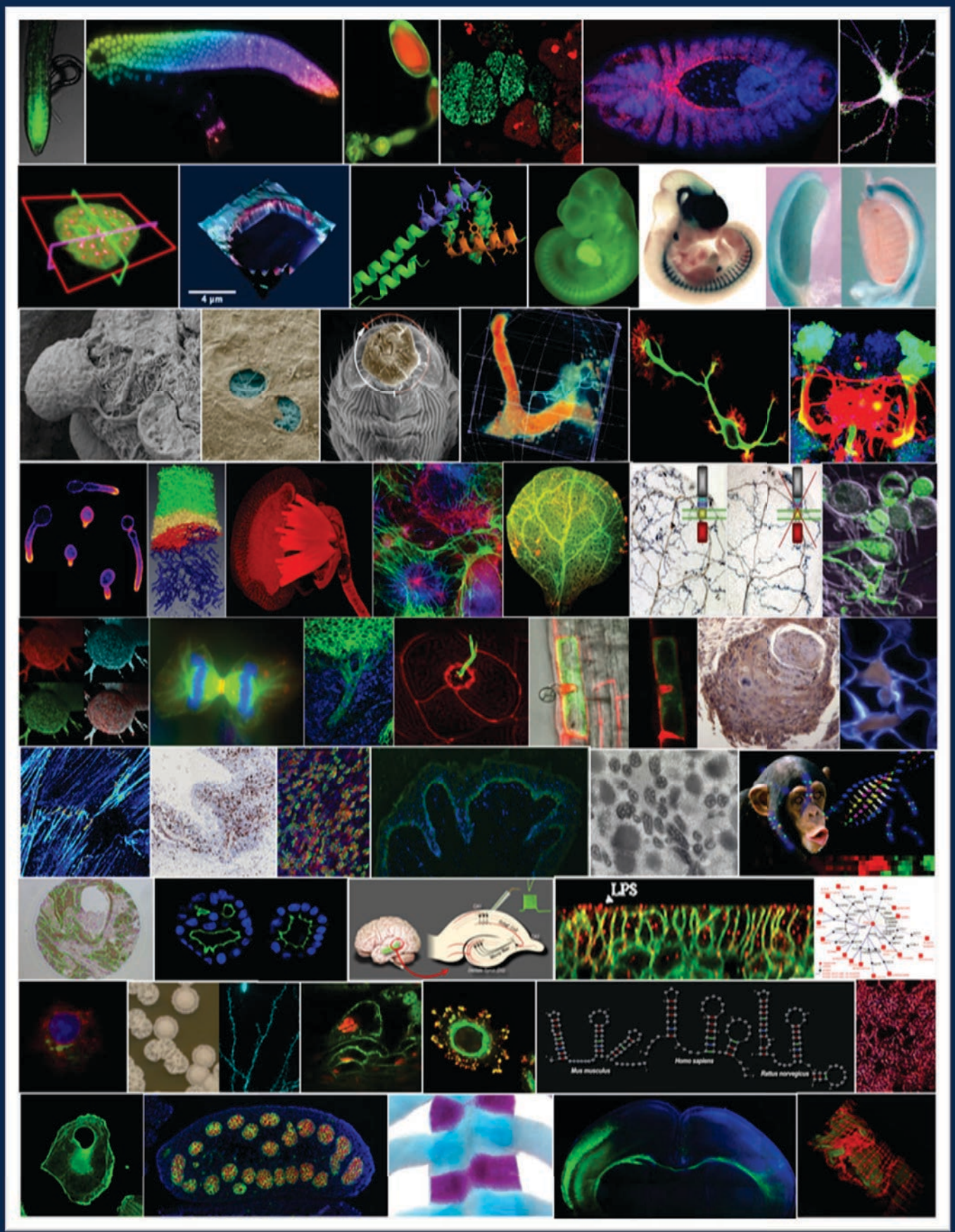
SIGNALIFE

INTERNATIONAL PhD PROGRAM

Network for Innovation on Signal Transduction Pathways in Life Sciences



OPEN DAYS June 14th and 15th, 2013
Valrose Campus, Nice, France

Front cover: Composite of images from 30 research groups

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Labex SIGNALIFE - Nice France

Network for Innovation on Signal Transduction Pathways in Life Sciences

Labex SIGNALIFE - Institut de Biologie Valrose - Centre de Biochimie -
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1. ON-SITE VISIT: Program of the open days, June 14th and 15th

Friday June 14:

8:15 – 9:00 Registration: Foyer of the Théâtre

9:00 – 9:30 **Labex SIGNALIFE international PhD program presentation**
Théâtre: *Robert Arkowitz and Andreas Schedl*

9:45 – 11:00 **Candidates' presentations**

	Théâtre	**Belvédère**
9:45 – 10:00	Getaneh Achenef	Silvia Cardellino
10:00 – 10:15	Maria Isabel Acosta Lopez	Nuria Casas Vila
10:15 – 10:30	Rania Ben Jouira	Pei-Yu Chang
10:30 – 10:45	Olga Bielska	Christos Coucoravas
10:45 – 11:00	Pierre Bourdely	Fabio Da Silva

11:00 – 11:30 **Coffee break**: foyer of the Théâtre

11:30-13:00 **Candidates' presentations**

	Théâtre	**Belvédère**
11:30 – 11:45	Nalja El Hachem	Natasa Ilic
11:45 – 12:00	Carmen Escudero Martinez	Alison Iroz
12:00 – 12:15	Aida Freire Valls	Samira Khiar
12:15 – 12:30	Ramona Galantonu	Mate Kiss
12:30 – 12:45	James Grey	Scherazad Kootar
12:45 – 13:00	Michal Hoppe	Maria Kopsida

13:00 – 14:00 **Lunch:** outside the Théâtre

14:00 – 15:30 **Candidates' presentations**

	Théâtre	**Belvédère**
14:00 – 14:15	Nikita Lukianets	Angela Moussa
14:15 – 14:30	Hey Rhyoung	Tiziana Napolitano
14:30 – 14:45	Katja Maierbrugger	Sameh Obeid
14:45 – 15:00	Christina Markouli	Laura Pacini
15:00 – 15:15	Francesca Mattioli	Loris Pratx
15:15 – 15:30	Elena Montagna	Victoria Reingold

15:30 - 16:00 **Coffee break:** foyer of the Théâtre

16:00 – 17:30 **Candidates' presentations**

	Théâtre	**Belvédère**
16:00 – 16:15	Marie-Ange Ritter	Clara Taffoni
16:15 – 16:30	Martina Rovere	Chhana Ullah
16:30 – 16:45	Ana Rita Salgueiro Pereira	Carla Usai
16:45 – 17:00	Tanasa Sorin	Agne Vilkoicaite
17:00 – 17:15	Emmanuel Soubies	Rohan Wakade

19: 00 **Dinner** : Maison du Séminaire : 29 boulevard Franck Pilatte

Saturday June 15:

8:00 – 9:00 **Breakfast buffet:** In front of Centre de Biochimie (CB)

9:00 – 9:15 **Candidates' presentations**

	CB seminar room	**CB small room**
9:00 – 9:15	Lynda Lamri	Ancuta Raclariu

9:30 - 12:30 **Interviews:** Centre de Biochimie

(For precise schedule please see separate planning)

12:30 - 13:00 Further discussions with PIs

13:00 - 13:30 **closing remarks at the Théâtre**

13:30 - 14:30 **Lunch**: outside the Théâtre

2. PhD PROGRAM

Molecular and cellular signaling is at the basis of all biological processes including development, host-pathogen interactions, diseases and cancer. Identifying new signaling pathways, understanding their circuitry and interactions is therefore of highest importance and represents a major goal. Given the complexity and diversity of signaling pathways, an integrative approach is required that combines the expertise of researchers with various scientific backgrounds and that takes advantage of different amd complementary model systems. Importantly, next generation researchers should be trained at the interface of various disciplines to provide them with a broad knowledge base and sophisticated tool sets that will allow them to tackle key questions in their future research career.

With these goals in mind, we have brought together 49 research teams of international recognition to create Labex SIGNALIFE, a unique and ambitious project that has been awarded 11 million Euros over 8 years from the French Government through a highly competitive Investment for the Future program (see part 3). The main focus of SIGNALIFE is an International PhD Program in Cell Signaling, Development, Health and Disease.

The primary objective of this unique international PhD program is to train the highest quality PhD researchers from all over the world at all interfaces of Cell signaling. The SIGNALIFE PhD program is a 3-year multi-stage project emphasizing training in Cell Signaling and exposure to a range of state-of-the-art technologies. This distinctive international PhD program is comprised of a complementary mixture of theoretical and practical courses coupled with laboratory research. At the core of this program is a consortium of high caliber, motivated Group Leaders studying different aspects of Cell Signaling in a broad range of model organisms at the University of Nice Sophia Antipolis, France.

2.1. Program

The primary objective of the **SIGNALIFE International PhD Program** is to provide the highest level of theoretical and practical training for international PhD researchers in Cell Signaling. This highly structured program will have a strong emphasis on concepts and state-of-the-art techniques, and approaches in modern Cell Signaling. Research towards a PhD degree can be carried out in any of the 49 different SIGNALIFE research groups, which are housed in 6 different institutes. SIGNALIFE members participate actively in training students training at the local, national and international level. Our previous experience with an EU funded Marie Curie International PhD Program forms the basis for this Labex PhD program.

The PhD program will include thesis research in addition to a well-developed training program.

2.2. Thesis research

Selected students will each carry out 4-week research rotations, in 3 different laboratories of the participating 49 teams. These rotations will expose students to a range of research topics, techniques and approaches. To select rotation labs, students will receive in September a list of potential projects and hear brief presentations from each team. Students will choose an order of preference for the rotations and we will make every effort to follow this ranking, however there will be no more than one student per lab per each rotation. The rotations will culminate with a ½ - 1 page report summarizing the main findings. At the end of the fall, students will rank the labs of their choice to allow the laboratory in which students will carry out their thesis research to be determined (with the restriction that there is no more than 1 student per lab).

In addition to their immediate thesis supervisor, each student will have one additional internal (University of Nice Sophia Antipolis) and one external advisor (an expert in the field). These advisors will constitute part of the student's thesis advisory committee, which will provide guidance and

evaluation for each student. Students will meet and discuss the progress of their thesis research with both the internal and external advisors during the 3 years. In addition to presentations within each institute, Labex meetings and summer schools, each student will be strongly encouraged to present their work at least at one national or international meeting.

2.3. Training Program

The SIGNALIFE International PhD program will provide an integrated approach to Cell Signaling with the ultimate aim of preparing students for future careers in science. The program is comprised of a complementary mixture of theoretical and practical courses coupled with intensive laboratory research. Top-level students will receive highly structured scientific instruction accompanied by language classes (French and English), data clubs, journal clubs, and oral and written presentation courses in addition to student retreats and a student-organized mini-symposium. Furthermore annual reports and presentations will be instrumental in improving writing and oral presentation skills.

The training program is composed of three main parts :

- Theoretical classes
- Practical classes
- Extra-curricular activities

2.3.1. Theoretical instruction:

A range of lectures on important topics in Cell Signaling will be given in the first and second year of the program. These in-depth theoretical classes on a range of topics in Cell Signaling will provide an up-to-date perspective on a range of research topics and emerging technologies. An effort will be made to integrate Physics, Math and Chemistry with respect to Cell Signaling to give students a broad knowledge base and a unique background. Presentations will be given by participating group leaders as well as by a range of invited experts. Major topics and areas are indicated below:

Module I	Module II	Module III	Module IV	Module V	Module V
Intracellular Signaling	**Intercellular Signaing**	**Signaling during Development**	**Signaling in Ageing & Disease**	**New principles & modeling**	**Techniques & Approaches**
Membrane transport	Mechanisms of growth control	Axis determination	Plant pathogen interactions	Modeling networks I	Genome-wide yeast methods
Cytoskeleton	Epithelial cell biology	Nervous system development	Lipids in pathologies	Modeling networks II	*C. elegans* as a model
Organelles	Asymmetric cell division	Gene expression	Stem cells and biotherapies	Large scale approaches I	Comparative genomics
Nuclear signaling	Morphogen signaling	Organ development	Infection and immunity	Large scale approaches II	Tracking objects
Rho GTPases	Population genomics and complex traits	Evolution, environment and the genome	Neurodevelop-mental disorders	Application of Control theory to biology	Toxins in cell biological studies
Lipid signaling	T lymphocyte signaling	Embryonic patterning	Wnt/beta-catenin in disease	Bioinformatics I	Plant biotechnology
Control of gene expression	Programmed cell death	Sex determination	Diabetes and the pancreas	Bioinformatics II	Mouse transgenics
Motors	Cell migration	Clocks and oscillators	Pathogen sensing	Quantitation of signaling	Microscopy
Protein modifications	Extracellular matrix	Brain development	CNS pathologies		Genomic/Proteo-omic approaches
	Cell contact	Adult vasculature	Innate immunity		Genetic methods
		Learning and memory	Congenital diseases		
		Limb development	Ageing		
			Cancer biology		

2.3.2. Practical instruction

Prior to the initiation of thesis research, students will participate in several practical courses focusing on the major methods in modern cellular and developmental biology. These courses will be organized as one or two half-day sessions. Practical courses will give hands on experience in topics such as Bio-informatics, Microscopy and live cell imaging, Ultrastructural analyses, Vertebrate embryology, Yeast, Fly, Worm and Plant Genetics, Cell culture, DNA, RNA, and Protein analyses, Mass spectrometry, Microarrays, Next generation sequencing, Chemical methods, RNAi approaches, FACS analyses, Modeling of biological processes, Biophysical approaches and Drug screening both by local scientists and international experts. These courses will be typically held on Saturday with ~ 5-10 topics per year. In addition, it is intended that students will go to EMBL to spend a week learning state-of-the art mass spectrometry and DNA array/next generation sequencing approaches.

2.3.3. Extra-curricular activities

Throughout the program, additional scientific activities will be organized, such as data clubs, journal clubs, scientific retreats, and classes on presentation skills, manuscript/grant writing and career

counseling. The goal of these activities is to maximize scientific interactions, critical discussions and communication skills.

English and French Language classes: Initially, where necessary, students will participate in a brief full-time French course. Subsequently, French and English classes will be available depending on need. The goal of these courses will be to facilitate integration in France and to ensure proficiency in English, the working language of the program and at our research institutes.

Grant writing classes: A key skill for success in science is the ability to write coherent and innovative grant applications. We will provide instruction in which strategies and pitfalls are discussed. In practical sessions students will be given the opportunity to train their grant writing skills and receive constructive criticism from group leaders with diverse grant writing experiences.

Student data club: A student-only forum for discussing research successes and failures. Additionally, students will have the opportunity to invite European scientists to give informal lectures on scientific career opportunities during their third year.

Journal club: Once a year each student will present a scientific paper in the form of a journal club followed by discussion on open questions and how they could be tackled. Students will receive instruction and training for these presentations. This will help the students to develop critical thinking, analyses of scientific work and planning of their own research.

Presentation skills/preparation of manuscripts: Within the middle of the second year students will participate in a 2-3-months course (one or two evenings per week) on the preparation of scientific manuscripts and oral presentation skills. Both of these topics are of outstanding importance for success in science and career development.

Student retreat/ ethics/ career counseling*:* To further enhance interaction between research projects and institutes, PhD students will meet once a year for a two-day SIGNALIFE Retreat. The aim of these retreats will be to provide a stage to discuss, in a relaxed atmosphere, research projects and foster exchange between scientists working on different topics and models. In addition, we intend to invite at least three external speakers for state-of-the-art lectures.

During the first day, students will present their progress of the thesis research project. Presentation will be followed by individual counseling, in which the strength and weaknesses of each student will be taken into account. The retreat will be used for career counseling in which various career options will be presented. This meeting will also provide an overview of research topics carried out in the SIGNALIFE consortium and serve to reinforce interactions between different disciplines. In addition, students will receive career counseling from a professional and a management-training course will be held (see below).

Student mini-symposium: In the late fall of the third year the students will organize themselves a mini-symposium, *i.e.* a meeting with 4-8 invited speakers. This mini-symposium will be a timely opportunity to get the students thinking about their post-doc or other post-PhD research opportunities, as well as a good way to learn coordination and organization skills.

Scientific meetings*:* Every student will be strongly encouraged to participate in at least one international meeting. These oral or poster presentations will give the student the opportunity to present his or her results and make contacts for a future postdoc or other career opportunities.

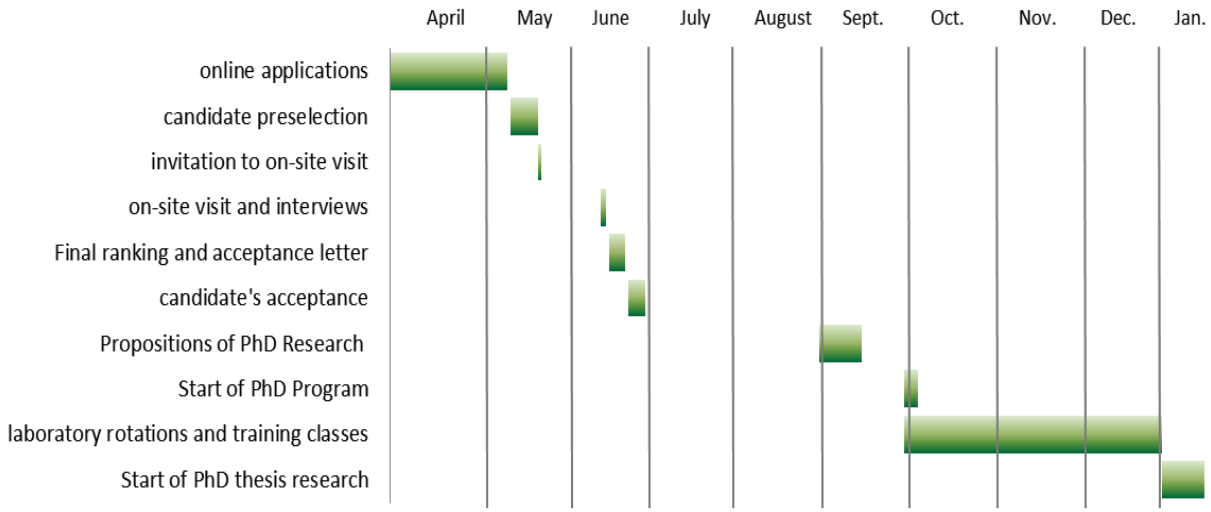
Career counseling: Career counseling will be provided by professional counselors (either Dr. A. Forde, Careers Adviser for Life Science, Cambridge University Careers Service or S. Blackford, Career Counselor and Coach). Thesis project management and career guidance will be provided by either Dr. B. Uber (Metisleadership, Germany) or Dr. Andrew Bottomley (BHR associates, UK). These specialists have ample experience in such skills and provide training courses at the PhD and postdoctoral levels.

