, Aimé Cézaire Adiko, Mira Tohmé, Sophia

- Maschalidi, Irini Evnouchidou, Luiz Ricardo Vasconcellos, Mariacristina De Luca, Francois-Xavier Mauvais, Meriem Garfa-Traore, Melanie M Brinkmann, Michel Chignard, Bénédicte Manoury, Loredana Saveanu. IRAP+ endosomes restrict TLR9 activation and signaling. *Nat Immunol.* 2017 May.
3. Sepulveda FE, Garrigue A, Maschalidi S, Garfa-Traore M, Ménasché G, Fischer A, de Saint Basile G. Polygenic mutations in the cytotoxicity pathway increase susceptibility to develop HLH immunopathology in mice. *Blood.* 2016 Apr.
 4. Goudin N, Chappert P, Mégret J, Gross DA, Rocha B, Azogui O. Depletion of Regulatory T Cells Induces

- High Numbers of Dendritic Cells and Unmasks a Subset of Anti-Tumour CD8+CD11c+ PD-1^{lo} Effector T Cells. *PLoSOne.* 2016 Jun.
5. Bizet AA, Becker-Heck A, Ryan R, Weber K, Filhol E, Krug P, Halbritter J, Delous M, Lasbennes MC, Linghu B, Oakeley EJ, Zarhrate M, Nitschké P, Garfa-Traore M, Serluca F, Yang F, Bouwmeester T, Pinson L, Cassuto E, Dubot P, Elshakhs NA, Sahel JA, Salomon R, Drummond IA, Gubler MC, Antignac C, Chibout S, Szustakowski JD, Hildebrandt F, Lorentzen E, Sailer AW, Benmerah A, Saint-Mezard P, Saunier S. Mutations in TRAF3IP1/IFT54 reveal a new role for IFT proteins in microtubule stabilization. *Nat Commun.* 2015 Oct.

CELL IMAGING PLATFORM

Fluorescence microscopy is an indispensable tool in biomedical research. New imaging techniques, in combination with powerful analysis software, have allowed scientists to move beyond the limits of optical resolution.

The Cellular Imaging Core Facility of the "Structure Fédérative de Recherche Necker Enfants Malades" is specialized in the visualization and analysis of the structure and dynamic processes from the cell and tissue to organism level.

The mission of the platform is to provide biologists and practitioners advanced optical instruments and analytic tools

The missions of the platform are:

- Providing users with advice and orientation towards microscopes adapted to their issues
- Helping and training users on all acquisition systems and analysis software
- Methodological development: multiphotonic microscopy, FLIM (Fluorescence Lifetime Imaging Microscopy), STED (Stimulated Emission Depletion), Lightsheet microscopy, Lightsheet microscopy
- Development of tools for image analysis: 2D, 3D, 4D analysing protocols, creation of macros
- Development of tools for metrology: metrology consists of measuring and analysing the stability of the different microscopes during time, by using stable samples (calibrated beads, chroma slides, etc.) with a standard protocol.

Equipment:

- **5 confocal microscopes:**
 - a Leica TCS SP5 (acquired in 2008 through *Imagine* funding)
 - a Zeiss LSM 700 (acquired in 2010 through SFR and Platform funding)
 - a Leica TCS SP8 SMD with Fluorescence Life Time Imaging (FLIM) and fluorescence correlation spectroscopy (FCS) option (acquired in 2012 through ARC funding)
 - a Leica TCS SP8 STED for ultrastructure imaging (acquired in 2014 through *Imagine* funding)
 - a Zeiss Spinning Disk for live imaging in confocal mode (acquired in 2016 through *Imagine* funding)
- **5 widefield microscopes**
 - a Nikon videomicroscope with Total Internal Reflection Fluorescence (TIRF) option (acquired in 2010 through *Imagine* funding)
 - 2 Zeiss Structured Illuminated Microscope ApoTome (acquired in 2011 through SFR and Platform funding + in 2014 through an INEM's Team)
 - 2 Zeiss epifluorescence microscopes
- **2 microscopes for deep imaging :**
 - a Lavis Biotec multiphoton microscope (acquired in 2007 through FRM funding)
 - a Zeiss lightsheet microscope (acquired in 2016 through *Imagine* funding)
- **Processing and analysis software:**
Imaris, Huygens, Metamorph, ImageJ/Fiji, Icy

CHIARA GUERRERA



Team:

Cerina Chhuon
Joanna Lipeccka
Vincent Jung

Publications:

1. Braun DA, Rao J, Mollet G, Schapiro D, Dauger MC, Guerra IC, Sanchez-Ferraz O, Hu JF, Boschat AC, Sanquer S, van Tilbeurgh H, Zenker M, Antignac C, Hildebrandt F. Mutations in KEOPS-complex genes cause nephrotic syndrome with

primary microcephaly. *Nature Genetics* 2017 Aug14, in press

2. Sicot G, Servais L, Dinca DM, Leroy A, Prigogine C, Medja F, Braz SO, Huguette-Lachon A, Chhuon C, Nicole A, Gueriba N, Oliveira R, Dan B, Furling D, Swanson MS, Guerra IC, Cheron G, Gourdon G, Gomes-Pereira M. Downregulation of the Glial GLT1 Glutamate Transporter and Purkinje Cell Dysfunction in a Mouse Model of Myotonic Dystrophy. *Cell reports*, 2017, Jun 27; 19(13):2718-2729.

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4. Chhuon C, Pranke I, Borot F, Tondelier D, Lipeccka J, Fritsch J, Chanson M, Edelman A, Ollero M, Guerra IC. Changes in lipid

raft proteome upon TNF-stimulation of cystic fibrosis cells. *J Proteomics*. 2016 Aug 11; 145:246-53.