Women in Science: Dr. G. Wallon (Deputy Director of EMBO and manager for the EMBO YIP and the Women in Science actions) will participate in this aspect of the program. We will take advantage of her expertise in European science education, training, leadership and career opportunities. She will give a seminar and lead discussion on these topics with a particular focus on gender issues.

Relation to Industry: We will also provide exposure and examples of research in an industrial setting. This will involve presentations and discussions by scientists from industry, as well as the possibility of short stays in industry labs with support provided by the competitivity pole Eurobiomed. We intend to provide funds for 1-2 month stays in industry labs where possible, taking advantage of companies in the Nice region (e.g. Arkopharma, CLL Pharma, Elaiapharm, Cevidra, Galderma, EA Pharma, Laboratoires Genévier and Allergan). Students will be encouraged to undertake brief research stays in such an industrial setting during the summer of either their second or third year.

2.4. International SIGNALIFE International PhD Milestones :

- Applications open until **May 12th 2013**
- Pre-selection of applicants and invitation to visit the University of Nice: **May 23rd 2013**
- Candidate's on-site visit and interview for final selection: **June 14th and 15th 2013**
- Final ranking and acceptance letter: **Third week of June 2013**.
- Student's acceptance: **End of June 2013, at the latest**.
- Propositions of PhD Research topics by Labex groups: **beginning of September 2013**.
- Start of PhD Program: **Mid to end of September 2013**.
- 4-week rotation in 3 laboratories and participation in training classes: **October to December 2013.**
- Start of PhD thesis research: **January 2014.**



2.5. Conclusion

One of the most important components for successful early stage scientific research training is a productive, motivating, and exciting research environment. Groups participating in this program work on a range of problems in Biology all examining different aspects of Signaling. The scientific excellence of the participating groups will ensure the best possible conditions for successful PhD research and training. The PhD positions will be financed directly from this SIGNALIFE program and all students will be part of the University of Nice Sophia Antipolis Life Science and Health Doctoral School. All research groups have sufficient funds from local, national and international organizations to ensure an ideal and stimulating research environment.

3. LABEX SIGNALIFE

3.1. Overview

The research program "SIGNALIFE" has been selected by the French Ministry of Research and Education during the highly competitive Labex "Laboratoire d'Excellence" call, within the framework of the governmental initiative "Investments for the Future" in 2011.

The research program of the Labex SIGNALIFE has been awarded 11 million euros over an 8-year period, starting in March 2012. The Labex SIGNALIFE aims to develop an interactive research network between six leading academic research institutes in Nice, focused on the study of signaling pathways in animal and plants, essential to our understanding of human health and fundamental biological processes.

The key initiative of the Labex SIGNALIFE is to advance postgraduate and research training through the recruitment of talented and highly motivated **PhD students** and **post-doctoral fellows**. A total of 85 recruitments are planned throughout the 8-year period.

The Labex SIGNALIFE is hosted by the Université Nice Sophia Antipolis (UNS) and unites teams investigating diverse aspects of signaling pathways: 49 teams, 500 scientists including 280 permanent positions. The Labex SIGNALIFE is supported by all major research organisms in the life and medical sciences (UNS, CNRS, Inserm, INRA, Inria, Nice University Hospitals, Antoine Lacassagne Cancer Center)(see part 4.1). Private companies as well as local authorities support the initiative of the Labex SIGNALIFE to build a novel interdisciplinary research network of excellence for life sciences and human health.

State of the art research platforms and facilities of participant institutes of Labex SIGNALIFE, coordinated by a Platform Committee, include: top-level microscopy imaging platforms at all member institutes (MICA, IBiSA label), animal housing facilities (mouse, zebrafish, *Drosophila*, nematodes), greenhouses and human tissue biobanks. SIGNALIFE is also a member of the National Infrastructure cluster for genomic studies in biology and health sciences (Investments for The Future, program 'France Génomique' 2010).

The individual research groups participating in the Labex SIGNALIFE represent scientifically outstanding and internationally recognized teams (4 ERC grants, 22 EU grants, 1 Marie Curie International PhD Program, 24 ATIP/AVENIR, 4 EMBO Members, 5 EMBO YIPs, 2 CNRS Silver Medals, 7 CNRS Bronze Medals, 2 Inserm Prizes, 10 Prizes of the French Academy of Sciences, and others).
Collectively, SIGNALIFE partners have published over 1479 articles between 2006 and 2012 (201 (14%) in journals with an Impact Factor>10 and 692 (47%) in journals with an Impact Factor>5).

3.2. Research

Signaling pathways are central to all biological processes and their dysregulation can lead to various congenital defects and diseases. Targeting signaling pathways by specific drugs is a major objective of the pharmaceutical industry to treat cancer, neurological, metabolic and cardiac disorders and therefore represents a major challenge for life sciences.
The SIGNALIFE network creates a unique scientific community covering the full spectrum of biological models (bacteria, fungi, plants, invertebrates, mammals) and approaches (biochemistry, genetics, imaging, high throughput screening, clinical approaches, comparative genomics, modeling) to study

signaling pathways globally, from their basic structure/composition to their modulation by endogenous or environmental stresses and their role and impact in human and plant health.

3.3. Organization

SIGNALIFE is coordinated by Dr. Stéphane Noselli, CNRS Directeur de Recherche, head of the Institute of Biologie Valrose (iBV) one of the 6th partner research institute. It is composed of 5 committees:

1. Labex Council: responsible for the strategy, management, coordination and communication of the SIGNALIFE program
2. Scientific Council: responsible for the inter- and intra-axes scientific coordination, scientific progress reports, organizing scientific activities, etc.
3. **Education Committee: PhD and post-docs recruitments, coordination of teaching and training, etc.**
4. Platform Committee: coordination of platform function and development
5. Valorization Committee: help in exploitation of the results and valorization projects.

4. RESEARCH

4.1. French Research Institutions involved in the Labex SIGNALIFE

4.1.1. CNRS

The *Centre National de la Recherche Scientifique* (National Center for Scientific Research) is a public organization under the responsibility of the French Ministry of Higher Education and Research.
Founded in 1939 by governmental decree, CNRS has the mission to evaluate and carry out all research capable of advancing knowledge and bringing social, cultural, and economic benefits for society.

CNRS research fields : As the largest fundamental research organization in Europe, CNRS carried out research in all fields of knowledge, through its seven institutes: Institute of Biological Sciences, Institute of Chemistry, Institute of Ecology and Environment, Institute for Humanities and Social Sciences, Institute for Information Sciences and Technologies, Institute for Engineering and Systems Sciences, Institute of Physics, and three national institutes: National Institute for Mathematical Science, National Institute of Nuclear and Particle Physics, National Institute for Earth Sciences and Astronomy.

Interdisciplinary research: CNRS encourages collaboration between specialists from different disciplines in particular with the university thus opening up new fields of enquiry to meet social and economic needs. CNRS has developed interdisciplinary programs that bring together various CNRS departments as well as other research institutions and industry.

CNRS laboratories (or research units) are located throughout France, and employ a large body of tenured researchers, engineers, and support staff.

Laboratories are all on renewable four-year contracts, with bi-annual evaluation by the National Center for Scientific Research. There are two types of labs: CNRS intramural labs: fully funded and managed by CNRS Joint labs: partnered with universities, other research organizations, or industry.

CNRS's annual budget represents a quarter of French public spending on civilian research. This funding comes from various sources: government and public funding; CNRS funds, primarily from industrial and EU research contracts and royalties on patents, licenses, and services provided

4.1.2. Inserm

The Institute Mission is to understand and improve human health. Founded in 1964, the French National Institute of Health and Medical Research (Inserm) is a **public scientific and technological institute** which operates under the joint authority of the French Ministry of Health and French Ministry of Research.

As the **only French public research institute to focus entirely on human health**, in 2008 Inserm took on the responsibility for the strategic, scientific and operational coordination of biomedical research. This key role as coordinator comes naturally to Inserm thanks to the scientific quality of its teams and its ability to conduct translational research, from the laboratory to the patient's bed.

The decree adopted in March 2009 will enable Inserm to perform its research missions in the face of the new scientific, health and economic challenges of the 21st century. **Scientific monitoring and expertise** are now part of the Institute's official missions.

From the outset, Inserm has forged close partnerships with the other public and private research establishments as well as hospitals to fulfill its missions. Indeed, **80% of Inserm's 318 research units** are currently set up in university hospitals or cancer research centers. The research campuses of the French National Center for Scientific Research (CNRS), along with the Pasteur and Curie Institutes, also house Inserm research divisions. Lastly, Inserm plays a leading role in creating the European Research

Area and boosts its standing abroad through close partnerships (teams and partner laboratories abroad).

4.1.3. INRA

INRA represents the French National Institute for Agricultural Research. In today's complex climatic, demographic and energy context, agricultural research must deal with major issues on various scales. Preparing worldwide food availability and security by 2050, reducing greenhouse gas emissions from agriculture, and promoting alternative agricultural and forestry practices that can respond to non-reversible climate change are challenges the entire world must face. Some of the many underlying concerns that must be tackled include understanding individual behaviour on a regional or market level; studying the relationships between plant, animal and human health; researching new ways of producing energy and materials from agricultural sources; and limiting overall environmental impacts.
To deal with these issues, the French National Institute for Agricultural Research produces scientific knowledge and works for economic and social innovation in the areas of food, agriculture and the environment.

4.1.4. Inria

Inria, a public science and technology institution. Inria was instigated in 1967, and is is the only public research body fully dedicated to computational sciences. Combining computer sciences with mathematics, Inria's 3,500 researchers strive to invent the digital technologies of the future.
Educated at leading international universities, they creatively integrate basic research with applied research and dedicate themselves to solving real problems, collaborating with the main players in public and private research in France and abroad and transferring the fruits of their work to innovative companies. The researchers at Inria published over 4,800 articles in 2010. They are behind over 270 active patents and 105 start-ups. In 2010, Inria's budget came to 252.5 million euros, 26% of which represented its own resources.
Located at the Sophia Antipolis science park since 1981, the Inria Sophia Antipolis Méditerranée Research Centre works in close collaboration with regional partners and universities. It is with great pleasure that we now see the materialisation on the Sophia Antipolis site of initiatives in which we have participated, such as the creation of the "ICST Campus" or the "Sophia Vision 2020" initiative and the "Sophia Antipolis White Paper", which fed into some of the proposals being submitted as part of Investments for the Future.

4.1.5. Nice University Hospitals, Antoine Lacassagne Cancer Center

Labex SIGNALIFE has close partnerships with the Nice university hospital and cancer center with the aim to develop biomedical and translational research and link medecine and science.

4.1.6. Nice Sophia Antipolis University .

GENERALITIES AND EXCELLENCE. The University of Nice Sophia Antipolis (UNS) was founded in 1965 and comprises three main historic campuses. It is organized into 9 faculties, 2 autonomous institutes and 1 engineering school. It provides training in Law, Political, Economic and Management Sciences, Institute of Peace and Development Rights, Spaces and Cultures, Arts and Humanities, Medicine, Odontology, Sciences, Sciences and Technology of Physical and Sporting Activities, Institute of Business Administration, University Institute of Technology, University Polytechnic School - Polytech Nice-Sophia.
Its scientific priorities fall into three main areas: Fundamental and Applied Sciences, Life and Health Sciences, and Humanities. The University of Nice Sophia-Antipolis (UNS) recently became autonomous through access to expanded responsibilities and competences ('Responsabilités et compétences élargies') thanks to the 'Libertés et Responsabilités des Universités' (LRU) law. In this context, the UNS is fully independent in its decisions with respect to its projects and corresponding long-term strategies, using state of the art management, applying international standards, and thereby improving its governance, management, competitivity, scientific research and international visibility.

The University of Nice is one of few pluri-disciplinary universities in France, ranking 11th among all French universities, despite its relatively small size. A main objectives of the UNS is to continuously improve its international visibility through training and excellence in research. Towards this goal, the UNS is actively developing partnerships with economic and industrial partners through the creation of four foundations. The international visibility of the UNS is illustrated by the number of cooperation agreements (1043) with 393 institutions in 68 countries. As a consequence, the UNS hosts a substantial number of foreign students (19%, compared to the national average of 12%).

TEACHING AND TRAINING. The University of Nice hosts 25 000 students. 1340 students are enrolled in one of the 5 PhD programs (Fundamental and Applied Sciences, Health and Life Science, Information and Communication Science and Technology, Arts and Humanities, Law Political Economic and Management Sciences). The « Collège des Etudes Doctorales » offers all UNS doctoral students a range of training courses that are aimed predominantly at facilitating their post-graduation professional integration. Finally, the university's Institute of Languages also provides lectures and summer courses in French to foreign students.

RESEARCH. The UNS develops science in all the important disciplines with priorities oriented to three domains enhancing interdisciplinary research on the Campus: Fundamental and Applied Sciences (37 %), Life and Health Sciences 27 %), and Humanities (36%).

Research at UNS is driven by 1200 researchers and lecturers (permanent positions), 770 engineers and technicians, 52 research units, half of them being affiliated to major national research agencies (CNRS, Inserm, INRA CEA, IRD, Inria, etc.), 9 scientific departments.

Evolving in the rich environment of a scientific park, a first rate technological platform with multidisciplinary approaches, benefiting from laboratories of scientific organizations and leading companies, the UNS has also enhanced the prestige of the research results, one of their fundamental missions, to encourage innovation. Basic research, applied research, technology transfer, technological platform, politics of the site, etc. all these specializations are part of the commitment of the UNS in its steps taken towards scientific excellence and international recognition. Excellence in research at UNS is shown by the 230 research grant recipients and the high number of awards and prizes including ERC and EU grants, members of the French Science Academy, the "Institut Universitaire de France (IUF)", ATIP (CNRS) or AVENIR (Inserm) programs, CNRS medals, etc.

4.2. Five Research Axes for the Labex SIGNALIFE

The SIGNALIFE project is organized into 5 main axes, building on existing research expertise and collaborative work from partners to address specific questions:

1 Cellular architecture of signaling pathways:
We will explore the structure, organization, compartmentalization and function of major signaling pathways. Genetic, proteomic and biochemical screens will be used for new component discovery.

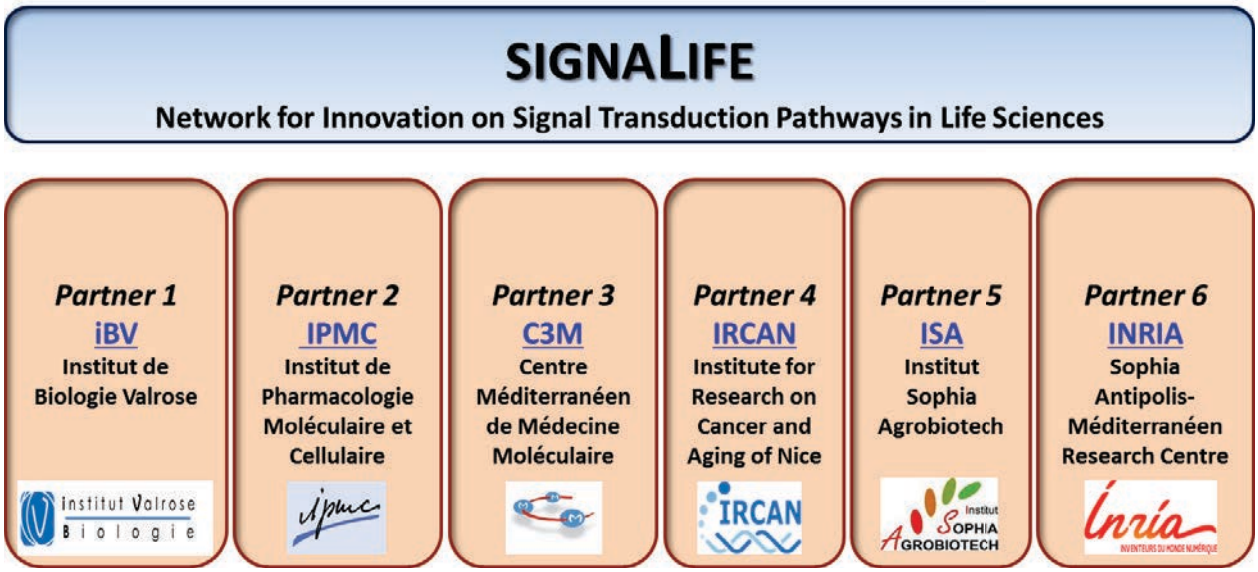
2 Plasticity and Signaling:
Using a range of model systems, we will explore the molecular mechanisms underlying cell plasticity through biological signaling pathways involved in stem cell renewal, cellular differentiation and reprogramming.

3 Stress Signaling:
We will explore the dynamics of a range of stress signals and their impact on cells, tissues and organisms through modifications of various signaling pathways.