5. Andrzejewska Z, Nevo N, Thomas L, Chhuon C, Bailleux A, Chauvet V, Courtoy PJ, Chol M, Guerra IC, Antignac C. Cystinosin is a Component of the Vacuolar H⁺-ATPase-Ragulator-Rag Complex Controlling Mammalian Target of Rapamycin Complex 1 Signaling. *J Am Soc Nephrol*. 2016 Jun;27(6):1678-88.

PROTEOMIC PLATFORM NECKER (PPN)

Proteomics approaches are essential to both clinical and basic research to study diseases at protein level and to help understand the underlying mechanisms.

The instrumental park of PPN includes two new-generation mass spectrometers dedicated to high throughput analysis and quantification of proteins.

Through its activities of service, collaboration and research and development, the PPN offers state of the art technology and expertise to help understanding disease (PTMs, differential and interaction proteomics) and to develop diagnostic/prognostic clinical tests by MS (translational and targeted proteomics).

The PPN is equipped with:

- Nano-RSLC coupled to a Q Exactive Plus Orbitrap (ThermoScientifics), bought with the support of *Imagine*
- UPLC coupled to a TQS Xevo (Waters) (shared with MS APHP Necker Platform)
- MALDI TOF TOF Autoflex (Bruker)
- Nano-HPLC coupled to a Ion Trap HCTplus (Bruker)
- Octet Red 96
- 1D and 2D PAGE equipment (Biorad)
- OFFgel Fractionator (Agilent)



The PPN has access to:

- Nano-RSLC coupled to a LTQ Orbitrap Lumos (ThermoScientifics) (on 3P5, Cochin campus)

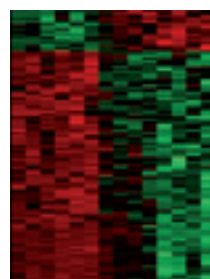
Expertise and service provided:

The PPN provides:

- Consulting for researchers and design of tailored strategy for their project
- Protein identification for simple or complex mixtures
- Protein identification and quantification (using SILAC, ITRAQ, Labelfree approaches)
- Protein absolute quantification (using MRM and PRM approaches)
- Statistical and bioinformatics data analysis (using mainly Mascot, Skyline, MaxQuant, Perseus software)
- System biology analysis through proteins network graph (using mainly Ingenuity, AmiGO software)

Proposed applications:

- Identification of novel protein-protein, RNA-protein, DNA-protein interactions
- Identification and quantification of PTMs, such as acetylation and phosphorylation
- Study of global differential proteome in disease vs control
- Multiplexed dosage of known proteins
- Biomarkers discovery and validation
- Exosomes analysis in biological fluids
- Quality checks of recombinant proteins



NATHALIE LEFORT



Team:

Nathalie Lefort (IR1 INSERM)
Celine Banal (Laboratory Technician, *Imagine* Institute)
Clémantine Dimartino (Master student)

Publications:

1. Feyeux M, Bourgois-Rocha F, Redfern A, Giles P, Lefort N, Aubert S, Bonnefond C, Bugi A, Ruiz M, Deglon N, Jones L, Peschanski M, Allen ND, Perrier AL. Early transcriptional changes linked to naturally occurring Huntington's disease mutations in neural derivatives of human embryonic stem cells. *Hum Mol Genet.* 2012 Sep 1;21(17):3883-95

2. Varela C, Denis JA, Polentes J, Feyeux M, Aubert S, Champon B, Piétu G, Peschanski M, Lefort N. Recurrent genomic instability of chromosome 1q in neural derivatives of human embryonic stem cells. *J Clin Invest.* 2012 Feb 1;122(2):569-74

3. Lefort N, Perrier AL, Laâbi Y, Varela C and Peschanski M. Human embryonic stem cells and genomic instability. *Regenerative Medicine* 2009 Nov; 4(6):899-909. *Revue*

4. Lefort N, Feyeux M, Bas C, Feraud O, Bannaceur-Griscelli AL, Tachdjian G, Peschanski M and Perrier AL. Human embryonic stem cells reveal recurrent genomic instability at 20q11.21. *Nat Biotechnol* 2008; 26: 1364-6

5. Aubry L, Bugi A, Lefort N, Rousseau F, Peschanski M and Perrier A. Striatal progenitors derived from human ES cells mature into DARPP32 neurons in vitro and in quinolinic acid-lesioned rats. *Proc Natl Acad Sci U S A.* 2008 Oct 15.

The iPS platform

Human induced pluripotent stem (iPS) cells have two main properties: self-renewal capacity that can produce unlimited number of undifferentiated cells and pluripotency, which provides the ability to differentiate them into all cell types of the human organism. The iPS platform is designed for the investigator who wishes to make an iPS cell line from peripheral blood mononuclear cells (PBMC) or from fibroblasts. The iPS platform allows the development of new cellular models for the study of rare diseases. The goals of the platform are three-fold:

- 1- The generation and maintenance of iPS cells
- 2- The characterization of iPS cell lines
- 3- User's training

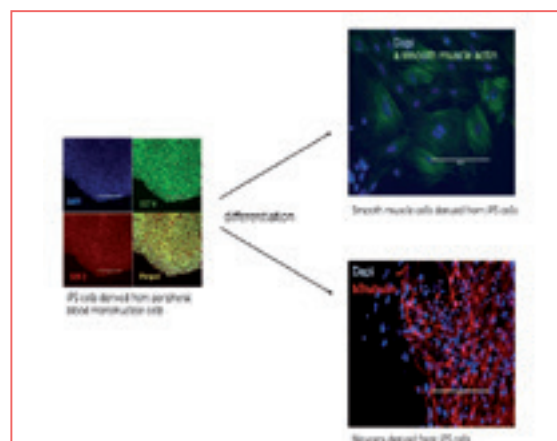
The missions of the platform are:

- Cellular reprogramming of human somatic cells from patients and healthy donors into iPS cells
- Expanding, maintaining, and banking of iPS cells
- Molecular and functional characterization of iPS cells
- Scientific and technical advice to users
- Assist users in the design of their project

Equipment

The iPS platform is equipped with:

- Three incubators including 1 with tris-gas option for both hypoxic and hyperoxic studies
- Two class II biological safety cabinets
- Inverted microscope with phase contrast optics
- Two Lynx Dynascope under class II biological safety cabinet
- Centrifuge
- Ultra-Low Temperature Freezers (-150°C)



PATRICK NITSCHKÉ



Team:

Marc Bras
Nicolas Cagnard
Cécile Fourrage
Fabienne Jabot-
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Emmanuelle
Ollivier
Jean-Marc Plaza
Frédéric Tores

Publications:

1. Bizet AA, Becker-Heck A, Ryan R, Weber K, Filhol E, Krug P, Halbritter J, Delous M, Lasbennes MC, Linghu B, Oakeley EJ, Zarhrate M, Nitschké P, Garfa-Traore M, Serluca F, Yang F, Bouwmeester T, Pinson L, Cassuto E, Dubot P, Elshakhs NA, Sahel JA, Salomon R, Drummond IA, Gubler MC, Antignac C, Chibout S, Szustakowski JD, Hildebrandt F, Lorentzen E, Sailer AW, Benmerah A, Saint-Mezard P, Saunier S. Mutations in TRAF3IP1/IFT54 reveal a new role for IFT proteins in microtubule stabilization. *Nat Commun*. 2015 Oct 21;6:8666. doi: 10.1038/ncomms9666. PubMed PMID: 26487268; PubMed Central PMCID: PMC4617596.
2. Guimier A, Gabriel GC, Bajolle F, Tsang M, Liu H, Noll A, Schwartz M, El Malti R, Smith LD, Klena NT, Jimenez G, Miller NA, Oufadem M, Moreau de Bellaing A, Yagi H, Saunders CJ, Baker CN, Di Filippo S, Peterson KA, Thiffault J, Bole-Feysot C, Cooley LD, Farrow EG, Masson C, Schoen P, Deleuze JF, Nitschké P, Lyonnet S, de Pontual L, Murray SA, Bonnet

D, Kingsmore SF, Amiel J, Bouvagnet P, Lo CW, Gordon CT. MMP21 is mutated in human heterotaxy and is required for normal left-right asymmetry in vertebrates. *Nat Genet*. 2015 Nov;47(11):1260-3. doi: 10.1038/ng.3376. Epub 2015 Oct 5. PubMed PMID: 26437028.

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Y, Adameyko I, Picard A, Breton S, Pierrot S, Biosse-Duplan M, Voisin N, Masson C, Bole-Feysot C, Nitschké P, Delrué MA, Lacombe D, Guion-Almeida ML, Moura PP, Garib DG, Munnich A, Ernors P, Hufnagel RB, Hopkin RJ, Kurihara H, Saal HM, Weaver DD, Katsanis N, Lyonnet S, Golzio C, Clouthier DE, Amiel J. Mutations in the endothelin receptor type A cause mandibulofacial dysostosis with alopecia. *Am J Hum Genet*. 2015 Apr 2;96(4):519-31. doi: 10.1016/j.ajhg.2015.01.015. Epub 2015 Mar 12. PubMed PMID: 25772936; PubMed Central PMCID: PMC4385188.

5. Six E, Lagresle-Peyrou C, Susini S, De Chappedelaine C, Sigrist N, Sadek H, Chouteau M, Cagnard N, Fontenay M, Hermine O, Chomienne C, Reynier P, Fischer A, André-Schmutz I, Gueguen N, Cavazzana M. AK2 deficiency compromises the mitochondrial energy metabolism required for differentiation of human neutrophil and lymphoid lineages. *Cell Death Dis*. 2015 Aug 13;6:e1856. doi: 10.1038/cddis.2015.211. PubMed PMID: 26270350; PubMed Central PMCID: PMC4558504.

PARIS DESCARTES & IMAGINE'S BIOINFORMATICS FACILITY

The *Imagine* Institute, as a partner of the Paris Descartes University and of the Faculty of Medicine, benefits from the support of the Paris Descartes Bioinformatics Platform to come-along with the scientists throughout their *Imagine* labeled projects (support for the experimental design planning, data handling and analysis, access to bioinformatic tools for data integration and interpretation). The amount of data generated by next generation sequencing technologies (NGS) created new challenging issues to store, analyze, integrate and visualize relevant information. To reach this goal, we have developed an original framework, PolyWeb, to analyze resequencing projects.

This framework, includes an original pipeline (Polypipeline) based on public tools (alignment, variation finding) as well as an original database design, PolyProject (storage and sample tracking) and finally two graphical interfaces, PolyQuery and PolyDiag (interpretation and visualization).

Our tools are completely generic and are independent from the sequencing technology used.

- PolyQuery is used for exome project analysis. It allows graphical real-time complex requests.
- PolyDiag, is a new interface to help scientist in genetic diagnostic. It provides reporting, sample tracking and sequencing quality-check.

These two interfaces are wholly integrated in PolyWeb, thus any kind of project (exome project or targeted genes project)

can be analyzed and viewed with either tool. This year we developed a new version of PolyWeb for "full genome" analysis. This version should be available in 2016.

Our team also supports various studies, providing expertise in either sequencing related method like ChIP-Seq, RNA-Seq, or more broadly array based projects like transcriptomic or SNP arrays and functional studies (enrichment and pathway analyses).