4 Signaling in aging and disease progression:
We will explore the molecular mechanisms leading to signaling pathways dysfunction during aging and in a range of pathologies including cancer, neurological, metabolic and inflammatory disorders.

5 New principles in signaling and applications:
In this transversal axis, we will set up conditions for maximal data/ideas sharing between all participants and develop modeling with the aim of making new hypotheses and concepts leading to innovative projects and large scale cross-platform screens.

4.3. Six Research Institutes



The participating institutes are localized in various sites in the Nice and Sophia Antipolis Region.

In Nice :

- In Valrose Campus : iBV
- In Pasteur University Hospital : iBV, IRCAN
- In Antoine Lacassagne Cancer Research Center : IRCAN
- In L'Archet University Hospital : C3M

In Sophia Antipolis Technopole : IPMC, ISA, Inria

4.3.1. Partner 1 : Institut de Biologie Valrose : iBV

The Institute of Biology Valrose (iBV) is an internationally recognized research Centre funded by CNRS, Inserm and the University of Nice-Sophia Antipolis. iBV has also partnerships with the A. Lacassagne anti-Cancer Center and Nice University Hospital.

The focus of the Institute is to understand the basic principles and mechanisms governing the development of normal cells, tissues and embryos and those leading to pathogenesis and cancer. We bring together research teams with complementary areas of expertise and with a common interest in translating basic research into knowledge for the clinic. For innovative research, we provide state of the art facilities and an active international scientific program. The Institute hosted the InterDec EU-funded Marie-Curie Early Stage Training Program (from 2004-2009) and was recently awarded the prestigious 'Laboratory of Excellence' SIGNALIFE LABEX grant. Several of our teams have been honored by prestigious awards from CNRS (ATIP, CNRS medals), EMBO (Young Investigator Program and Membership), HFSP, Schlumberger Foundation, French Academy of Sciences, ANR (National Research Agency), *etc.*

iBV hosts 250 persons from 20-30 different countries (researchers, technical staff, common facilities, students, post-docs) working in 20 independent research teams. Collectively, our groups address several important biological questions (signaling, development, cell biology, physiology, neurobiology, growth, patterning, cancer, *etc.*) using major model organisms including mouse, zebrafish, sea urchin, Drosophila, nematode, yeast as well as human cell lines and tissues. iBV teams publish their work in leading scientific journals, contribute commissioned reviews, are invited to international conferences and participate to numerous national and international committees. The wide expertise and visibility of iBV teams provides a unique and rich scientific environment.

From the "Centre de Biochimie" to the "institute of Biology Valrose"

Inspired by the pioneering work of Jacques Monod in Paris, a new Biochemistry Center ('Centre de Biochimie') started in 1973 as a CNRS laboratory located in the Valrose Campus of the University of Nice Sophia-Antipolis. Created and directed by Pr M. Lazdunski, the 'Centre de Biochimie' was the first Biology institute in Nice. It was later directed by Pr. G. Ailhaud, J. Pouysségur (becoming 'institut de signalisation, biologie du développement & cancer', ISBDC) and S. Noselli ('institut de biologie du développement & cancer', IBDC). Due to strong interactions with the A. Lacassagne anti-cancer Center and Hospital to develop translational research, some teams are located on the Pasteur campus, bridging and reinforcing the links between the Science and Medical campuses.

In 2012, *a new institute is created, the 'institute of Biology Valrose', iBV (Dir. S. Noselli).* iBV is an ambitious project merging two well established laboratories, IBDC (Dir. S. Noselli; 200 persons) and U636 Inserm (Dir. F. Cuzin and M. Rassoulzadegan; 40 persons), creating the largest biology institute in Nice (250 persons).

iBV founding units have been given the highest possible ranking (5 A+) by the AERES evaluation agency (international evaluation committee). iBV continues its development and will be recruiting new highly motivated and collaborative young group leaders with international experience to be located on new laboratory space (1000 m2) on the Valrose Campus.

Together with the existing research groups, the new investigators will participate in reinforcing excellence at iBV and build a strong international Biology Institute in Nice.

http://ibv.unice.fr/EN/index.php

4.3.2. Partner 2 : Institut de Pharmacologie Moléculaire et Cellulaire : IPMC

Founded in 1989 in the outstanding environment of the Sophia Antipolis scientific park, the IPMC (rated A+ in 2010 by the National Evaluation Agency for Research and Higher education, AERES) is a joint lab of the CNRS partnered with the University Nice Sophia Antipolis (UNS), headed by Dr Pascal Barbry since 2004. Its 18 international research groups (representing about 200 people) are accommodated on 8,000 m^2, and take advantage of the highest level technological equipments in molecular & cellular biology, functional genomics, integrative biology and cellular imaging. IPMC has been distinguished by the French Program "Investissements d'Avenir" with 1 National Infrastructure in Biology & Health (France Génomique) and 3 Laboratories of Excellence (SIGNALIFE, ICST, DistAlz).

IPMC studies key functions of the organism, in link with human pathologies of the nervous and cardiovascular systems, inflammatory diseases or cancers. Many seminal works on normal or pathological biological entities have made possible the discovery and development of new pharmacological approaches. For example several ion channels, receptors, hormones & toxins have been discovered and studied, and revealed specific cellular responses to chemical, mechanical or biological stress by IPMC researchers. IPMC also contributes to the development of new treatments against several human diseases. Neurosciences, pharmacology, cell biology, biochemistry, structural biology, integrative biology and functional genomics represent important axes of development for the future of IPMC. They will help strengthen the foundations of tomorrow's medicine.

Through numerous collaborations with clinicians, physicists, chemists, computer scientists and mathematicians, the IPMC teams have been developing original tools and methods of analysis, based on several advanced technologies: microscopy, sequencing of nucleic acids, physicochemical characterization of proteins, functional phenotyping…

IPMC scientists publish in the most renowned international journals (New England Journal of Medicine, Cell, Nature, Science, Nature Genetics, Nature Cell Biology, PLOS Biology, Nature Neuroscience, Nature Structural & Molecular Biology, Neuron, PNAS, EMBO Journal, EMBO reports, Journal of Biological Chemistry, Journal of Neuroscience, *etc.*).

The IPMC gathers several national and international awards (CNRS Silver and Gold medals, Prizes of the Academies of Sciences & Medicine and the Medical Research Foundation) and Academies memberships: Academy of Sciences, EMBO…

The IPMC collaborates with many national and international academic teams (Brazil, Canada, Egypt, Italy, Japan, UK, USA, *etc.*), scientific organizations (ERC, FP7 of European Commission, EMBO, FEDER, GIS IBiSA, Cancéropole PACA, *etc.*) and foundations (ARC, Fondation de France, FRM, Fondation Plan Alzheimer, Vaincre La Mucoviscidose, *etc.*). It is also a partner of the competitive clusters Eurobiomed and PASS.

The IPMC promotes biology in Sophia Antipolis and fosters fruitful interactions with industry, through research contracts & consulting; more than 150 national and international patents have been filed, thus facilitating the creation of several innovative biotechnology start-up companies.

IPMC researchers participate in several Master and PhD programs, regularly welcome technician trainees and represent almost half of the teaching staff in biochemistry of the UNS, and of Polytech'Nice-Sophia's bioengineering department. Since its creation, 130 PhD graduated.

The IPMC also contributes to popular science, and participates in public conferences and events, such as the Brain Awareness Week and the Science Festival.

http://www.ipmc.cnrs.fr/

4.3.3. Partner 3 : Centre Méditerranéen de Médecine Moléculaire : C3M

The Mediterranean Centre for Molecular Medicine (C3M) was created on January 1st, 2008, under the responsibility of INSERM (National Institute of Health and Medical research) and UNS (University of Nice Sophia Antipolis). For its creation, several research groups from the Faculty of Medicine joined together. These groups aim to develop strong interactions amongst themselves and with clinical departments. The localization of C3M within the Archet Hospital, one of the largest hospitals in Nice, allows the possibility of translational research, from bench to bedside and vice versa.

This multidisciplinary centre currently includes 13 joint INSERM/University teams, representing 150 people, that focus on three major research topics:

- Proliferation, Cellular Death, Differentiation and Cancer
- Biology of Host-microorganism interactions
- Metabolic diseases

The diversity of research interests at C3M create an enriching work environment, facilitating interdisciplinary collaborations which benefit from complementary approaches and the expertise knowledge of each team. Since 2013, four platforms of the centre benefit from an ISO 9001 certification.
One of the main goals of the C3M was to expand via the integration of new research teams of the highest scientific quality, and whose research complemented that of the existing teams.

Exquisite research technologies:
The Centre provides shared facilities for the individual teams including, an imaging facility with the most recent types of equipment (confocal microscopes, TIRF, laser micro dissector), a genomic facility and an animal facility. In addition, the centre provides technical assistance for all facilities.
A Research Training Centre:
C3M develops various research training activities for Masters and PhD students. All teams are affiliated with the "Ecole Doctorale des Sciences de la Vie et de la Santé" (Graduate School of Life and Health Sciences). Scientific seminars are organized regularly.

Direction of the Centre:
Dr Patrick Auberger, is the Director and Dr Jean-François Tanti, is the Scientific Deputy Director. The board of directors, which includes all the individual research team PIs, meets monthly.
The Centre also has an institutional committee that consists of the members of the board of directors as well as representatives from all other scientific levels: research fellows, postdocs, research assistants, PhD students, and undergraduate students. This committee meets once every three months to discuss and give advice on all aspects of C3M organization and scientific strategy.

http://www.unice.fr/c3m/EN/indexEn2.html

4.3.4. Partner 4 : Institute for Research on Cancer and Aging of Nice : IRCAN

The institute

The **I**nstitute of **R**esearch on **C**ancer and **A**ging in **N**ice (IRCAN), created in January 2012, is located at the Pasteur Campus of the School of Medicine, part of the University of Nice. The main purpose of IRCAN is to develop outstanding research projects, which bridge the common biology between cancer and ageing, including stress response, self-renewal of tissues, DNA repair, metabolism and microenvironment. Ultimately, the research performed in IRCAN should increase our fundamental knowledge, create new experimental models, reveal news connections between ageing and cancer biology and lead to further improvements in the cure of cancer and age-related pathologies as well as in the prevention of the biological damages resulting from environmental insults.

The Director of this new research center, Professor Eric Gilson, is assisted by an international scientific committee, chaired by Professor Jean-Marc Egly, Member of the Academy of Sciences.

Focus on…

The IRCAN brings together 15 outstanding teams working on the common pathways between cancer and ageing, be it at the basic or translational levels. The IRCAN teams use a variety of models (yeast, sea anemone, human cells, mouse, rat and clinical samples) and approaches (biophysics, biochemistry, genetics, cell biology, genomics, *etc.*) in order to develop multidisciplinary approaches that embraces the evolution of modern biology, which in itself does not remain confined to selected model systems but tends towards an integrated description of the global functions of all kind of living organisms. They have already made a substantial contribution to the areas of genome maintenance (telomere, retrotransposition, DNA repair), energetic metabolism (hypoxia signaling, angiogenesis, nutritional stress, aberrant metabolism in tumors and pathogenesis of insulin resistance), cell microenvironment (integrin, skin homeostasis, innate immunity, *etc.*) as well as inflammation (cytokin signalling in cancer stroma fibroblasts, genetics of Crohn's disease, *etc.*).

The means

This new research center houses more than 150 researchers, engineers and technicians. In addition, IRCAN accommodates a variety of state of art platforms for molecular and cellular Imaging (IBISA label as part of the platform of Microscopy Imaging Côte d'Azur "MICA"), cytometry, animal research and genomics (deep sequencing and bioinformatics services). A common tumour bank to the hospital center and the anti-cancer center of Nice is also accessible.

http://ircan.org/

4.3.5. Partner 5 : Institut Sophia Agrobiotech : ISA

Research at the **Sophia Agrobiotech Institute (ISA)** is situated at the interface of environmental and agricultural science, and addresses questions that concern the biotic interactions between plants, microbial pathogens and -symbionts, and insects (pests and auxiliaries). The Institute brings together strong expertise in **comparative, evolutionary and functional genomics**, in **community ecology and agronomy**. The ultimate goal is to integrate this knowledge in the development of **innovative agronomic strategies** that are safe for the **environment** and **human health.**

The analysis of molecular **interactions** between plants and their associated organisms aims at improving plant health in agro-ecosystems. One of the main research topics concerns the **molecular signalling pathways** that determine the establishment and evolution of biotic interactions with important **eukaryotic pests** such as nematodes, insects and oomycetes, or with **symbiotic bacteria**. Interactions of these pests with their own antagonists (such as insect host-insect parasites interactions) are also deciphered, in order to improve and promote biological control strategies.

Recent studies have shown that both pathogenic and symbiotic microorganisms modify **key cellular functions in plants** to establish compatible interactions that lead either to **disease or symbiosis**. One of our goals is to characterize these key cellular functions in plants, in order to contribute to the development of strategies that allow reducing plant diseases, and improving symbiosis.

Pathogens and pests developed specific strategies that allow them to interact directly or indirectly with their hosts. To decipher these strategies, ISA engaged in the investigation of genomes of organisms that interact with plants. Several ISA research teams lead **sequencing project initiatives**, by either revealing complete genome sequences, by performing comparative genomic synteny analyses, or by focusing on gene expression patterns in specialized tissues. These **genomics approaches** will help improving our knowledge of both **mechanistic and evolutionary** aspects of the **adaptation** of pests to their host plants and of parasitoids to pests.

One of the strengths of ISA teams lies in their ability **to identify and compare mechanisms** that determine plant-microbe interactions (pathogenesis and symbiosis), **insect behavior** and **adaptation** of pests to their host plants and of insect parasitoids to pests. Our global aim is to understand the **reasons for success or failure** of these interactions. Signalling pathways that actively participate in biotic interactions are deciphered via common approaches (biochemistry, proteomics, interactomics), and include the analysis of **genetic and epigenetic driving forces**.

http://www6.paca.inra.fr/institut-sophia-agrobiotech_eng

4.3.6. Partner 6 : Sophia Antipolis Méditerranéen Research Center : Inria

Inria, a major player on computational sciences in the Mediterranean Basin

Located at the heart of Sophia Antipolis technology park since 1983, Inria's Sophia Antipolis - Méditerranée research centre has premises in Sophia Antipolis/Nice, and Montpellier, bringing together almost 600 staff within 38 research teams, over half of which have established partnerships with French public science and technology institutions, universities, *etc.* The centre's scientific priorities are (i) Ubiquitous Communications and Computing, (ii) Computational Medicine and Biology, (iii) Modelling, Simulation and Interaction with the real world.

A true engine driving research on computational sciences, Inria Sophia Antipolis - Méditerranée centre is an important part of the "*training-research-industry*" ecosystem in Sophia Antipolis, thanks to its role in the campus SophiaTech and its scientific leadership within the park – it is actively present in all the main clubs and associations in the department and across the Provence Alpes Côte d'Azur (PACA) region as a whole. The centre is also fully committed to working alongside local partners as part of the *ICT Labs* project of the *European Institute of Innovation and Technology*, which is hosted on the Campus SophiaTech. Through its contribution into 4 Labex, it strengthens its presence through partnerships in PACA and Languedoc-Roussillon regions, and more generally with players from the Mediterranean Basin.

The centre is a founding member of the global Secured Communicating Solutions Cluster and is active in 7 clusters in the PACA region. It has set up numerous collaborative initiatives with companies and organisations at a local, national or international level within the framework of contracts, research networks or European programmes. Bolstered by its technology transfer and start-up support missions, it can now boast 16 start-ups that stem from research conducted by its teams. Inria is the host of the European group ERCIM (European Research Consortium for Informatics and Mathematics), which is itself the European host of the W3C (World Wide Web Consortium).

To conclude, Inria Sophia Antipolis - Méditerranée research centre, in conjunction with its partners, is increasing scientific communication by striving to promote scientific culture amongst young people and a non-specialized audience.

http://www.inria.fr/en/centre/sophia

4.4. Fourty nine Research Groups

A general list with abstract and keywords will be followed a more detailed description of each group.

Abad Pierre **Plant nematode interactions (p 29)**
Plant-parasitic nematodes have evolved sophisticated strategies for exploiting plants. These pathogens induce the redifferentiation of plant cells into specialized multinucleate feeding sites. We develop an integrated approach combining plant pathology and plant biotechnology to identify key players involved in signalling pathways of host–parasite molecular dialogue, plant development and immunity.
Keywords: *Plant, Nematode, Interaction, Development, Immunity*
Antonny Bruno **Dynamics of lipid membranes and protein coats (p 30)**
We study (1) protein coats, which deform membranes into transport vesicles; (2) molecular strings, which tether vesicles at the Golgi; and (3) lipid transporters, which change the membrane composition and hence contribute to the maturation of membrane-bound organelles.
Key words*: membrane traffic, liposomes, cell biology, biochemistry and biophysics*
Arkowitz Robert **Polarized growth in yeast (p 31)**
Our primary interest is how cells spatially and temporally regulate their growth. We are examining the mechanisms of polarized growth and cell morphogenesis in both *S. cerevisiae* and *C. albicans*, in particular investigating the roles of G-proteins and lipids in these processes.
Key words: *Polarized growth, morphogenesis, G-protein, lipids, cell shape*
Auberger Patrick **Cell Death, Differentiation, Inflammation and Cancer (p 32)**
Our team investigates the deregulation in cell death processes and autophagy in hematopoietic malignancies. We are also developping new alternative therapeutic strategies to circumvent the resistance to conventionnal chemotherapies focusing our interest on leukemia, myelodysplastic syndromes and myeloma.
Keywords: *Autophagy, Cell Deaths, Hematopoietic Malignancies, Resistance to Chemotherapies, New Anti-cancerous Therapies*
Ballotti Robert **Biology and pathology of melanocytic cells: from cutaneous pigmentation to melanomas (p 33)**
The work of our team is focused on the study of the molecular mechanisms involved in melanocyte differentiation and in melanoma development, with special emphasis on MITF, a transcription factor that controls the expression on numerous genes playing a crucial role in melanocyte and melanoma biology.
Keywords: *Pigmentation, Cancer, therapy, transcription, epigenetic*
Barbry Pascal **Physiological Genomics of the Eukaryotes (p 34)**
Regulatory RNAs in normal and physiopathological function of epithelial tissues. Their roles in respiratory diseases. Technological developments for multi-parametric measurements in different biological models.
Keywords: *Gene expression, high throughput sequencing, bioinformatics, epithelium, cancer*
Bardoni Barbara **Physiopathology of intellectual disability (p 35)**
The purpose of our research is to understand the molecular function of the RNA-binding protein FMRP, whose altered expression is linked to Fragile X syndrome, the most common form of intellectual disability and autism, and FXTAS, a late-onset neurodegenerative disorder.
Keywords: *Intellectual disability, autism, neurodegeneration, RNA-binding protein, RNA metabolism*
Besse Florence **Post-transcriptional control of axon growth and guidance in *Drosophila* (p 36)**
Our group studies the post-transcriptional regulatory mechanisms underlying the response of growing axons to external guidance signals in vivo, in particular the role of intracellular mRNA transport. Various approaches (genetics, live-imaging, biochemistry, bioinformatics) are combined.
Keywords: *developmental cell biology, polarized axon growth, RNA transport, genetics, live-imaging*
Braendle Christian **Gene-environment interactions in development and evolution (p 37)**
We use the nematode *Caenorhabditis elegans* as a study organism to better understand how development responds to environmental variation and how such responses evolve. Our research combines different approaches at the interface of developmental genetics, evolution and ecology.
Keywords: *Gene-environment interactions, developmental plasticity, evolution of development*
Braud Véronique/Anjuère Fabienne **Immune regulation at muco-cutaneous surfaces (p 38)**
Our ongoing research aims to understand the fine tune dialog between both the epithelium and the tissue-associated innate immune cells during inflammation and skin carcinoma development. This understanding is critical for the development of rationale immunotherapeutic approaches.
Keywords: *Carcinomas, epithelium, immunity, dendritic cells, natural killer cells.*
Chaboissier Marie-Christine **Genetics of sex determination and fertility (p 39)**
Sex determination depends on a fine tuned balance between the SRY/SOX9 pathway, which precipitates testis differentiation, and the R-spondin/beta-catenin signaling pathway involved in ovarian differentiation. Our aim is to understand how these pathways regulate sexual differentiation in normal and pathological conditions.
Keywords: *Sex determination, germ cells, R-spondin, Sox, signaling*
Collombat Patrick **Diabetes Genetics (p 40)**
Our laboratory focuses on type 1 diabetes and, more particularly, on finding ways to induce the regeneration of pancreatic insulin-producing beta-cells using different transgenic mouse models.

Keywords: *Diabetes, Regeneration, Insulin, Endocrine pancreas, Glucagon*

Cristofari Gaël **Retrotransposon and genome plasticity (p 41)**

Retrotransposons are mobile genetic elements and represent half of our genome. Their mobility can drive profound genome rearrangements, which occasionally results in genetic diseases or cancer. We combine biochemistry, molecular and cellular biology and genomics to understand how the activity of these "jumping genes" is controlled and what is their impact on human health.

Keywords: *Retrotransposon, LINE-1, Reverse Transcriptase, Next-Generation Sequencing, Cancer*

Dani Christian **Stem cells and differentiation (p 42)**

We do study factors regulating differentiation of human adipose-derived stem cells (hMADS cells) into white and brown adipocytes. We have also differentiated human induced Pluripotent Stem cells into adipocytes as a novel model to investigate the embryonic origins of human adipocytes and the earliest steps of their generation.

Key words: *Adipocytes, Differentiation, adipose-derived stem cells, human induced pluripotent stem cells*

Delaunay Franck **Circadian System Biology (p 43)**

Our group studies the role of circadian clocks in mammals. This research is focused on the interactions between clock genes and the molecular networks regulating two essential biological processes: energy metabolism and the cell cycle.

Keywords: *Circadian clocks, metabolism, cell cycle, system biology*

Descombes Xavier **Computational Morphometry and Morphodynamic of Cellular & Supracellular Structures (MORPHEME team : Inria/iBV/I3S) (p 44)**

The scientific objectives of MORPHEME are to characterize and model the development and the morphological properties of biological structures from the cell to the supra-cellular scale. Being at the interface between computational science and biology, we plan to understand the morphological changes that occur during development combining in vivo imaging, image processing and computational modeling.

Keywords: *Image processing, computational biology, morphology, development, modeling*

Feral Chloé **Epithelial homeostasis and tumorigenesis (p 45)**

Our work aims at determining how the interactions of CD98, a dual function protein, which modulate integrin signaling and participate in amino acid transport, contribute to epidermal homeostasis and tumorigenesis. To do so, we use both murine conditional KO and cellular models.

Keywords: *integrins, CD98, skin cancer, signaling, amino acid transport*

Frendo Pierre **Nitrogen-fixing symbiosis and redox state (p 46)**

The team analyses the specific role of regulatory molecules of redox state in signalling, gene regulation and redox metabolism during nitrogen-fixing symbiosis. The molecular players involved in senescence of symbiosis are also investigated.

Keywords: *Plants, nitrogen-fixing symbiosis, redox state, legumes, rhizobia.*

Fürthauer Maximilian **Membrane dynamics and cell signaling in animal development (p 47)**

Through our work at the interface of cellular and developmental biology we study how the activity of membrane-bound signalling molecules is regulated by 1, the localization of signalling molecules in the cell and 2, the dynamic remodelling of cellular membranes in the course of animal development.

Key words: *Endocytosis, Cilia, Exovesicles, Delta/Notch signalling, Zebrafish*

Gilson Eric **Telomere, senescence and cancer (p 48)**

Our general aim is to increase our understanding of the basic mechanisms governing telomere functions and to explore their relevance in cancer and aging.

Keywords: *Telomere, cellular senescence, cancer, chromatin, aging*

Glaichenhaus Nicolas **Immunology and immune tolerance (p 49)**

We are broadly interested in immunology and more specifically in the interactions between the neural and immune system.

Keywords : *Immunology, T lymphocytes, innate immunity, adaptive immunity*

Gouzé Jean-Luc **Biological Control of artificial ecosystems (BIOCORE team: INRIA/INRA/CNRS/UPMC) (p 50)**

We build and study dynamical models of biological systems: intracellular models (of genetic and/or metabolic type,…), models of populations or at the scale of the ecosystems. Our tools are dynamical systems and control theory.

Keywords: *Biological models Control Bioreactor Bioenergy Biosystems Ecosystems*

Gual Philippe/Tran Albert **Hepatic complications in obesity (p 51)**

Hepatic complications in obesity (from fatty liver to hepatocellular carcinoma) is one of the most common forms of chronic liver diseases. Our main objectives are to better understand the molecular mechanisms leading to the progression of liver complications and also to develop a non-invasive index allowing the diagnosis of hepatic inflammation

Keywords: *Obesity, Liver complications, NAFLD, human, Mice*

Hofman Paul **Carcinogenesis related chronic active inflammation (p 52)**

This team focuses its basic research on the cross talk between the microenvironment (mainly the neutrophils) and the cancer cells in order to understand the polarization of protumoral or antitumoral neutrophils during the initiation, the progression and the dissemination of cancer. A more translational research project includes the development of new targeted therapies for lung cancer.

Keywords: *Cancer, neutrophils, tumor associated neutrophils, lung cancer, microRNA*

Hueber Anne-Odile **Death receptors signaling and cancer therapy (p 53)**

How the plasticity of death receptor signalling is controlled is a significant aspect in the balance of life and death decision of the cell, and a clear insight in the understanding of cancer biology. We focus our interest on finding out what directs Fas signalling to death or to tumorigenic non-death pathway to understand colorectal cancer initiation and progression.

Key words: death and survival signaling, colorectal cancer, membrane receptors dynamics, transport & sorting mechanisms, live cell imaging.

Lalli Enzo **Regulatory mechanisms of gene expression in physiopathology (p 54)**

Our team investigates the mechanisms of gene expression regulation, with a special interest in the development, function and pathology of the adrenal cortex, using in an integrated fashion cellular and animal models together with genomic and pharmacological tools

Keywords: *Gene expression, transcription factors, nuclear receptors, endocrinology, cancer*

Lambeau Gérard **Molecular physiopathology of phospholipases A2 and their mediators (p 55)**

Our team works on phospholipases A2, an emerging family of enzymes that hydrolyze phospholipids. Our current challenge is to identify their biological functions in physiological and disease conditions including reproduction, inflammation, atherosclerosis, cancer and a rare human kidney disease.

Keywords: *Phospholipase A2, lipid mediators, inflammation, human diseases, therapeutic targets.*

Lemichez Emmanuel **Microbial Toxins in host-pathogen interactions (p 56)**

Our aim is to decipher the mode of action of bacterial toxins and their cellular targets by conducting cell biology and molecular biology approaches. This encompasses i) Rac1 GTPase regulation by ubiquitin-mediated proteasomal degradation and ii) induction of large transendothelial cell tunnels.

Keywords: *Toxins, Pathogenic bacteria, endothelium, small GTPases, actin cytoskeleton*

Leopold Pierre **Genetics and Physiology of growth in *Drosophila* (p 57)**

Animal growth is linked to the developmental program in order to form an adult of species-specific size and proportions. We study the various environmental and developmental checkpoints and tissue crosstalks leading to the determination of final adult size and body proportions. We use Drosophila as a model and tackle these mechanisms using an array of genetic, cell and molecular biology tools.

Keywords: *development, growth, insulin/IGF, genetics, Drosophila*

Liti Gianni **Population genomics and complex traits (p 58)**

In our lab, we use the budding yeast, S. cerevisiae, to dissect the genetic architecture of multiple traits related to ageing and cancer. In all aspects of our research, we exploit natural variation in the budding yeast as a tool for understanding how a phenotype is genetically regulated.

Keywords: *yeast, forward genetics, genome analysis, ageing, experimental evolution*

Luton Frédéric/Franco Michel **Arf proteins, cell morphology and membrane transport(p 59)**

The plasma membrane is a dynamic structure whose coordinated remodeling with the associated cortical actin cytoskeleton is required for numerous biological functions. Our studies focus on the roles of the small G proteins of the Arf family in membrane trafficking and epithelial polarity.

Keywords: *Small G proteins, membrane trafficking, actin cytoskeleton, epithelial polarity, breast cancer*

Magnaldo Thierry/Meneguzzi Guerrino **Genetics and physiopathology of epithelial cancers (p 60)**

Using cells from human skin of patients suffering from genetic condidtions prone to cancer as a system model, we study the content and mechanisms of action underlying interactions between stroma and cancer cells that favor tumor growth and dissemination.

Keywords*: cancer, micro environment, stem cell, DNA repair, invasion*

Marie Hélène **Molecular mechanisms of neuronal plasticity in health and disease (p 61)**

We study the molecular mechanisms underlying memory formation and how these mechanisms become defective in Alzheimer's disease by combining various techniques such as electrophysiology, biochemistry, *in vivo* viral mediate recombinant expression systems and behavior.

Keywords: *neuroscience, brain, memory, Alzheimer's disease, synapse*

Martin Stéphane **Activity-dependent dynamics and roles of synaptic sumoylation (p 62)**

Our focus is on sumoylation, a key posttranslational modification for many proteins including some involved in brain disorders. Using biochemical and state-of-the-art imaging techniques we investigate the regulatory mechanisms of the sumoylation pathway and functionally characterize novel sumoylated proteins in neurons.

Keywords: *SUMO, Synapse, Trafficking, Brain disorders, Neuron.*

Nahon Jean-Louis **Genomics and Evolution in Neuroendocrinology (GENE) (p 63)**

The central thema of our research is: functional characterization of interactions between "primate-specific" genes and "common" genes involved in development, cellular activity and survival of neuronal networks regulating neuroendocrine functions : the *PMCHL* gene family /MCH signaling paradigm.

Keywords: *Evolution, Primate Genomes, Hypothalamus, Feeding behavior, melanin-concentrating hormone.*

Noselli Stéphane **Epithelial morphogenesis and left-right asymmetry in *Drosophila* (p 64)**

We study the role of JNK signaling and cell reprogramming in epithelia morphogenesis during Dorsal Closure. Using Border Cell Migration, we analyze the molecular mechanisms controlling epithelial-mesenchymal transition and cell invasion *in vivo*. We recently identified the genetic basis of left-right asymmetry establishment in *Drosophila*, deciphering the role of Myosin ID and of new players.

Keywords: *Development, Drosophila, dorsal closure, cell migration, left-right asymmetry*

Panabières Franck **Plant oomycete interactions (p 65)**

The aim of the research group is to elucidate the molecular mechanisms, which govern pathogenic strategies of the oomycete, and which are responsible, in plants, for the success (susceptibility) or the failure (resistance) of the infection process.

Keywords: *Oomycetes, molecular dialogue, susceptibility, resistance, virulence*

Poirié Marylène **Evolution and Specificity of Multitrophic Interactions (ESIM) (p 66)**
ESIM aims at elucidating the interactions between insect hosts, their parasitoids, and if relevant their symbionts, from the genetic and physiological level to "omic" approaches. It notably focuses on the evolution of immune interactions involving venom components of parasitoids.
Keywords: *Parasitoid wasps, Venom, Immunity, Evolution, Integrative biology*
Rassoulzadegan Minoo **RNA-mediated epigenetic heredity (p 67)**
Our discovery of a non-Mendelian mode of paternal heredity, based on transfer of epigenetic information by sperm RNAs was recently extended to the heredity of obesity and type II diabetes induced by unhealthy diet. Currents projects develop the molecular analysis of RNA-mediated epigenetic heredity.
Keywords: *RNA, sperm, epigenetics, genetics, mouse*
Ricci Jean Ehrland **Metabolic control of cell deaths (p 68)**
Cancer cells are very diverse. However they are sharing a few commune features including escape from cell death and a particular metabolism (Warburg effect). We are studying how the metabolism can prevent cell deaths and if targeting it could improve chemotherapeutic treatments.
Keywords: *Cancer, Metabolism, apoptosis, non-apoptotic death, pre-clinical models*
Robichon Alain **Genome Plasticity and Environment (p 69)**
Insect models to understand the molecular mechanisms controlling phenotypic adaptation to the fluctuating environment. Role of epigenetic regulations and heritability of epigenetic marks.
Keywords: *Insects , environment , adaptation, DNA methylation, heredity of epigenetic marks*
Schedl Andreas **Molecular programs controlling development and tissue homeostasis (p 70)**
Development and tissue repair are highly interrelated processes. In our research program we try to understand the transcriptional control underlying organ development, define stem/progenitor cells and determine the signaling pathways involved in tissue maintenance and repair.
Keywords: *Kidney disease, mouse models, stem cells, β-catenin signalling, Wilms' tumor*
Studer Michèle **Genetics of mouse cortical development (p 71)**
Our research aims to understand the cellular and molecular mechanisms underlying the areal and laminar organization of the mouse cerebral cortex and how functional cortical circuits are established during development. We combine mouse genetics, in vivo and in vitro gene manipulation and morphological characterization to dissect signalling pathways and molecular cascades involved in cortical cell-type specification.
Keywords: *cerebral cortex, development, mouse genetics, cortical circuits, transcription factors*
Tanti Jean-François/Cormont Mireille **Cellular and Molecular Pathophysiology of Obesity and Diabetes (p 72)**
Activity: Our research focuses on the understanding of the cellular and molecular mechanisms involved in the development of insulin resistance and adipose tissue dysfunction in obesity and type 2 diabetes. Our goal is to identify new therapeutic targets for the treatment of obesity-associated pathologies.
Keywords: *Inflammation, senescence, hypoxia, miRNA, endosomal traffic, signaling*
Tartare-Deckert Sophie **Microenvironment, signaling and Cancer (p 73)**
We study crosstalk between cancer cell and its stroma within the lymph node microenvironment in two tumor models, melanoma and lymphoma. We perform candidate gene and unbiased screen approaches for new mediators of therapeutic response and we explore pathways that enable melanoma to invade lymphatics and to execute the metastatic cascade.
Keywords: *Cancer-Cell signaling- Molecular medecine-Mouse models*
Thérond Pascal **Secretion and Signaling of Morphogens in *Drosophila* development (p 74)**
Our projects are focused on the mechanisms that regulate morphogen movement and transduction during pattern formation in *Drosophila*. By developing novel *in vivo* life imaging analysis and genetic screen we determine how the morphogen distribution and signalling activity are controlled by intra and extra-cellular regulators.
Keywords: *Animal Development, Morphogen, Hedgehog, Cell Biology, Life Imaging*
Trabucchi Michele **Control of Gene Expression (p 75)**
Our group is studying the molecular mechanisms underlying the regulation of NON-CODING RNAs expression as well as their function during the inflammatory response in macrophages by using different experimental approaches, including mass-spectrometry, siRNAs screening, and high-throughput deep sequencing analyses.
Keywords: *NON-CODING RNAs; gene expression control, macrophages, cancer, metabolic disorders*
Van Obberghen Emmanuel **Ageing and diabetes (p 76)**
Our research efforts are on Aging and Diabetes. Our main focus is on the following investigations:
1) how metabolic disturbances are responsible for insulin resistance and beta cell failure, and how ischemic hearts repair ; 2) how epigenetic mechanisms contribute to the increased risk of diabetes in offsprings after unfavorable *in utero* conditions.
Keywords: *diabetes, cardiovascular complications, epigenetics, microRNAs*
Van Obberghen-Schilling Ellen **Adhesion Signaling and Regulation of Cell Plasticity in the Tumor Microenvironment (p 77)**
Our research is focused on adhesion-based signaling in head and neck cancer and glioblastomas. Ongoing projects address i) the impact of tumor-stroma interactions on tumor angiogenesis and invasion and ii) mechanisms that regulate the stem-cell state of cancer-initiating cells.
Keywords: *tumor microenvironment, adhesion, cancer-initiating cells, head and neck cancer, glioblastomas.*

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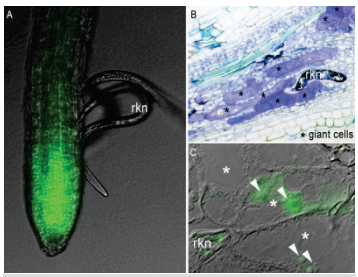
Plant nematode interactions



Root-knot nematodes (rkn) induce host giant cells. A. Arabidopsis GFP line & rkn larvae; B. Giant cells; C. Rkn proteins target host nuclei

Plant-parasitic nematodes have evolved sophisticated strategies for exploiting plants. These pathogens establish a long-lasting, intimate relationship with their hosts. Interaction involves the redifferentiation of root cells into specialised multinucleate feeding cells, named giant cells that provide nutrients to the parasite. Plant parasitic nematodes inject proteins into the host to modulate both plant developmental and immune signalling pathways. Our main model system is the root-knot nematode (RKN) Meloidogyne incognita. RKN is one of the most devastating plant pathogens able to infect thousand of plant species. We coordinated the international network on the genome sequence. We develop an integrated approach on both partners of the interaction combining plant pathology, plant biotechnology, molecular genetics, comparative genomics and advanced microscopy. Our aim is to identify key players involved in signalling pathways of host–parasite molecular dialogue i.e. the targets of RKN effectors in roots of the plant model Arabidopsis, the molecular mechanisms underlying the trade-off between development and immunity in plant roots and nematode adaptation to the host. Research into nematode parasitism thus tackles fundamental questions in plant development and plant pathology with the aims to design sustainable and environmentally friendly new methods to control nematodes.