Equipment

- High Performance Cluster: 1 master Node + 16 slave Node: 24 Cores, 256 Go Ram 1To SSD disk.
- 1 Application server: 16 Cores 128 Go Ram
- 1 Database Server: 8 Cores 48 Gb Ram, 40 Tb Disk
- Disk Server: Isilon 500 Tb.



EMILIE PANAFIEU



Team:
Scientific manager:
Vincent Goffin

Technical manager on *Imagine* site:
Emilie Panafieu

Technical co-manager:
Nadia Elganfoud

Members of the team:
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Claire Oury
Sarah Gellotte
Thomas Ferre
Moussa Balde
Geoffrey Felix
Lolita Allais
Amandine Mainreck
Houari Bentahar
Virginie Caulet
Sarah Marinier
Gwendoline Djemaâ

Publications:

1. Martin E, et al. CTP synthase 1 deficiency in humans reveals its central role in lymphocyte proliferation. *S.Nature*. (2014) 12;510(7504):288-92.

2. Bizet AA, et al. Mutations in TRAF3IP1/IFT54 reveal a new role for IFT proteins in microtubule stabilization. *Nat Commun*. (2015) 21;6:8666.

3. Maschalidi, S., et al. Therapeutic effect of JAK1/2 blockade on the manifestations of hemophagocytic lymphohistiocytosis in mice. *Blood* (2016) 128: 60-71.

4. Michel L, et al. Sense and Antisense DMPK RNA Foci Accumulate in DM1 Tissues during Development. *PLoS One*. (2015) 4;10(9):e0137620.

5. Guimier A, et AL. MMP21 is mutated in human heterotaxy and is required for normal left-right asymmetry in vertebrates. *Nat Genet* (2015); 47:1260-3

THE ANIMAL EXPERIMENTATION AND TRANSGENESIS LABORATORY (LEAT)

This facility is organized on two different sites:

- LEAT Broussais Facility
- LEAT *Imagine* Facility

This 8,000-cage animal facility currently houses 20,000 rodents and breeds over 250 mouse strains.

It is composed of:

- one breeding area for mutant and transgenic mice (SPF status)
- two experimentation zones (BSL 1)
- one gene therapy zone
- one quarantine zone (used for imported strains)
- two infectious zones (BSL 2)
- one axenic/gnotoxenic zone

On LEAT *Imagine* Facility, the zebrafish facility is composed of a quarantine zone and an experimentation zone for a total of 650 aquariums.

In 2015, the transgenesis platform was opened at the LEAT *Imagine* Facility. Its main mission is the generation of mutated murine strains using the CRISPR/Cas9 technology.

We offer several services:

- Housing and breeding mice in IVC (Individual Ventilated Cages) or isolators
- Maintenance of mouse strains and animal production for experiments according to established protocols
- Housing and maintenance of zebrafish lines
- Technical support for the implementation of experimental manipulations on animals
- Sperm Cryopreservation
- Transgenesis



The clinical facilities

The clinical facilities

Key to complementation of the *Imagine* project is the interface with the clinical activities within the campus. Many facilities have been developed to meet these needs. They include:

- 1/ Reference centers for rare diseases
- 2/ A Rett Center
- 3/ Eight clinical facilities & laboratory departments
- 4/ A center for clinical investigation and clinical research unit
- 5/ Clinical research at *Imagine*

1/ Reference centers for rare diseases

According to the 2005-2008 Rare Diseases National Plan, the French Health Ministry has identified centers recognised for their competence, that have been accredited as Reference Centers ("Centre de référence", CR) for a specific or for a group of rare diseases. 18 reference centers at Necker-Enfants malades, directly related to childhood genetic diseases, have been accredited. These CR are as follows: genetic diseases of the skin, genetic diseases of the gut, inherited diseases of metabolism, mitochondrial diseases, rare form of epilepsy, kidney inherited diseases, inherited diseases of the immune system, juvenile arthritis, complex cardiac malformation, rare eye diseases, crano-facial dysostosis, sickle cell diseases, Ondine's syndrome, inherited bone diseases, cystic fibrosis, foetal developmental genetic anomalies, neuromuscular diseases on non-syndromic mental genetic deficiencies. The centers serve as clinical platforms for research projects within the *Imagine* Institute.

These centers, built around highly specialized teams, improve and offer multidisciplinary innovative care in collaboration with all medical professionals involved. The reference centers also allow a unique dialogue with patients associations and families and have an important role to play in the development of clinical trials. Many reference centers for rare diseases in the Necker-Enfants malades hospital involved in genetic diseases are included in the *Imagine's* scope.

Regarding to the 3rd National plan for rare diseases, the labelisation of reference centers is ongoing by the Ministry of Health and Solidarity. According to *Imagine's* clinical research strategy and will of opening, this list will be consequently updated in concertation with each reference center and the Necker university hospital.