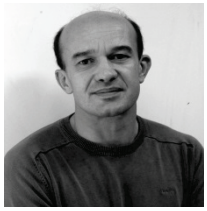
Selected Publications

1. A root-knot nematode-secreted protein is injected into giant cells and targeted to the nuclei
   Jaouannet M, Perfus-Barbeoch L, Deleury E, Magliano M, Engler G, Vieira P, Danchin EG, Da Rocha M, Coquillard P, Abad P, and Rosso MN
   (2012) **New Phytol** 194, 924-931
2. Multiple lateral gene transfers and duplications have promoted plant parasitism ability in nematodes
   Danchin EGJ, Rosso M-N, Vieira P, de Almeida-Engler J, Coutinho P, Henrissat B, Abad P
   (2010) **Proc. Natl. Acad. Sci. USA.** 107, 17651-17656
3. MAP65-3 microtubule-associated protein is essential for nematode-induced giant cell ontogenesis in Arabidopsis
   Caillaud MC, Lecomte P, Jammes F, Quentin M, Pagnotta S, Andrio E, de Almeida Engler JD, Marfaing N, Gounon, P Abad P, and Favery B
   (2008) **Plant Cell** 20, 423-437
4. Genome sequence of the metazoan plant-parasitic nematode Meloidogyne incognita
   Abad P, Gouzy J, Aury J-M, Castagnone-Sereno P, Danchin EGJ, Deleury E, Perfus-Barbeoch L et al
   (2008) **Nature Biotech** 26, 909-915
5. Arabidopsis formin AtFH6 is a plasma membrane–associated protein upregulated in giant cells induced by parasitic nematodes
   Favery B, Chelysheva L, Lebris M, Jammes F, De Almeida-Engler J, Marmagne A, Lecomte P Vaury C, Arkowitz RA, Abad P
   (2004) **Plant Cell** 16, 2529-2540

Awards

2012: Prize of the Academy of Sciences – Grand prix de l'Académie des Sciences Roger-Jean et Chantal Gautheret – Plant Physiology & Biotechnology

ANTONNY Bruno



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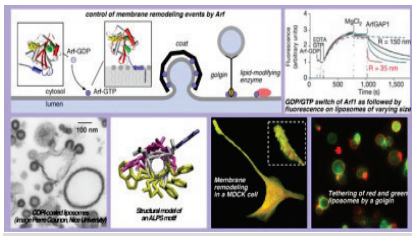
Dynamics of lipid membranes and protein coats



Studying membrane remodeling reactions using biochemical, biophysical, computer-based and cellular approaches

Various proteins remodel the membranes of organelles involved in intracellular transport. Protein coats deform membranes to promote the budding of vesicles. Golgins, sort of molecular strings, tether vesicles to restrict their diffusion. Lipid transporters adjust the membrane composition. Although very different, most of these mechanisms are controlled by small G proteins of the Arf family and by the physical chemistry of membranes.

We study these mechanisms through molecular, cellular and in silico approaches. With original assays based on fluorescence and light scattering, we follow elementary reactions such as the assembly cycle of protein coats, the tethering of liposomes by a golgin or the transfer of lipids. With fluorescence light microscopy and electron microscopy, we visualize these events in cells and in reconstituted systems. With molecular dynamics, we describe at the atomic level how specific protein motifs sense the chemistry and curvature of lipid membranes.

Recent achievements:
- Discovery of a general motif to sense membrane curvature: the ALPS motif
- Elucidation of the mechanism by which alpha synuclein, a protein involved in Parkinson disease, recognizes the curvature of endocytic vesicles.
- Discovery of a mechanism by which cholesterol is transported through the coupled transfer and hydrolysis of phosphoinositides.

Selected Publications

1. Amphipathic lipid packing sensor motifs: probing bilayer defects with hydrophobic residues
   Vanni S, Vamparys L, Gautier R, Drin G, Etchebest C, Fuchs PF and Antonny B
   (2013) **Biophys J** 104, 575-584
2. Curvature, lipid packing, and electrostatics of membrane organelles: defining cellular territories in determining specificity
   Bigay J and Antonny B
   (2013) **Dev Cell** 23, 886-895
3. Osh4p exchanges sterols for phosphatidylinositol 4-phosphate between lipid bilayers
   de Saint-Jean M, Delfosse V, Douguet D, Chicanne G, Payrastre B, Bourguet W, Antonny B and Drin G
   (2011) **J Cell Biol** 195, 965-978
4. alpha-Synuclein and ALPS motifs are membrane curvature sensors whose contrasting chemistry mediates selective vesicle binding
   Pranke IM, Morello V, Bigay J, Gibson K, Verbavatz JM, Antonny B and Jackson CL
   (2011) **J Cell Biol** 194, 89-103
5. Asymmetric tethering of flat and curved lipid membranes by a golgin
   Drin G, Morello V, Casella JF, Gounon P and Antonny B
   (2008) **Science** 320, 670-673

Awards

2010: CNRS bronze medal, Guillaume Drin
2010: ERC advanced grant, Bruno Antonny
2009: CNRS silver medal, Bruno Antonny
2008: EMBO member, Bruno Antonny

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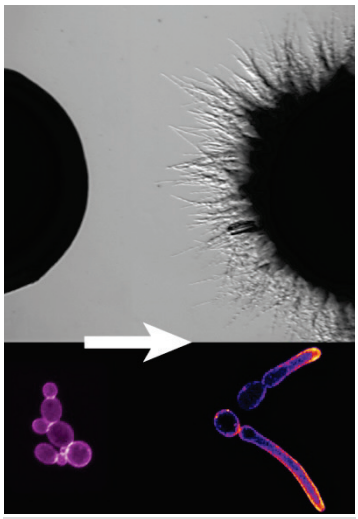
Polarized growth in yeast



The yeast (left) to filamentous (right) transition is critical for *Candida albicans* virulence. Colonies (top) & individual cells (bottom).

Polarized growth is essential for both internal organization of cells and generation of complex multi-cellular structures. Our main interest is how cells spatially and temporally regulate their growth.

Our goal is to understand the mechanisms of polarized growth and cell morphogenesis in yeast. The yeast *Saccharomyces cerevisiae* reproduces during its haploid mitotic life cycle by budding. When haploid cells of the opposite mating type come in contact they direct their growth towards one another, forming pear shaped polarized cells, which ultimately fuse to form diploids. Upon nitrogen starvation diploid yeast switch from unicellular budding to a filamentous form comprised of chains of elongated cells. The opportunistic human pathogenic yeast *Candida albicans* switches from an oval form to an invasive, filamentous hyphal form, a process critical for its pathogenicity.

In these 3 growth processes asymmetric cell growth is accomplished by polarization of the actin cytoskeleton and subsequent localized growth by directed membrane traffic. During budding, polarized growth is initiated by internal signals whereas during mating and hyphal formation, it is dictated by external signals. We are interested in how internal and external signals are linked to site-specific growth, with particular focus on the roles of small G-proteins and phospholipids both in *S. cerevisiae* and *C. albicans*.

Selected Publications

1. Phosphoinositides-bis-phosphate is required for Saccharomyces cerevisiae invasive growth.
   Guillas I, Vernay A, Vitagliano JJ and Arkowitz RA.
   (2013) **J Cell Sci** in press
2. A steep phosphoinositide bis-phosphate gradient forms during fungal filamentous growth
   Vernay A, Schaub S, Guillas I, Bassilana M and Arkowitz, RA
   (2012) **J Cell Biol** 198, 711-730
3. Polarized growth in fungi: symmetry breaking and hyphal formation
   Arkowitz RA and Bassilana M
   (2011) **Semin Cell Dev Biol** 22, 806-815
4. The Candida albicans ELMO homologue functions together with Rac1 and Dck1, upstream of the MAP Kinase Cek1, in invasive filamentous growth
   Hope H, Schmauch C, Arkowitz RA and Bassilana M
   (2010) **Mol Microbiol** 76, 1572-1590
5. Activation of Rac1 by the Guanine Nucleotide Exchange Factor Dck1 Is Required for Invasive Filamentous Growth in the Pathogen Candida albicans
   Hope H, Bogliolo S, Arkowitz RA and Bassilana M
   (2008) **Mol Biol Cell** 19, 3638-3651

Awards

2013: Marie Curie ITN Consortium
2001-2010: Fondation pour la Recherche Médicale – BNP Paribas Award
2002-2004: La Ligue Contre le Cancer – Selected Team
2001-: EMBO Young Investigator Programme
2000-2003: CNRS ATIP (start up package)

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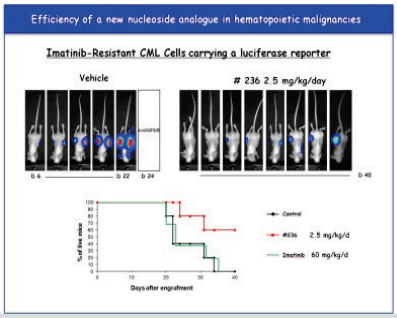
Cell deaths, Differentiation, Inflammation and Cancer



Effect of a new triazole nucleoside (#236) on tumor formation in athymic mice. Overall survival rates in treated mice .

Our team investigates the deregulation of cell death processes and autophagy in hematopoietic malignancies and during skin inflammatory processes. We are also developping new alternative therapeutic strategies to circumvent the resistance to conventionnal chemotherapies focusing our interest on Leukemia, Myelodysplastic Syndromes and Myeloma. We are also interested in the role of teh tyrosine kinase Lyn and of inflammatory caspases in the physiopathology of human psoriasis. In this context our mains focus of interest are:

1- The mechanisms of resistance to tyrosine kinase inhibitors in Chronic Myelogenous Leukemia (CML)

2- The mechanisms of resistance to nucleoside analogues in MyeloDysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)

3- The role of BCL2L10 (BCL-B), an anti-apoptotic member of the BCL2 family in the homeostasis of plasma cells and the physiopathology of Multiple Myeloma (MM)

4- Role of the inflammatory caspases in the context of skin disorders such as prosiasis: pre-clinical and clinical study.

5- Regulation of the pro-apoptotic function of a bcl-2 family member by oncogenic tyrosine kinases of the Src family.

Our research project is at the Biology / Chemistry / Clinical interface and aims at validating new biomarkers and drug candidates for the treatment of some hematopoietic malignancies (CML, MDS, AML, MM) and psoriasis.

Keywords : Autophagy, Cell

Selected Publications

1. The caspase 6 derived N-terminal fragment of DJ-1 promotes apoptosis via increased ROS production
   Robert G, Puissant A, Dufies M, Marchetti S, Jacquel A, Cluzeau T, Colosetti P, Belhacene N, Kahle P, Da Costa CA, Luciano, F Checler, F and Auberger P
   (2012) **Cell Death Differ** 19, 1769-1778
2. Imatinib triggers mesenchymal-like conversion of CML cells associated with increased aggressiveness
   Puissant A, Dufies M, Fenouille N, Ben Sahra I, Jcquel A, Robert G, Cluzeau T, Deckert M, Tichet M, Cheli Y Cassuto JP, Raynaud S, Legros L, Pasquet JM, Mahon FX, Luciano F and Auberger P
   (2012) **J Mol Cell Biol** 4, 207-220
3. Autophagy is required for CSF-1induced macrophagic differentiation and acquisition of pahgocytic function
   Jacquel A, Obba S, Boyer L, Dufies M, Robert G, Gounon P, Lemichez E, Luciano F, Solary E and Auberger P
   (2012) **Blood** 119, 4527-4531
4. Cathepsin B release after imatinib-mediated lysosomal membrane permeabilization triggers BCR-ABL cleavage and elimination of chronic myelogenous leukemia cells
   Puissant A, colosetti P, Robert G, cassuto JP, Raynaud S and Auberger P
   (2010) **Leukemia** 24, 115-124
5. The caspase-cleaved form of LYN mediates a psoriatic-like inflammatory syndrome in mice
   Marchetti S, Gamas P, Belhacene N, Grosso S, Pradelli L, Colosetti P, Johansen C, Iversen L, Dekert M, Luciano P, Hofman P, Ortonne N, Khemis A Mari B, Ortonne JP, Ricci JE and Auberger P
   (2009) **EMBO J** 28, 2449-2460

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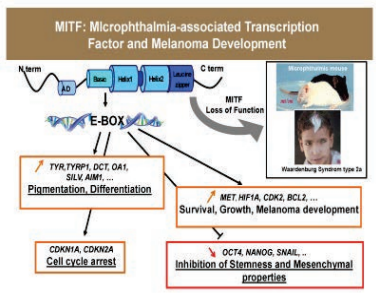
Biology and pathology of melanocytic cells: from cutaneous pigmentation to melanomas



Schematic representation of MITF functions in melanocytes and melanomas

Our projects are based on very recent and original data obtained in our laboratory, i.e., (i) the identification of a MITF-negative population endowed with melanoma-initiating properties; and (ii) the discovery of a new MITF mutant (E318K) that favours melanoma development.

1) We will study the effects of stresses relevant to melanoma development on MITF SUMOylation. We will focus our attention on UV radiation and hypoxia, and then to study the role of MITF SUMOylation, we will compare, in melanoma cells or in mouse model expressing WT or E318K MITF, the effects (migration, invasion, tumorigenicity) of various stimuli identified in the first part of the project to modulate MITF SUMOylation.

2) We identified a MITF-negative population, expressing stem cell markers (OCT4, NANOG), displaying high tumorigenic potential and slow growing rate that fits perfectly with the definition of tumor initiating cells. Taking advantage of a new cell surface marker for melanoma initiating cells that we identified recently, we will (i) purify the MIC population (ii) study their biological properties such as growth, migration, differentiation, tumorigenicity, drug resistance and response to environmental stimuli, (iii) Identify the repertoire of gene expressed in the melanoma initiating cells and (iv) validate this marker in human melanoma samples, in correlation the clinical outcome.