Véronique Abadie
Pierre Robin
sequence



Christine Bodemer
Genetic diseases
with cutaneous
expression



Damien Bonnet
Complex
Congenital Heart
Defects



Valérie Cormier-Daire
Constitutional
bone diseases



Alain Fischer
Hereditary
immunodeficiencies



Olivier Goulet
Rare digestive
tract diseases



Olivier Hermine
Mastocytosis



Pascale de Lonlay
Hereditary
metabolic diseases



Sandrine Marlin
Genetic deafness



Arnold Munnich
Mitochondrial diseases



Rima Nabbout
Rare epilepsies



Michel Polak
Rare gynecological pathologies



Pierre Quartier dit Maire
Juvenile arthritis



Rémi Salomon
Hereditary kidney diseases of the child and the adult



Sabine Sarnacki
Rare anorectal and pelvic anomalies

2/ A Rett center



The Rett center at *Imagine*, the only clinical and multidisciplinary center, is specialized in diagnosis, treatment and follow-up care of children and adolescents with Rett disorders, rare and severe neurological disorders that predominantly strike girls. The Rett center in *Imagine* is involved in three major activities: caring, education and research. It aims at improving care for patients and offers a comprehensive, multidisciplinary evaluation and innovative care in collaboration with all medical, "paramedical" and "social" staff involved. The Rett

center at *Imagine* is coordinated by Prof. **Nadia Bahi-Buisson** and a case manager, Ms Elisabeth Celestin. It is composed of a multidisciplinary team of health professionals. Several physicians are clinically involved at the Necker-Enfants malades University Hospital and contribute to the research portion at *Imagine*. We provide care not only for those living in Ile de France area, but also for those from all parts of France, and around the world. It has an important role to play on the development of clinical trials.

3/ Eight clinical facilities & laboratory departments



Stéphane Blanche
Pediatric immunology, hematology and rheumatology



Marina Cavazzana
Biotherapy center



Olivier Hermine
Adult hematology



Christophe Legendre
Adult kidney transplantation



Olivier Lortholary
Infectious and tropical diseases



Arnold Munnich
Medical genetics



Rémi Salomon
Pediatric nephrology



Michel Vekemans
Histology, embryology and cytogenetics. Biology department



Another clinical research unit headed by Professor **Marina Cavazzana** has been designed to implement the development of clinical trials involving cells and/or genes (around 15 clinical trials ongoing in 2017). This is a mixed INSERM/ APHP structure. It has been accredited by the French Competent Authority (ANSM) and is fully operational for the manufacturing of advanced-

therapy medicinal products (ATMP or MTI-PP in France). It offers the capacity of performing cells and gene therapy trials based on research projects developed within *Imagine*. This Research Unit enables the translational research with the pre-clinical part at *Imagine* (UMR1163) and the conduct of gene therapy and cell therapy clinical trials in the Biotherapy Department (Hospital Necker).

4/ A center for clinical investigation and clinical research unit



Jean-Marc Tréluyer's Clinical research will benefit from a strong interaction with a clinical investigation center (a mixed INSERM/APHP Hospital structure) located in close vicinity to the Institute. The INSERM structure comprises a dedicated place to perform clinical investigations

in children, as well as a methodological platform (Unité de recherche clinique, URC). The APHP Hospital structure provides advice and assistance to scientists to design clinical research projects, monitor quality control and ensures conformity of projects with current applicable regulations.

5/ Clinical research at *Imagine*

IMAGINE'S CLINICAL RESEARCH OBJECTIVES

Double the number of innovative therapeutic studies by 2020, particularly in gene and cell therapies, and transform knowledge into effective treatments as rapidly as possible, through drug therapies, biotherapies, cell therapies and gene therapies. Increase the number of patients taking part in these trials.

Imagine's clinical research team, headed by Elisabeth Hulier-Ammar, PhD, provides support to clinical departments and works on clinical research projects in collaboration with the Center for Clinical Research at Necker Children's Hospital, with:

A team of mobile clinical research nurses, trained to care for patients included in clinical trials in the hospital, and also to collect blood samples from patients and their families on behalf of research teams.

Recruitment of three **Clinical Research Coordinators** to provide specific assistance to structure clinical research in several key departments and/or centers. The coordinators work respectively with the Pediatric Nephrology, Pediatric

Gastroenterology and General Pediatrics departments, and with the centers of reference for constitutional bone diseases and metabolic diseases.

Imagine also remains active as a sponsor with the set-up of 4 new interventional studies in 2016.

Clinical drug trials and an international clinical trial on an In Vitro Diagnostic Medical Device (IVD) are planned for 2017.

Along with setting up research projects, the team is involved in cross-disciplinary missions concerning all the teams at *Imagine*, such as, in particular, the implementation and distribution of generic research consent form templates. These consent forms, which enable the Institute's researchers to add minimally invasive or non-invasive samples (blood, urine, saliva, etc.) to their collections, are fit for purpose thanks to close cooperation between *Imagine's* Clinical Research team and the legal, clinical and ethical teams at Necker Children's Hospital.

Industrial partnerships

Industrial partnerships

Within *Imagine*, we consider that industrial partners are essential components of the therapeutic and diagnostic innovation process we are involved in. They can provide expertise and resources that will successfully complement our research and clinical activities. Furthermore, they have the ability to exploit our work by developing novel treatments or diagnostic tools for the benefit of patients. Out-licensing is obviously a frequently adopted approach, along with pre-competitive and collaborative work where risks and benefits are shared. This is especially suitable for early-stage, highly innovative projects. Our efficient IP, regulatory and partnering policies underpin this type of partnership.

PARTNERING WITH *IMAGINE* INSTITUTE

Innovative and patient-centred research programs. Our activities mainly focus on genetic and rare diseases in a wide range of therapeutic areas. In most cases, our research programs are initially catalysed by the observation of patients. The ultimate goal is to develop new treatments and/or diagnostic tools by investigating medically-relevant targets and biomarkers (genes, gene products or pathways), developing disease models and testing the most appropriate therapeutic approaches from preclinical studies through to clinical trials in various contexts. In addition to addressing unmet medical needs in the field of rare diseases, our research can also lead to new ways of considering more frequent conditions. Indeed, rare diseases sometimes share the same genes, pathways or therapeutic targets as more prevalent diseases.

Translational research. *Imagine* Institute provides unique assets to foster translational research and accelerate the development of new diagnostic and therapeutic solutions for patients:

- scientists and physicians working together in an ultramodern 19,000 sq.m building located on the Necker Children's Hospital campus,
- cutting-edge technical facilities (e.g. genomics/NGS, bioinformatics, cell sorting/imaging, proteomics, animal facilities and transgenesis, histo-morphology, biological resource center and iPS cells),
- clinical facilities that can provide methodological advice as well as access to large, rationalized cohorts of accurately phenotyped and genotyped patients.

Advantageously, business development and administrative teams are closely interfaced with the R&D staff; the focus is on shortening timelines and reducing complexity in bench-to-bedside projects, in collaboration with other *Imagine* teams and/or academic or industrial partners. Efficient processes and policies have been established for handling intellectual property and enabling win-win partnerships. We believe our activities can be achieved in collaboration with pharmaceutical and biotech companies, whose expertise and resources will necessarily shorten the time lines for the delivery of solutions meeting the patients and their families' needs. Thus, *Imagine* is striving to become a key player and collaborative partner throughout the value chain in patient-centred therapeutic and diagnostic innovation.

PARTNERING OPPORTUNITIES INCLUDE:

- Drug discovery or repurposing projects: testing/screening drug candidates against medically relevant targets studied at *Imagine* and access to unique preclinical resources (in vitro and in vivo).
- Clinical proof-of-concept and drug development projects: access to cohorts of phenotypically and genotypically welldefined patients for the performance of clinical trials.
- Innovative therapeutic approaches: gene therapy, exon skipping, cell therapy, transplantation, novel enzyme replacement therapy and drug therapy, etc.
- Innovative diagnostic approaches: prenatal and preimplantation diagnoses, prenatal screening, susceptibility/prognostic/follow-up biomarkers, etc.

MAIN FIGURES AND HIGHLIGHTS

- 38 active patent families + 5 proprietary software programs (December 2016)
- 4 patent license agreements signed
- 141 active industrial agreements including 37 signed in 2016
- 2 companies founded

ONGOING COLLABORATIONS

Imagine clinical and research teams were involved in 141 industrial collaborations in 2016. For example: Sophie Saunier's lab undertook major research in the field of nephrology with Alexion, which opened an R&D center at the *Imagine* Institute site in 2015; Prof. Marina Cavazzana's biotherapy department carried out pioneering work with bluebird bio on gene therapy for hemoglobinopathies. In early 2017, *Imagine* signed a collaboration agreement with Sanofi involving Frédéric Rieux-Laucat's lab in autoimmunity.

**CIL'LICO PROJECT SELECTED FOR THE THIRD CALL
"RECHERCHE HOSPITALO-UNIVERSITAIRE EN SANTÉ"
UNDER FRANCE'S MAJOR INVESTMENTS FOR THE
FUTURE PROGRAM**

This project, awarded 5 976 Keuros and led by *Imagine* institute, in association with other institutes, hospitals and industrial partners, aims at developing innovative, ground-breaking, and transformative diagnostic, prognostic and tailored therapeutic approaches for patients suffering from ciliopathies leading to renal failure.

**LAUNCH OF THE *IMAGINE* BIOENTREPRENEURS
PROGRAM**

In September 2016, we were very proud to welcome an intake of 10 students on the *Imagine* M2/MSc in bioentrepreneurship. This unique program was devised and developed by the École Polytechnique, HEC Paris, Paris Descartes University and *Imagine* Institute. The Director of the Bioentrepreneurs program Olivier Hermine is also a research group leader at *Imagine* and head of the Adult Hematology Department at Necker Hospital. The aim of the Master's program is to develop a new generation of transdisciplinary bioentrepreneurs working alongside the Institute's scientists and doctors. To encourage them creating start-up companies, the students are assigned real projects in the fields of biotechnology, medical technology and e-health. Divided into groups of three or four, the students bring and develop complementary skills in science, engineering and business.

Romain Marlange, head of the Innovation and Technology Transfer department:
romain.marlange@institutimagine.org

**MAJOR ADVANCES FOR *IMAGINE*'S SPIN-OFF COMPANY,
STEP PHARMA**

In 2014, *Imagine* proved the efficacy of a novel business model aimed at discovering and developing new drug therapies based on the therapeutic targets profiled at the Institute within Sylvain Latour's lab. With a relevant target as the starting point, *Imagine* teamed up with investors, Kurma Partners, and medicinal chemistry company, Sygnature Discovery, in a new company, STEP Pharma, formed to screen therapeutic molecules and develop a new drug currently in clinical proof-of-concept stage. In 2015, the company won an award in the French national innovative start-up assistance competition (the Concours national d'aide à la création d'entreprises de technologies innovantes) run by the Ministry for Education, Higher Education and Research, and *Imagine* was also successful in the European Research Council (ERC) Proof-of-Concept call for projects. In 2016, the company managed to raise €5.7m in funding, allowing it to continue its development of the initial series identified.

***IMAGINE* INSTITUTE AWARDED TREMLIN CARNOT**

In 2016, the French Ministry of Education, Higher Education and Research designated *Imagine* Institute as a Tremplin Carnot, in recognition of its track record and strong commitment to promoting research partnerships with industry. This distinction means the Institute is part of a network of French research institutes dedicated to fostering links with industrial partners and can avail of financial support for business development and value creation.





The *Imagine* building

An innovative building

At the outset, the founders of the *Imagine* Foundation believed that the best way to accomplish their scientific and humanistic goals was to bring together all the actors involved in genetic research and care. At *Imagine*, fundamental research, clinical research and innovative care are under the same roof, close to the patients. The connections thus created have been further increased by the implementation of a new organization centered on better interactivity to speed up the entire process of research and save lives by saving time.