Selected Publications

1. Major clinical response to a BRAF inhibitor in a patient with a BRAF L597R mutated melanoma
Bahadoran, P., Allegra, M., Le Duff, F., Long-Mira, E., Hofman, P., Giacchero, D., Passeron, P., Lacour, JP., Ballotti, R.
(2013) **J Clin Oncol** in press, 1-2
2. A SUMOylation-defective MITF germline mutation predisposes to melanoma and renal carcinoma
Bertolotto, C., Lesueur, F., Giuliano, S., Strub, T., de Lichy, M., Bille, K., Dessen, P., d'Hayer, B., Mohamdi, H., Remenieras, A., Maubec, E., de la Fouchardiere, A., Molinie, V., Vabres, P., Dalle, S., Poulalhon, N., Martin-Denavit, T., Thomas, L., Andry-Benzaquen, P., Dupin, N., Boitier, F., Rossi, A., Perrot, J.L., Labeille, B., Robert, C., Escudier, B., Caron, O., Brugieres, L., Saule, S., Gardie, B., Gad, S., Richard, S., Couturier, J., Teh, B.T., Ghiorzo, P., Pastorino, L., Puig, S., Badenas, C., Olsson, H., Ingvar, C., Rouleau, E., Lidereau, R., Bahadoran, P., Vielh, P., Corda, E., Blanche, H., Zelenika, D., Galan, P., Aubin, F., Bachollet, B., Becuwe, C., Berthet, P., Bignon, Y.J., Bonadona, V., Bonafe, J.L., Bonnet-Dupeyron, M.N., Cambazard, F., Chevrant-Breton, J., Coupier, I., Dalac, S., Demange, L., d'Incan, M., Dugast, C., Faivre, L., Vincent-Fetita, L., Gauthier-Villars, M., Gilbert, B., Grange, F., Grob, J.J., Humbert, P., Janin, N., Joly, P., Kerob, D., Lasset, C., Leroux, D., Levang, J., Limacher, J.M., Livideanu, C., Longy, M., Lortholary, A., Stoppa-Lyonnet, D., Mansard, S., Mansuy, L., Marrou, K., Mateus, C., Maugard, C., Meyer, N., Nogues, C., Souteyrand, P., Venat-Bouvet, L., Zattara, H., Chaudru, V., Lenoir, G.M., Lathrop, M., Davidson, I., Avril, M.F., Demenais, F., Ballotti, R*., and Bressac-de Paillerets*, B
(2011) **Nature** 480, 94-98
3. Hypoxia and MITF control metastatic behaviour in mouse and human melanoma cells
Cheli, Y., Giuliano, S., Fenouille, N., Allegra, M., Hofman, V., Hofman, P., Bahadoran, P., Lacour, J.P., Tartare-Deckert, S., Bertolotto, C., and Ballotti, R
(2012) **Oncogene** 31, 2461-2470
4. Senescent cells develop a PARP-1 and nuclear factor-{kappa}B-associated secretome (PNAS
Ohanna, M., Giuliano, S., Bonet, C., Imbert, V., Hofman, V., Zangari, J., Bille, K., Robert, C., Bressac-de Paillerets, B., Hofman, P., Rocchi, S., Peyron, J.F., Lacour, J.P., Ballotti, R., and Bertolotto, C
(2011) **Genes & Dev** 25, 1245-1261
5. Mitf is the key molecular switch between mouse or human melanoma initiating cells and their differentiated progeny
Cheli, Y., Giuliano, S., Botton, T., Rocchi, S., Hofman, V., Hofman, P., Bahadoran, P., Bertolotto, C., and Ballotti, R
(2011) **Oncogene** 30, 2307-2318

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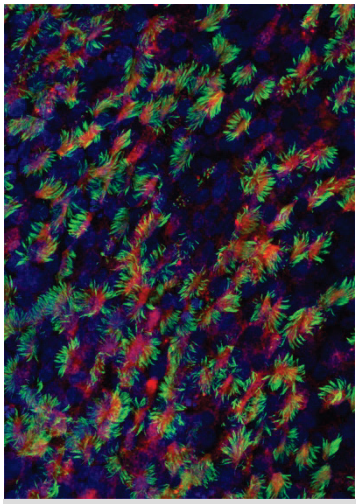
Physiological Genomics of the Eukaryotes



Immunolabelling of multiciliated airway epithelial cells (RED=basal bodies; GREEN=motille cilia; BLUE=nuclei)

Respiratory cells develop specific differentiation programs, for instance to synthesize hundreds of motile cilia at the apical surface of the airway epithelial cells. This allows an efficient protection of the respiratory tract mucosa against various external aggressions, and provides specific responses against stresses (allergens, bacteria, viruses, chemicals…). Airway epithelial cells represent a unique cellular model, which is central to important health questions (asthma, lung cancer, cystic fibrosis, fibroproliferative diseases,…). Our group is more specifically interested by the regulations by small regulatory RNAs that can take place in lung cells. In that context, we have recently reported the identification of microRNAs of the miR-34/miR-449 families as evolutionary conserved key regulators of vertebrate multiciliogenesis. We also found that miR-199a-5p behaves as a major regulator of tissue fibrosis with interesting therapeutic potency to treat fibroproliferative diseases. Our interest for dysregulated microRNAs expression during lung cancer and fibrosis led to investigate the impact of other microRNAs, such as miR-210 and miR-483, on cell metabolism, viability, apoptosis, migration and wound healing. For all these studies, our group develops new approaches in functional genomics and bioinformatics, with a special interest for high throughput sequencing.

Selected Publications

1. CDC25A targeting by miR-483-3p decreases CCND-CDK4/6 assembly and contributes to cell cycle arrest.
   Bertero T, Gastaldi C, Bourget-Ponzio I, Mari B, Meneguzzi G, Barbry P, Ponzio G, Rezzonico R.
   (2013) **Cell Death Diff** 4, e544
2. miR-199a-5p is upregulated during fibrogenic response to tissue injury and mediates TGFbeta-induced lung fibroblast activation by targeting caveolin-1
   Cardenas CLL, Henaoui IS, Courcot E, Roderburg C, Cauffiez C, Aubert S, Copin MC, Wallaert B, Glowacki F, Dewaeles E, Milosevic J, Maurizio J, Tedrow J, Marcet B, Lo-guidice JM, Kaminski N, Barbry P, Luedde T, Perrais M, Mari B, Pottier N.
   (2013) **PLoS Genet** 9(2), e1003291
3. Gene expression profiling reveals distinct epithelial phenotypes in child respiratory allergy
   Giovannini-Chami L, Marcet B, Moreilhon C, Chevalier B, Illie MI, LeBrigand K, Robbe-Sermesant K, Bourrier T, Michiels JF, Mari B, Crénesse D, Hofman P, de Blic J, Castillo L, Albertini M, Barbry P. (2012) **Eur Resp J** 39(5), 1197-205
4. Small RNA sequencing reveals miR-642a-3p as a novel adipocyte-specific microRNA and miR-30 as a key regulator of human adipogenesis.
   Zaragosi LE, Wdziekonski B, Le Brigand K, Villageois P, Mari B, Waldmann R, Dani C, Barbry P.
   (2011) **Genome Biol** 12(7) , R64
5. miR-449 microRNAs trigger vertebrate multiciliogenesis through direct repression of the Notch ligand Delta-like 1.
   Marcet B, Coraux C, Chevalier B, Luxardi G, Zaragosi LE, Robbe-Sermesant K, Jolly T, Cardinaud B, Moreilhon C, Giovannini-Chami L, Birembaut P, Waldmann R, Kodjabachian L, Barbry P. (2011) **Nature Cell Biology.** 13(6), 694-701

Awards

2011: CNRS PES award
2010: Coordinator of InDiGen, a component of France-Génomique

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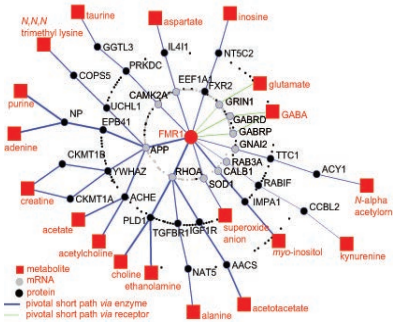
Physiopathology of Intellectual disability



FMR1 integrated Metabolome and Interactome Mapping (iMIM) Network (Davidovic et al., Genom. Res. , 2013)

Fragile X syndrome (FXS) is the most common form of inherited intellectual disability (ID) due to the silencing of the FMR1 gene, which encodes for FMRP, an RNA-binding protein involved in translational regulation at the synapse.
In the past, we focused our studies on the characterization of partners (proteins and RNAs) of FMRP. More recently we addressed our efforts to the identification and characterisation of pathways involving FMRP function in adult neurons and during neuronal differentiation using chemical, bioinformatic, molecular biology, cellular and genomic analyses. Indeed, we identified novel pathways involving FMRP and that are perturbed in FXS. In some cases, modulation of these cellular signaling pathways improves the phenotype of the FXS mouse model.
Our interests include the molecular mechanisms of action of FMRP and of its two paralogs FXR1P and FXR2P and search of biomarkers for FXS.
We are also interested in the functional characterization of another gene silenced in another form of ID and autism, AFF/FMR2, coding for a transcription factor involved in Fos and Jun expression. We have defined its role also in splicing and we are currently searching for its RNA targets.
We are studying the role of some miRNAs (targeting the mRNA of FMR1) in neuronal maturation by characterizing their mRNA targets and evaluating their implication in other forms of ID/autism.

Selected Publications

1. A Novel Function of Fragile X Mental Retardation Protein in translational activation
   Bechara E, Didiot, MC, Melko M, Davidovic L, Bensaid M, Martin P, Castets M, Pognonec P, Khandjian E, Moine H, Bardoni B
   (2009) **PLoS Biol.** Jan 20 7(1), e16
2. Functional characterization of the AFF (AF4/FMR2) family of RNA binding proteins: insights into the molecular pathology of FRAXE intellectual disability.
   Melko M, Douguet D., Bensaid M, Zongaro S, Verheggen C, Gecz J, Bardoni B
   (2011) **Hum. Mol. Genet.** 20, 1873-1885
3. A metabolomic and system biology perspective on the brain of the Fragile X syndrome mouse model
   Davidovic L, Navratil V, Bonaccorso C.M., Catania M.V., Bardoni B, Dumas M
   (2011) **Genome Res.** 21, 2190-2202
4. The 3' UTR of FMR1 mRNA is a target of miR-101, miR-129-5p and miR-221: implications for the molecular pathology of FXTAS at the synapse
   Zongaro S, Hukema R, D'Antoni S, Davidovic L, Barbry P, Catania M.V., Willemsen R, Mari B, Bardoni B
   (2013) **Hum. Mol. Genet.** 22, 1971-1982
5. A novel role for the RNA-binding protein FXR1P in myoblasts cell-cycle progression by modulating p21/Cdkn1a/Cip1/Waf1 mRNA stability.
   Davidovic L, Durand N, Khalfallah O, Tabet R, Barbry P, Mari B, Sacconi S, Moine H, Bardoni B
   (2013) **Plos. Genet.** Mar;9(3), e1003367

Awards

2004: CNRS ATIP
2007: CNRS ATIP PLUS

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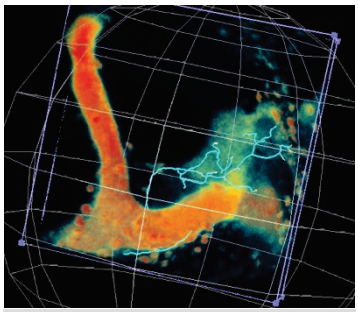
Post-transcriptional control of axon growth and guidance in *Drosophila*



3D reconstruction of a wild-type axonal tree

While post-transcriptional regulation of mRNAs has recently emerged as a major step in the spatial and temporal regulation of gene expression, very few studies have analyzed its underlying mechanisms and biological functions in vivo, during CNS maturation. Intracellular targeting of mRNAs coupled to local translation is a major component of the post-transcriptional toolkit, and is a powerful means to asymmetrically accumulate protein products within polarized cells. Ten years ago, local translation of transcripts localized to axons has been shown to be essential for growth cone turning in response to guidance cues in cultured neurons. Since then, several mRNAs have been shown to be recruited to growing axons and translated locally. Strikingly, the biological relevance of this process remains to be demonstrated in vivo, and the underlying molecular mechanisms are still largely unknown. We are using Drosophila CNS neurons as a genetically tractable system to 1) identify the components (mRNAs and associated proteins) of axonally-transported ribonucleoprotein complexes (RNP), and 2) characterize their function and regulation during development. To this end, we are combining different approaches including genetic screens, biochemical purifications, live imaging and bioinformatic analyses.

Selected Publications

1. Principles and roles of mRNA localization in animal development.
   Medioni C., Mowry K. and Besse F.
   (2012) **Development** 139(18), 3263-76.
2. Drosophila PTB/hnRNPI promotes formation of high-order oskar RNP complexes and represses oskar translation.
   Besse F.*, Lopez-de-Quinto S.*, Marchand V., Trucco A. and Ephrussi A.
   (2009) **Genes Dev.** 23(2), 195-207
3. Translational control of localized mRNA: restricting protein synthesis in space and time.
   Besse F. and Ephrussi A.
   (2008) **Nat Rev Mol Cell. Biol.** 9(12), 971-80
4. The Ig-CAM Basigin controls compartmentalization and vesicle release at Drosophila synapses.
   Besse F., Mertel S., Kittel R., Wichman C., Rasse T, Sigrist S. and Ephrussi A.
   (2007) **J. Cell. Biol.** 177(5), 843-55.

Awards

2009: HFSP Career Development Award
2008: ATIP CNRS

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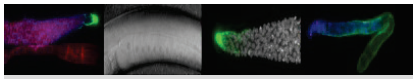
Gene-environement interactions in development and evolution



The study system: the Caenorhabditis germline

How does an organism adjust its reproduction and underlying developmental processes in response to environmental variation? How do such environmental responses evolve, given that populations and species have adapted to contrasted ecological niches? We address these questions by studying how molecular and cellular processes of the Caenorhabditis germline respond to environmental variation and how such responses evolve. The objective is to conduct an integrative analysis of such germline plasticity and its evolution by characterizing the processes of germ cell proliferation, gamete differentiation and maturation, which ultimately define the reproductive output of the organism. Specifically, we aim (1) to quantify plasticity and genotype-by-environment interactions for molecular and life history phenotypes in different Caenorhabditis species and isolates; (2) to determine the mechanisms underlying plastic phenotypic responses to environmental variation; (3) to identify molecular changes underlying genotype-by-environment interactions, using QTL mapping approaches and developmental genetics; (4) to track the evolution of plasticity in variable environments using experimental evolution; (5) to search for ecological correlates of the observed genotype-by-environment interactions by studying natural Caenorhabditis populations and defining their ecological context.

Selected Publications

1. Species richness, distribution and genetic diversity of Caenorhabditis nematodes in a remote tropical rainforest
   Félix MA, Jovelin R, Ferrari C, Han S, Cho YR, Andersen EC, Cutter AD and Braendle C
   (2013) **BMC Evol Biol** 13, 10
2. Pheromones: Evolving language of chemical communication in nematodes
   Braendle C
   (2012) **Curr Biol** 22, R294-296
3. Bias and evolution of the mutationally accessible phenotypic space in a developmental system
   Braendle C, Baer C and Félix MA
   (2010) **PLoS Genetics** -, e1000877
4. Plasticity and errors of a robust developmental system in different environments
   Braendle C and Félix MA
   (2008) **Dev Cell** 15, 714-724

Awards

2010: Schlumberger Award
2008: ATIP

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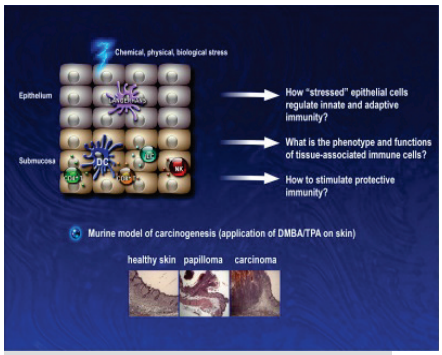
Immune regulation at muco-cutaneous surfaces



Appropriate immunity at epithelial sites contributes to host integrity

Non-melanoma skin carcinomas are the most frequent human cancers worldwide. Malignant transformation of epithelial tissues is controlled by immune mechanisms in place within the epithelium itself. A fine-tune dialog between epithelial and immune cells is crucial to resolve local injury/damage caused to keratinocytes by external aggressions.
Our research will therefore aim to provide a better understanding of the molecular and cellular responses of both the epithelium and the tissue-associated innate immune cells during the different stages of carcinoma development. We have obtained an extensive gene signature of innate immune cells and epithelial tumors at different stages of carcinoma development. Ongoing studies focus on the study of candidate genes and signalling pathways regulating carcinogenesis. The knowledge gained from these studies will allow the building of an integrative genomic picture of the tumor within its immune microenvironment and the identification of therapeutic targets not only for skin carcinomas such as basal-cell carcinomas (BCC) and more aggressive squamous cell carcinomas (SCC) but also for other epithelial cancers that are often refractory to treatments.

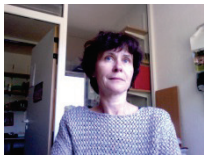
Selected Publications

1. Antigen-bearing dendritic cells from the sublingual mucosa recirculate to distant systemic lymphoid organs to prime mucosal CD8 T.
   Hervouet C , Luci C, Bekri S, Juhel T, Bihl F, Braud VM, Czerkinsky and F Anjuère
   (2013) **Mucosal Immunol** in press, -
2. Induction of LLT1 cell surface expression by pathogens and IFN-g contributes to modulate immune responses.
   Germain C, Meier A, Jensen T, Knapnougel P, Poupon G, Lazzari A, Neisig A, Håkansson K, Dong T, Wagtmann N, Galsgaard ED, Spee P, and V. M. Braud
   (2011) **J Biol Chem** 286, 37964-37975
3. Langerhans cells prime IL-17-producing T cells and dampen genital cytotoxic responses following mucosal immunization
   Hervouet C, Luci C, Rol N, Rousseau D, Kissenpfennig A, Malissen B, Czerkinsky C, Anjuère F
   (2010) **J Immunol** 184(9) , 4842-4851
4. Dendritic cell-mediated induction of cytotoxic responses following intravaginal immunization with the non-toxic B subunit of cholera toxin.
   Luci C, Hervouet C, Rousseau D, Holmgren J, Czerkinsky C and Anjuère F.
   (2006) **J Immunol** 176, 2749-2757
5. Cutting Edge: Lectin-Like Transcript 1 Is a Ligand for the CD161 Receptor
   Aldemir H, Prod'homme V, Dumaurier MJ, Retiere C, Poupon G, Cazareth J, Bihl F, and Braud VM
   (2005) **J Immunol** 175, 7791-7795

Awards

2002: Price from the Fondation pour la Recherche Médicale: V. Braud
2000-2003: Young investigator fellowship ATIP BLANCHE CNRS: V. Braud

CHABOISSIER Marie-Christine



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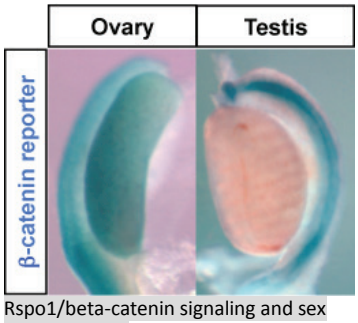
Genetics of sex determination and fertility



Rspo1/beta-catenin signaling and sex determination

Disorders of sexual differentiation (DSD) are frequent diseases that present considerable challenges for physicians, parents and affected individuals. These challenges include surgical correction, management and, in some cases, gender assignment. Unfortunately a large fraction of human cases of DSD are unexplained, despite substantial progress in our understanding of the molecular regulation of testicular and ovarian differentiation and maintenance. Our group aims at identifying new factors involved in sex detrmination with the goal of developing new genetic tests for individuals with DSD. Using mouse models, we have contributed to show that sex determination depends on a fine tuned balance between the SRY/SOX9 pathway, which precipitates testis differentiation, and the R-spondin/beta-catenin signaling pathway involved in ovarian differentiation. Our aim is now to decipher how these pathways and newly identified ones regulate sexual differentiation in normal and pathological conditions.