Imagine's 19,000 sq.m building was constructed on a site provided by the Assistance publique-Hôpitaux de Paris (AP-HP) according to a convention governing the use of public domain property. The cost of the building was only €1.800 by sq.m., very unexpensive in Paris. Its architecture houses a 14,000 sq.m research section with laboratories supported by cutting-edge core facilities and a 4,250 sq.m clinical section, a clinical investigation center, a biological resources center, reference centers for rare diseases and a 183 seats conference center.

AN INTEGRATIVE CONCEPT

The pioneering architectural concept was designed to create synergies between the different research groups and care teams. The building is centered on a vast atrium filled with natural light. It houses research laboratories, cutting-edge technical facilities and areas for patient care (consultation rooms, a clinical investigation center, a biological resource center and rare disease reference centers). Its facades are decorated with western blots - a symbolic illustration of the Institute for Genetic Diseases' mission.



*"The corner of boulevard du Montparnasse and rue du Cherche-Midi is quintessentially Parisian. We would like it to be hospitable, in all senses of the word. Of course, the *Imagine* building must be functional but not in a restrictive sense. If people enjoy working in the building, their research is likely to be more productive. The *Imagine* Institute will convey an image of hospitality and openness. The high-precision architectural light management symbolizes the cutting-edge nature of today's research."*

Jean Nouvel and Bernard Valéro

The organization

Imagine's organization

The day-to-day coordination of research activities on genetic diseases and the integration of this research within Necker Children's Hospital is performed by the *Imagine* Institute's support services department and is supported by an IHU Council comprising representatives of the research laboratories, the Clinical Research Centre, the Biotherapy Clinical Research Centre, the clinical departments, the Director of the hospital and the director of the SFR.

The Executive committee has a strategic mission, including decision-making on scientific policy, changes to laboratories and core facilities (together with the SFR), recruitment of new groups and support for the development of the Clinical Research Center. The executive committee is also in charge of preparing an action plan (approved by the Institute's Board) and its implementation within the defined budget. The IHU's missions include the development of novel educational programs. Another important mission of the IHU is technology transfer.

The *Imagine* Institute raises, administers, invests and distributes funding and allocates the available budget according to the SAB's recommendations.

The Board of trustees is composed of representatives of the founding members (Paris Public Hospitals group (AP-HP), the French National Institute for Health and Medical Research (INSERM), Paris Descartes University, the French Muscular Dystrophy Association (Association Française contre les Myopathies, AFM), the Hôpitaux de Paris-Hôpitaux de France charitable foundation and Paris City Council), representatives of *Imagine*'s scientists and qualified individuals from the private sector. Three additional qualified people provide expertise in governance, technology transfer, science and international relations.

An independent international Scientific Advisory Board (SAB) (composed of renowned scientists from around the world) advises the Board and the management team throughout the implementation and operation of the Institute. This includes the planned construction, strategic policy decisions, the selection of new research groups (following an international call for proposals) and the development of the Institute's groups and facilities.

Board of trustees of the *Imagine* Foundation (as of June 2017)



PRESIDENT
Arnold MUNNICH



TREASURER
Caroline YOUNG

FOUNDING MEMBERS REPRESENTATIVES:

UNIVERSITY OF PARIS DESCARTES (PARIS V)
Frédéric DARDEL

FRENCH NATIONAL INSTITUTE OF HEALTH
AND MEDICAL RESEARCH (INSERM)
Yves LÉVY

PARIS HOSPITALS
(ASSISTANCE PUBLIQUE-HÔPITAUX DE PARIS)
Martin HIRSCH

FRENCH ASSOCIATION AGAINST MUSCULAR
DYSTROPHIES (AFM)
Laurence TIENNOT-HERMENT

FOUNDATION OF HOSPITALS OF PARIS-HOSPITALS
OF FRANCE
Bernadette CHIRAC and Danuta PIETER

CITY OF PARIS
Bernard JOMIER

REPRESENTATIVES OF THE SCIENTISTS:

Alain HOVNANIAN
Laurent ABEL
Frédéric RIEUX-LAUCAT

INDEPENDENT MEMBERS APPOINTED FOR THEIR EXPERTISE:

Geneviève FIORASO
Claude GRISCELLI, Founder President
Arnold MUNNICH
Christel NOURISSIER
François STASSE
Caroline YOUNG

GOVERNMENT COMMISSIONER:

Thierry MALINGE

PERMANENT GUESTS:

Vincent-Nicolas DELPECH
Gérard FRIEDLANDER
Arnaud MICHEL
Robert PANHARD
Claude-Agnès REYNAUD

The Support Services Department: administrative and operational staff

The support services at *Imagine* Institute provide daily assistance to the research laboratories and platforms.

They are supervised by the General Secretariat and management at *Imagine* Institute. The roles of each of these teams are listed below.

INNOVATION AND TECHNOLOGY TRANSFER

TECHNOLOGY TRANSFER

- Identify advances, help to obtain patents and licenses
- Identify partners in the private sector for research and innovative programs

CLINICAL RESEARCH

- Facilitate and structure the establishment of all clinical research projects
- Prepare and monitor clinical trials for pathophysiological studies

COMMUNICATION AND FUNDRAISING

- Develop and run fundraising campaigns to accelerate discoveries and their application through financing for new equipment and strategic recruitment
- Raise the Institute's profile among stakeholders and the general public

FINANCE

- Manage the Institute's accounts
- Monitor and administer communal expenditure in the building and, where necessary, in the laboratories and platforms

TEACHING AND THE SEMINAR CENTER

- Privatize the auditorium and other areas in the building for scientists, associations, partners, clients or patrons
- Continue the development of programs: Bioentrepreneurship, MD-PhD, PhD International, and Time for Research