Selected Publications

1. Testicular differentiation occurs in absence of R-spondin1 and Sox9 in mouse sex reversals.
   Lavery R, Chassot AA, Pauper E, Gregoire EP, Klopfenstein M, de Rooij DG, Mark M, Schedl A, Ghyselinck NB. and Chaboissier MC
   (2012) **PLoS Genet & Faculty 1000** e, 1003170
2. WNT4 and RSPO1 together are required for cell proliferation in the early mouse gonad.
   Chassot AA, Bradford ST, Auguste A, Gregoire EP, Pailhoux E, de Rooij DG, Schedl A and Chaboissier MC
   (2012) **Development** 139, 4461-4472
3. XY Sox9 loss-of-function mouse mutants show complete sex reversal and can produce fertile XY oocytes
   Lavery R, Lardenois A, Ranc-Jianmotamedi F, Pauper E, Gregoire EP, Vigier C, Moreilhon C, Primig M and Chaboissier MC
   (2011) **Dev Biol & Faculty 1000** 354, 111-122
4. Activation of b-catenin signalling by Rspo1 controls differentiation of mammalian ovary.
   Chassot AA, Ranc F, Gregoire E, Roepers-Gajadien HL, Camerino G, de Rooij DG, Schedl A and Chaboissier MCFunctional analysis of Sox8 and Sox9 during sex determination in the mouse.
   (2008) **Human Mol Genet & Faculty 1000** 17, 1264-1277
5. R-spondin1 plays an essential role in sex determination, skin differentiation and malignancy.
   Parma P, Radi O, Vidal VPI, Chaboissier MC, Dellambra E, Valentini S, Guerra L, Schedl A, and Camerino G.
   (2006) **Nat Genet & Faculty 1000** 38, 1304-1309

Awards

2008: Albert Sézary Prize for Medicine (to AA Chassot, post doc for R-spondin1

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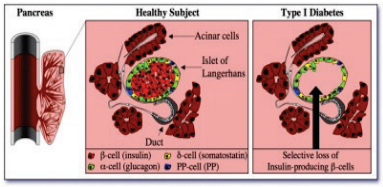
Diabetes Genetics



Type I diabetes in mouse and human

Our group is involved in understanding the molecular mechanisms underlying Diabetes and finding ways to counter this condition. Both Type I Diabetes (insulinodependent) and Type II (non insulinodependent) diabetes ultimately result in the selective loss of insulin-producing beta-cells in the endocrine pancreas (Figure). The subsequent lack in insulin hormone induces a blood hyperglycemia that may be attenuated by daily injection of exogenous insulin hormone. Nevertheless, despite the best of actual therapies, Type 1 Diabetic patients display a shortened life expectancy as compared to their healthy counterparts.

We belong to a NIH-/JDRF-funded consortium whose goal is to regenerate lost beta-cells in the context of type 1 diabetes. Using the mouse as a model, we have identified two transcription factors, Arx and Pax4, playing a crucial role in the genesis of the different endocrine cell subtypes, including insulin-secreting beta-cells. Importantly, the forced expression of Pax4 in specific cells of the pancreas can induce their proliferation and conversion in beta-cells. Of note, these cells are functional and can counter several cycles of chemically-induced diabetes.

Our group is now looking into ways to "drug » these beta-cell regeneration processes and determine whether our results could be applied to human.

Selected Publications

1. Adult duct-lining cells can reprogram into β-like cells able to counter repeated cycles of toxin-induced diabetes
   Al-Hasani K, Pfeifer A, Courtney M, Ben-Othman N, Gjernes E, Vieira A, Druelle N, Avolio F, Ravassard P, Leuckx G, Lacas-Gervais S, Ambrosetti D, Benizri E, Hecksher-Sorensen J, Gounon P, Ferrer J, Gradwohl G, Heimberg H, Mansouri M, Collombat P
   (2013) **Dev Cell** In press, In press
2. The homeodomain-containing transcription factors arx and pax4 control enteroendocrine subtype specification in mice
   Beucher A, Gjernes E, Collin C, Courtney M, Meunier A, Collombat P, and Gradwohl G
   (2009) **Plos One** 7, Pe36449
3. The ectopic expression of Pax4 in the mouse pancreas converts progenitor cells into alpha and subsequently beta cells
   Collombat P, Xu X, Ravassard P, Sosa-Pineda B, Dussaud S, Billestrup N, Madsen OD, Serup P, Heimberg H, and Mansouri,A
   (2009) **Cell** 138, 449-62
4. Embryonic endocrine pancreas and mature beta cells acquire alpha and PP cell phenotypes upon Arx misexpression
   Collombat P, Hecksher-Sørensen J, Krull J, Berger J, Riedel D, Herrera PL, Serup P, Mansouri A
   (2007) **J Clin Invest** 117(4), 961-70
5. Opposing actions of Arx and Pax4 in endocrine pancreas development.
   Collombat P, Mansouri A, Hecksher-Sorensen J, Serup P, Krull J, Gradwohl G, Gruss P.
   (2003) **Genes Dev** 17, 2591-603

Awards

2013: Appolinaire Bouchardat Award
2011: ERC Starting Grant
2009: JDRF Career Development Award
2009: Avenir Excellency INSERM
2009: Schlumberger Prize

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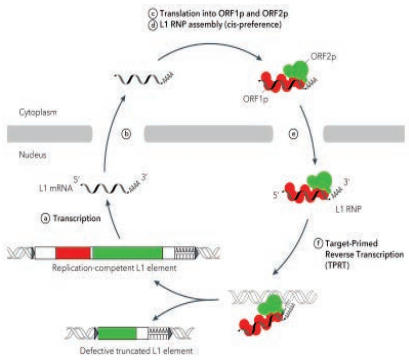
Retrotransposon and genome plasticity



A model for the replication of human L1 retrotransposons

The abundance of transposable elements in the human genome was one of the most surprising discoveries of genomics. More than 40% of our DNA is made of mobile genetic elements, also called »jumping genes ». Retrotransposons, such as the LINE-1 elements (L1), replicate through a reverse transcription process and are the most abundant active elements in our genome. They play a fundamental role in the current evolution and plasticity of the human genome and can result in the appearance of new genetic diseases or in tumorigenesis. They are repressed in most somatic cells in the adult. However, very recent genome-wide sequencing studies have revealed extensive retrotransposition in several epithelial cancer types (colorectal, lung, ovarian & prostate cancers) but none in glioblastoma or myeloma, suggesting that all tumors are not equal with respects to retrotransposon activation and that transformation or tissue-specific pathways might influence the extent of their mobilization. Our lab explores the link between retrotransposon mobility and tumor genome dynamics and instability. We also aim at understanding how the retrotransposition machinery is regulated at the molecular and cellular levels. To address these goals, we combine biochemistry, molecular & cellular biology, genomics and bioinformatics. We work in close collaboration with clinicians to get access to tumor samples.

Selected Publications

1. The specificity and flexibility of l1 reverse transcription priming at imperfect T-tracts.
   Monot C, Kuciak M, Viollet S, Mir AA, Gabus C, Darlix JL, Cristofari G.
   (2013) **PLoS Genet** 9, e1003499
2. Structure of active dimeric human telomerase.
   Sauerwald A, Sandin S, Cristofari G, Scheres SH, Lingner J, Rhodes D.
   (2013) **Nat Struct Mol Biol** 20, 454-60
3. RNA-mediated interference and reverse transcription control the persistence of RNA viruses in the insect model Drosophila.
   Goic B, Vodovar N, Mondotte JA, Monot C, Frangeul L, Blanc H, Gausson V, Vera-Otarola J, Cristofari G, Saleh MC.
   (2013) **Nat Immunol.** 14, 396-403
4. Human telomerase RNA accumulation in Cajal bodies facilitates telomerase recruitment to telomeres and telomere elongation.
   Cristofari G, Adolf E, Reichenbach P, Sikora K, Terns RM, Terns MP, Lingner J.
   (2007) **Mol Cell.** 27, 882-889
5. A 5'-3' long-range interaction in Ty1 RNA controls its reverse transcription and retrotransposition.
   Cristofari G, Bampi C, Wilhelm M, Wilhelm FX, Darlix JL.
   (2002) **EMBO J.** 21, 4368-79

Awards

2009: Laureate of the European Research Council (ERC Starting Grant)
2009: Laureate of the French National Academy of Medicine ('Albert Sézary' Prize)
2008: Awardee of the AVENIR program
2003-2004: EMBO long-term fellow
2003: Laureate of the 'Jacques Piraud' Prize, French Foundation for Medical Research (FRM)

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Stem cells and differentiation

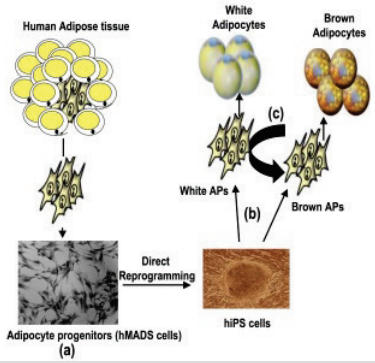

Illustration of cell models established in the team and the main questions we are addressing.

While there has been major progress in defining the transcriptional networks that control terminal differentiation of white and brown adipocyte progenitors (APs), much less is known regarding the developmental steps preceding AP generation in mouse, and nothing is known in humans. We propose to identify signalling pathways and molecular events that regulate the earliest events of brown and white adipocyte generation during differentiation of human induced pluripotent stem (hiPS) cells. We have recently shown that retinoic acid (RA) pathway activation promotes white adipocyte generation, whereas it inhibits the brown adipocyte lineage. In contrast, the TGFβ pathway is required for brown adipocyte generation. Based on these findings, we have developed a procedure to selectively derive brown and white APs. We propose to characterize them at a molecular level to identify regulators of AP fate.

Selected Publications

1. Transplantation of a multipotent cell population from human adipose tissue induces dystrophin expression in the immunocompetent mdx mouse.
   Rodriguez AM, Pisani D, Dechesne CA, Turc-Carel C, Kurzenne JY, Wdziekonski B, Villageois A, Bagnis C, Breittmayer JP, Groux H, Ailhaud G, and Dani C.
   (2005) **J Exp Med** May 2;201(9), :1397-405.
2. Autocrine FGF2 signaling is critical for self-renewal of Human Multipotent Adipose-Derived Stem Cells
   Zaragosi LE, Ailhaud G, and Dani C
   (2006) **Stem Cells** 24(11), 2412-9
3. Human Multipotent Adipose-derived Stem Cells Differentiate into Functional Brown Adipocytes
   Elabd C, Chiellini C, Carmona M, Galitzky J, Cochet O, Petersen R, Penicaud L, Kristiansen K, Bouloumie A, Casteilla L, Dani C, Ailhaud G, and Amri EZ
   (2009) **Stem Cells** 27(11), 2753-60
4. Activin A plays a critical role in proliferation and differenrentiation of human adipose progenitors
   Zaragosi LE, Wdziekonski B, Villageois P, Keophiphath M, Maumus M, Tchkonia T, Bourlier V, Mohsen-Kanson T, Ladoux A, Elabd C, Scheideler M, Trajanoski Z, Takashima Y, Amri EZ, Lacasa D, Sengenes C, Ailhaud G, Clément K, Bouloumie A, Kirkland JL , and Dani C
   (2010) **Diabetes** 56, 2513-2521
5. Small RNA sequencing reveals miR-642a-3p as a novel adipocyte-specific microRNA and miR-30 as a key regulator of human adipogenesis
   Zaragosi LE, Wdziekonski B, Le Brigand K, Villageois P, Mari B, Waldmann R, Dani C, and Barbry P.
   (2011) **Genome Biol.** 18, 12(7):R64.

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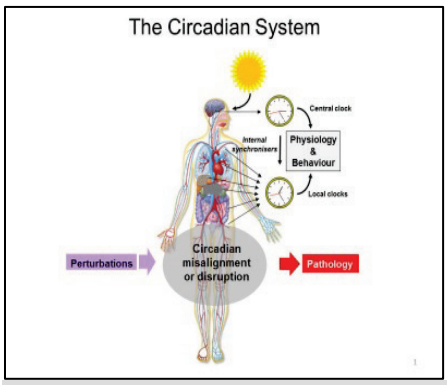
Circadian System Biology



Current model of the mammalian circadian timing system.

Most organisms show daily rhythms in physiology and behaviour. These rhythms are driven endogenous clocks oscillating with a circadian (~ 24 h) period and synchronized with the external light/dark cycle. In mammals, circadian clocks are organized in a hierarchical and highly integrated system comprising a central clock in the brain that synchronises local clocks throughout the periphery. The clock-controlled transcriptional programme is highly tissue-specific and nearly all key biological processes appear to be linked to the circadian timing system, including for instance the sleep/wake cycle, core body temperature, hormone secretion, metabolism, blood pressure, cell division, and immune function. Consequently, circadian disruption or misalignment is increasingly recognized as an important factor in the context of major diseases including cancer and metabolic disorders. Our aim is to understand how circadian clocks regulate physiological outputs in mammals and reciprocally, determine the mechanisms whereby key biological processes influence the circadian timing system. We currently investigate the interactions between core clock genes and energy metabolism with a focus on the role of specific transcriptional regulators. A second line of research is dedicated to the analysis of the coupling between the circadian clock and cell cycle oscillators in normal and cancer cells.

Selected Publications

1. The nuclear receptor REV-ERBalpha is required for the daily balance of carbohydrate and lipid metabolism
   Delezie J, Dumont S, Dardente H, Oudart H, Grechez-Cassiau A, Klosen P, Teboul M, Delaunay F, Pevet P, and Challet E.
   (2012) **FASEB Journal** 26, 3321-3335
2. Kruppel-like factor KLF10 is a link between the circadian clock and metabolism in liver
   Guillaumond F, Grechez-Cassiau A, Subramaniam M, Brangolo S, Peteri-Brunback B, Staels B, Fievet C, Spelsberg TC, Delaunay ., and Teboul M
   (2010) **Mol Cell Biol** 30, 3059-3070
3. Cancer inhibition through circadian reprogramming of tumor transcriptome with meal timing.
   Li XM, Delaunay F, Dulong S, Claustrat B, Zampera S, Fujii Y, Teboul, M, Beau, J, and Levi F
   (2010) **Cancer Research** 70, 3351-3360
4. The circadian clock component BMAL1 is a critical regulator of p21WAF1/CIP1 expression and hepatocyte proliferation
   Gréchez-Cassiau A, Rayet B, Guillaumond F, Teboul M, Delaunay F
   (2008) **J Biol Chem** 238, 4535-4541

Awards

2001: ACI Jeune Chercheur

DESCOMBES Xavier

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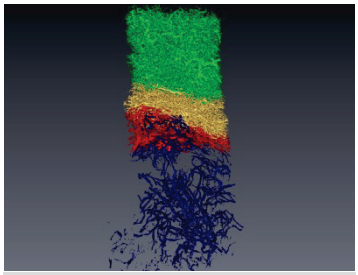
Computational Morphometry and Morphodynamic of Cellular & Supracellular Structures



Vascular network segmentation from X-ray micro-tomography : Necrosis (blue), Tumor (red), Tumor Periphery (yellow) and Sane Tissue (green)

The scientific objectives of MORPHEME are to characterize and model the development and the morphological properties of biological structures from the cell to the supra-cellular scale. Being at the interface between computational science and biology, we plan to understand the morphological changes that occur during development combining in vivo imaging, image processing and computational modelling.

Selected Publications

1. Amplitude-based data selection for optimal retrospective reconstruction in micro-SPECT
   Breuilly M, Malandain G, Guglielmi J, Marsault R, Pourcher T, Franken P and Darcourt J.
   (2013) **Physics in Medicine and Biology** 58(8), 26-57
2. Sparse Poisson Noisy Image Deblurring
   Carlavan M and Blanc-Féraud L.
   (2012) **IEEE Transactions on Image Processing** 21(4), 1834-1846
3. Trends in Bio Imaging and Signal Processing
   Olivo-Marin JC, Blanc-Feraud L, Unser M, Laine A and Lelieveldt B.
   (2011) **IEEE Signal Processing Magazine** ., .
4. Axon Extraction from Fluorescent Confocaql Microscopy Images
   Mottini A, Descombes X and Besse F.
   (2012) **ISBI – International Symposium on Biomedical Imaging** ,
5. Automatic Dendrite Spines Detection from X-Ray Tomography Volumes
   Descombes X, Malandain G, Fonta C, Negyessy L and Mosko R.
   (2013) **ISBI – International Symposium on Biomedical Imaging** ,

Awards

2008: Prix de la Recherche – Human Health category

FERAL Chloé

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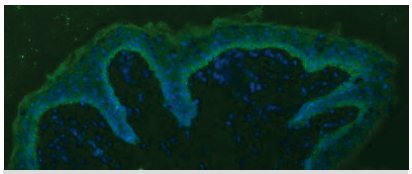
Epithelial homeostasis and tumorigenesis



CD98hc Expression in the basal layer of human epidermis (green CD98hc, blue DAPI)

The cells that compose the epithelium are constantly renewed and they rest on a basal membrane composed of highly organized network of extracellular matrix (ECM) proteins. To maintain homeostasis in an adult tissue, cell proliferation must be tightly regulated, yet how this is controlled is not fully understood. When this balance is lost epithelial cancers (or carcinomas) arise. In particular, squamous cell carcinoma (SCC) is the second most common type of skin cancer and its incidence increases with age. Our lab is investigating the role of CD98hc, a dual function transmembrane protein, in epidermal tumor formation.