HUMAN RESOURCES

- Recruit the Foundation's employees and manage their administration
- Coordinate human resources management with that of our institutional partners

HEALTH, SAFETY AND ENVIRONMENT

- Ensure compliance with health and safety regulations
- Develop a culture of health and safety standards
- Encourage measures to protect the environment

TECHNICAL DEPARTMENT

- Ensure maintenance of equipment and the building
- Coordinate interventions by service providers

IT DEPARTMENT

- Assist teams in using, updating, and securing their digital tools
- Ensure the auditorium's IT and audiovisual system works well

INTERNAL SERVICES

- Ensure the shop and laundry run smoothly
- Organize nitrogen distribution

The SFR Necker, Structure Fédérative de Recherche Inserm US24, CNRS UMS 3633

The role of the SFR is to develop and coordinate core facilities that meet the technological needs of projects developed at the Necker campus. The main objective of the SFR has been to optimize the use of financial, technological and human resources to create favorable conditions for basic and clinical research at the highest level. The SFR Necker was created in 2014, and took over the core facilities that were part, together with multiple independent research units, of the IFR94. The restructuration of research at Necker *that resulted* in the creation of two independent institutes, INEM (Institut Necker-Enfants malades) and *Imagine*, was thus accompanied by gathering the main technological platforms into an independent "mixed unit of services" (UMS).

Through their activities of service, collaboration and research and development, the core facilities of Necker offers state of the art technology and expertise to help understanding disease and to develop diagnostic/prognostic clinical tests. Each platform has a scientific referent and a manager. Steering committees or users committees are set up by platforms according to their needs. 58 staff members are currently working for the different platforms of the SFR Necker, 41 as members of the unit and 17 appointed to the SFR from other institutions notably *Imagine* Institute. Some of these platforms are accessible to researchers and partner institutions from Région Ile de France. The core facilities play a crucial role in enabling scientists to achieve ambitious research goals in a cost effective way.

The SFR Necker, in addition to developing and optimizing the core facilities, is contributing to scientific exchanges between the two institutes, *Imagine* and INEM, together with 9 clinical poles. These exchanges are illustrated through the annual "SFR Scientific Day", where scientists, clinicians and engineers of the Necker campus meet and share recent advances.

The teams of the two institutes work in close interactions with the clinical departments to develop innovative therapeutic and diagnostic strategies focused on medical specialties represented in the Necker hospital.

The SFR Necker and part of the core facilities of which the new animal facility with a housing capacity of 40000 rodents will be relocated in autumn 2018 in the renovated building of the Necker Faculty of Medicine, along with all the units of the INEM Institute.

FINANCES

The funding members of the SFR and the core facilities are INSERM, Université Paris Descartes, Assistance publique - Hôpitaux de Paris, and the CNRS. University Paris Descartes, INSERM and *Imagine* provide staff for the administrative and technological platforms and support the updating equipment of the core facilities

MANAGEMENT



SCIENTIFIC DIRECTION:
CLAUDE-AGNÈS
REYNAUD



VICE-DIRECTOR:
NADINE
CERF-BENSUSSAN

ADMINISTRATIVE DIRECTOR:
MARIE-ANNE REY-CUILLE

ADMINISTRATIVE COORDINATOR:
STÉPHANIE MASSARE

BUDGETARY MANAGEMENT:
DANUTA AUGU

ORGANIZATION

The SFR managing team is assisted by the executive committee for the elaboration and implementation of its priorities.

The executive committee is composed of the managing team and representatives of the constitutive research units (15 people). The executive committee is in charge of human resources and budget-related matters, the creation of new platforms and scientific and technical strategies in relation to existing platforms.

Finances

SEVERAL PARTNERS, PUBLIC AND PRIVATE, SUPPORT *IMAGINE*

The founding members are Assistance publique - Hôpitaux de Paris, INSERM, University Paris Descartes, City of Paris, AFM (French association against muscular dystrophy) and Fondation Hôpitaux de Paris-Hôpitaux de France.

Their global contribution to the endowment of the *Imagine* Foundation is 12.9 million euros including the contribution of the government. Financial products from the investment of the endowment of the *Imagine* Foundation can fund operations (recruitments, communication and administration).



CONTRIBUTIONS AND INVESTMENTS

The founding members of the *Imagine* Foundation are also providing technological and human resources.

University Paris Descartes and INSERM provide both staff for the administrative and technological platforms. INSERM also financially supports the updating equipment of the core facilities and the current existing INSERM units involved in the project. The government is also investing 6 million euros on the core facilities.

THE IHU BUDGET

The *Imagine* Foundation is the legal structure that hosts the *Imagine* "Institut Hospitalo-Universitaire" the perimeter of which includes all the contributing forces of the campus to the fundamental, translational and clinical research in the field of genetic diseases. The business model evaluates the financial needs at a global amount of 50.6 million euros per year (2016 estimation). Human resources and dotations of public founders are estimated at an amount of 24 million euros ; academic & industrial grants and partnerships hosted by those public founding members represent an estimate global amount of 11 million euros. The additional resources granted by the Foundation financial management represent 15.6 million euros, among which the French government has provided 6.2 million euros per year (IHU grant, 2010-2019). Fundraising, partnerships, services and technology transfer help us to get the last 9 million euros.

TOTAL "OVERALL *IMAGINE*" IHU PERIMETER = 51 M€ (I+II+III)

- I - Public founding members resources: **24 M€**
- II - Grants & industrial partnerships of the public founding members: **11 M€**
- III - Fondation *Imagine* financial management: **15.6 M€**
 - Subventions including PIA-IHU: 6.8 M€
 - Industrial partnerships & services provision: 2.0 M€
 - Fundraising: 6.8 M€



Our scientific publications in 2017

Our scientific publications

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