CD98 (4F2), is highly expressed in epithelium, which is a heterodimer of a common heavy chain (CD98hc, SLC3A2), and an acid transporter subunit. CD98hc also interacts with ECM receptors, integrins. Thus, via these interaction, CD98hc has two main functions: amino acid transporter and integrin signaling modulator.

Our work aims at determining how CD98 interactions contribute to epithelial homeostasis and tumorigenesis.

Selected Publications

1. CD98hc (SLC3A2) Regulation of Skin Homeostasis Wanes with Age.
   Boulter E, Estrach S, Errante A, Pons C, Cailleteau L, Tissot F, Meneguzzi G, Féral CC.
   (2013) **J Exp Med.** 210(1), 173-90.
2. Dependence of proliferative vascular smooth muscle cells on CD98hc (4F2hc, SLC3A2).
   Fogelstrand P, Féral CC, Zargham R, Ginsberg MH.
   (2009) **J Exp Med.** 206(11), 2397-406.
3. CD98hc (SLC3A2) participates in fibronectin matrix assembly by mediating integrin signaling.
   Féral CC, Zijlstra A, Tkachenko E, Prager G, Gardel ML, Slepak M, Ginsberg MH.
   (2007) **J Cell Biol.** 178(4), 701-11
4. CD98hc (SLC3A2) mediates integrin signaling.
   Feral CC, Nishiya N, Fenczik CA, Stuhlmann H, Slepak M, Ginsberg MH.
   (2005) **Proc Natl Acad Sci U S A** 102(2), 355-60

Awards

2009-2013: Avenir

FRENDO Pierre

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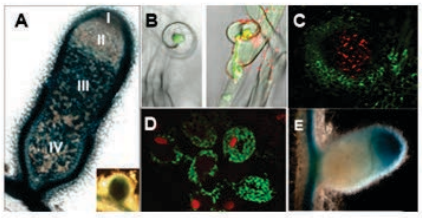
Nitrogen-fixing symbiosis and redox state



Leguminous – Rhizobium symbiosis : Nodule (A); Detection of NO (B) and of H2O2 (C); bacteroids (D) and gene expression in nodule (E).

The team focuses on improving our knowledge of plant/nitrogen-fixing bacteria (Rhizobium) by studying the role of the cellular redox state during the symbiotic interaction. Work is focused on two essential steps in the symbiotic relationship: the study of reception mechanisms of the symbiotic partner leading to a functional nodule and the understanding of the nodule senescence phenomenon leading to the breakdown of the symbiotic association. Within this framework, it especially studies three major molecules involved in the regulation of the cellular redox state: hydrogen peroxide (H2O2), nitrogen monoxide (NO) and glutathion (GSH).

Selected Publications

1. Hydrogen peroxide and nitric oxide: key regulators of the legume – Rhizobium and mycorrhizal symbioses
   Puppo A, Pauly N, Boscari A, Mandon K, Brouquisse R.
   (2013) **Antioxid Redox Signal** 18, 2202-2219
2. Expression Dynamics of the Medicago truncatula Transcriptome during the Symbiotic Interaction with Sinorhizobium meliloti: Which Role for Nitric Oxide? 161, 425–439.
   Boscari A, del Giudice J, Ferrarini A, Venturini L, Zaffini AL, Delledonne M, Puppo A.
   (2013) **Plant Physiol.** 161, 425-439
3. Peribacteriod space acidification: a marker of mature bacteroid functioning in Medicago truncatula nodules.
   Pierre O, Engler G, Hopkins J, Brau F, Boncompagni E, and Hérouart D.
   (2013) **Plant Cell Environ** Doi: 10.1111/, pce.12116
4. Hydrogen peroxide-regulated genes in the Medicago truncatula– Sinorhizobium meliloti symbiosis.
   Andrio E, Marino D, Marmeys A, Dunoyer de Segonzac M, Damiani I, Genre A, Huguet S, Frendo P, Puppo A and Pauly N.
   (2013) **New phytol** 198, 179-189
5. (homo)glutathione Deficiency Impairs Root-knot. Nematode Development in Medicago truncatula
   Baldacci-Cresp F, Chang C, Maucourt M, Deborde C, Hopkins J, Lecomte P, Brouquisse R, Moing A, Abad P, Hérouart D, Puppo A, Favery B and Frendo P.
   (2012) **PloS Pathogens** 8, e1002471

FURTHAUER Maximilian

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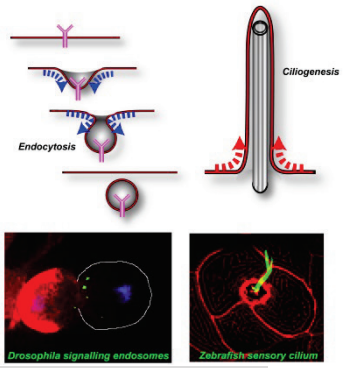
Membrane dynamics and cell signaling in animal development



Membrane deformations in endocytosis and ciliogenesis

The regulation of membrane shape has important consequences for cell signalling: While endocytic invaginations internalize signalling molecules from the cell surface, membrane protrusions probe the cellular environment. Our work at the interface of cellular and developmental biology uses Zebrafish and Drosophila to study how membrane architecture contributes to the regulation of cell signalling in animal development:

1) Membranes are organized into distinct functional domains. Consequently, signalling molecules have to be targeted to precise environments to exert their function. We have developed a novel live imaging approach that allows for the first time to visualize the endocytic transport of endogenous signalling molecules in intact living embryos. Using this approach we are studying how Delta/Notch signalling, one of the major cellular signalling pathways, is regulated during the development of the nervous system.

2) Cilia are specialized membrane protrusions that allow cells to communicate with their environment by chemosensation, mechanosensation and the creation of fluid flows. We have recently uncovered important new functions of intracellular transport proteins in the formation and function of ciliated organs. Presently we are using a combination of genetic, cell biological and live imaging approaches to characterize novel aspect of ciliary organ function.

Selected Publications

1. Directional Delta and Notch trafficking in Sara endosomes during asymmetric cell division.
   Coumailleau F, Fürthauer M, Knoblich JA, and González-Gaitán M.
   (2009) **Nature** 458, 1051-1055
2. Endocytic regulation of notch signalling during development.
   Fürthauer M and González-Gaitán M.
   (2009) **Traffic** 10, 792-802
3. Endocytosis, asymmetric cell division, stem cells and cancer: unus pro omnibus, omnes pro uno.
   Fürthauer M and González-Gaitán M.
   (2009) **Mol Oncol** 3, 339-353
4. Fgf signalling controls the dorsoventral patterning of the zebrafish embryo.
   Fürthauer M, Van Celst J, Thisse C and Thisse,B.
   (2004) **Development** 131, 2853-2864
5. Sef is a feedback-induced antagonist of Ras/MAPK-mediated FGF signalling.
   Fürthauer M, Lin W, Ang SL, Thisse B and Thisse C.
   (2002) **Nat Cell Biol** 4, 170-174

Awards

2012 : ARC Projet
2011: HFSP Career Development Award
2010: ATIP/Avenir Junior Group Leeder Programme
2005: HFSP Long Term Postdoctoral Fellowship
2004: EMBO Postdoctoral fellowship

GILSON Eric

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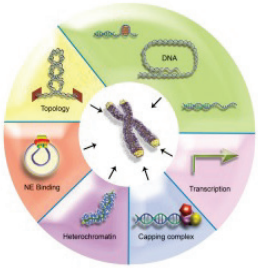
Telomere, senescence and cancer



Data from our team indicate that topological stress may constitute a conserved signaling pathway to recruit capping proteins.

Task #1: Structure and function of of telomeric chromatin in normal and cancer cells
1) The role of nucleosomes in telomere biology
We plan to study in human cells :
- the telomere chromatin organization by in vitro reconstitution, biochemical analyses and in vivo imaging combining AFM with fluorescence microscopy;
- the functional interactions between shelterin components and nucleosomes;
- the nature of the epigenetic changes that occurred at the onset of replicative senescence.
2) The role of TRF2 as a DNA topology stress sensor
We will measure the topological status of telomeres in living cells and to screen for genes that may be direct actors or participate in the regulation of telomeric topological barrier(s). We will also analyze telomeric replication using an in vitro system.
Task #2 Roles of shelterin in long-range chromatin structure and gene expression
We will study the mechanism(s) by which extratelomeric TRF2 binding sites regulate the expression of extratelomeric genes.
Task # 3 Role of telomeres in oncogenesis
We develop three approaches to better understand the role of telomeres in oncogenesis : 1) To assay the tumorigenicity of cancer cells expressing separation–of-function mutants of TRF2; 2) Based on our results identifying genes involved in NK cell biology and angiogenesis as TRF2 targets; 3) Based on our results involving IL-6 in telomere capping.

Selected Publications

1. TRF2 and apollo cooperate with topoisomerase 2alpha to protect human telomeres from replicative damage
   Ye J, Lenain C, Bauwens S, Rizzo A, Saint-Leger A, Poulet A, Benarroch D, Magdinier F, Morere J, Amiard S, Britton, P Calsou, B Salles, A Bizard, M Nadal, E Salvati, L Sabatier, Y Wu, A Biroccio, A Londoño-Vallejo, MJ Giraud-Panis and E. Gilson. (2010) **Cell** 142(2), 230-242
2. A two-step model for senescence triggered by a single critically short telomere
   Abdallah P, Luciano P, Runge KW, Lisby M, Géli V, Gilson E, Teixeira MT. (2009) **Nature Cell biol.** 11, 988-93
3. TRF2 inhibits a cell-extrinsic pathway through which Natural Killer cells eliminate cancer cells
   Biroccio AM, Cherfils-Vicini J, Augereau A, Pinte S, Bauwens S, Ye J, Jamet K, Cervera L, Mendez-Bermudez A,Poncet D, Grataroli R, T'kint de Rodenbeeke C, Salvati E, Rizzo A, Zizza P, Ricoul M, Cognet C, Kuilman T, Duret H, Lépinasse F, Marvel J, Verhoeyen E, Cosset FL, Peeper D, Smyth M, Londoño-Vallejo A, Sabatier L, Picco V, Pages G, Scoazec JY, Stoppacciaro A, Leonetti C, Vivier E, Gilson E. (2013) **Nature Cell biol** in press, na
4. Telomere protection and TRF2 expression are enhanced by the canonical Wnt signalling pathway
   Diala I, Wagner N, Magdinier F, Shkreli M, Sirakov M, Bauwens S, Schluth-Bolard C, Simonet T, Renault VM, Ye J, Djerbi A, Pineau P, Choi J, Artandi S, Dejean A, Plateroti M, Gilson E. (2013) **EMBOr** 14, 356-63
5. The human TTAGGG Repeat Factors 1 and 2 bind to a subset of interstitial telomeric sequences and satellite repeats
   T Simonet, LE Zaragosi, C Philippe, K Lebrigand, C Schouteden, A Augereau, S Bauwens, J Ye, M Santagostino, E Giulotto, F Magdinier, B Horard, P Barbry, R Waldmann, and E Gilson . (2011) **Cell research** 21, 1028-38

Awards

2010: Prize EUROCANCER
2010: Prize Allianz-Institut de france
2003: Elected EMBO member
2003: Prize Marguerite Delahautemaison of "Fondation de la Recherche Médicale"

GLAICHENHAUS Nicolas

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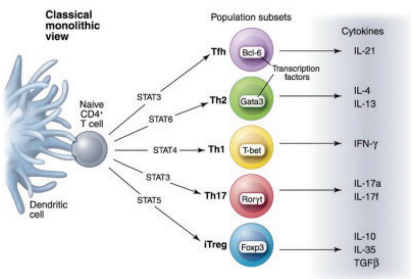
Immunology and immune tolerance



Helper T cell differentiation (O'Shea and Paul. 2010. Science)

Our team has a broad interest in immunology, and more specifically on T cell differentiation, antigen presentation and immune tolerance. Our current specific aims are (1) to identify the molecular and cellular mechanisms by which the environment perceived by brain influences immune response to foreign antigens or to cancer cells, (2) to elucidate the role of chemokine and chemokine receptors in airway inflammation and (3) to decipher the mechanisms by which viruses could exacerbate airway inflammation in individuals with allergic asthma.

Selected Publications

1. Langerin+ dendritic cells are responsible for LPS-induced reactivation of allergen-specific Th2 responses in postasthmatic mice
   Ortiz-Stern A, Kanda A, Mionnet C, Cazareth J, Lazzari A, Fleury S, Dombrowicz D, Glaichenhaus N, Julia V
   (2011) **Mucosal Immunol** 4, 343-53
2. The oral administration of bacterial extracts prevents asthma via the recruitment of regulatory T cells to the airways
   Navarro S, Cossalter G, Chiavaroli C, Kanda A, Fleury S, Lazzari, A. Cazareth J, Sparwasser T, Dombrowicz D, Glaichenhaus N, Julia V
   (2011) **Mucosal Immunol** 4, 53-65
3. Direct visualization of peptide/MHC complexes at the surface and in the intracellular compartments of cells infected in vivo by Leishmania major
   Muraille E, Gounon P, Cazareth J, Hoebeke J, Lippuner C, Davalos-Misslitz A, Aebischer T, Muller S, Glaichenhaus N, Mougneau E
   (2010) **PLoS Pathog** 6, e1001154
4. Breast milk immune complexes are potent inducers of oral tolerance in neonates and prevent asthma development
   Mosconi E, Rekima A, Seitz-Polski B, Kanda A, Fleury S, Tissandie, E. Monteiro R, Dombrowicz D, Julia V, Glaichenhaus N, Verhasselt V
   (2010) **Mucosal Immunol** 3, 461-474
5. CX3CR1 is required for airway inflammation by promoting T helper cell survival and maintenance in inflamed lung
   Mionnet C, Buatois V, Kanda A, Milcent V, Fleury S, Lair D, Langelot M, Lacoeuille, Y. Hessel E, Coffman R, Magnan A, Dombrowicz D, Glaichenhaus N, Julia V
   (2010) **Nat Med** 16, 1305-1312

Awards

2010: Elected senior member of the Institut Universitaire de France (IUF)
1998: Elected senior member of the European Molecular Biology Organisation (EMBO)

GOUZE Jean-Luc

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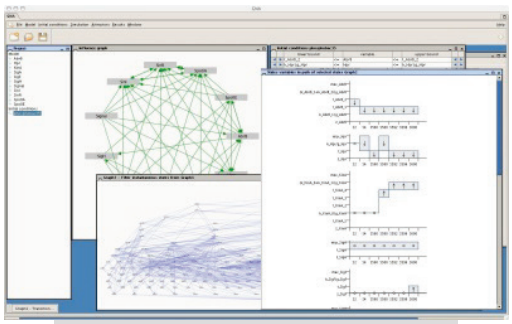
Biological Control of artificial ecosystems (BIOCORE team: INRIA/INRA/CNRS/UPMC)



Genetic Network Analyzer (de Jong et al.)

We build and study mathematical dynamical models of biological systems: intracellular models (of genetic and/or metabolic type : genetic networks, metabolic networks, signalling networks), models of populations or at the scale of the ecosystems. Our tools are dynamical systems and control theory.
These models are qualitative or quantitative. Parameters are then fitted with experimental data.

Selected Publications

1. A theoretical exploration of birhythmicity in the p53-Mdm2 network
   Abou-Jaoudé W, Chaves M. and Gouzé J.-L.
   (2011) **PLOS one** 6(2), e17075
2. Oscillations induced by different timescales in signal transduction modules regulated by slowly evolving protein–protein interactions
   Ndiaye, I and Chaves, M and Gouzé, J-L
   (2010) **IET systems biology** 4 (4), 263-276
3. Robustness and fragility of Boolean models for genetic regulatory networks
   M. Chaves, R. Albert and E.D. Sontag.
   (2005) **J. Theoretical Biology** 235 (3), 431-449
4. Qualitative simulation of genetic regulatory networks using piecewise-linear models
   De Jong, H. , Gouzé J-L, Hernandez, C, Page, M., Sari, T. and Geiselmann, J
   (2004) **Bulletin of mathematical biology** 66 (2), 301-340

GUAL Philippe/TRAN Albert

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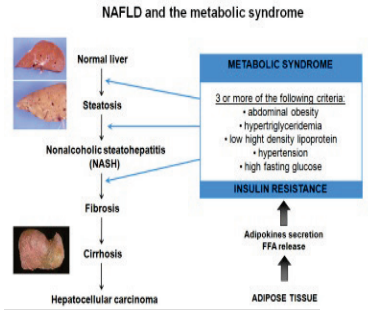
Hepatic complications in obesity



Hepatic complications in obesity

The hepatic complications of obesity, one of the most common forms of chronic liver diseases. range from steatosis to steatohepatitis (Non Alcoholic SteatoHepatitis, NASH), fibrosis, cirrhosis and finally hepatocellular carcinoma. The diagnosis of NASH requires a liver biopsy. The pathophysiological mechanisms of the progression of these diseases are complex, including insulin-resistance, cellular stress and upregulation of pro-inflammatory factors. These factors can originate from intra- or extra-hepatic sites, particularly the adipose tissue.
Our main objectives are:
1) To develop a non invasive index from clinical data and the identified markers allowing the diagnosis of NASH in our cohort of 800 obese patients, for whom serum and hepatic and adipose tissue biopsies have been obtained.
2) To study the role of identified and new players in the progression of liver complications. This will be evaluated in different cellular and animal models.
3) To study the development of the liver complications in achondroplasia in animal models.
4) To evaluate the effect of pharmacological and chirurgical treatment on prevention and correction of liver complications in animal models.
The results of the present project should bring new insights in the understanding of the mechanistic of hepatic complications in obesity and to propose better diagnostic and therapeutic approaches.

Selected Publications

1. Regular coffee but not Espresso drinking is protective against fibrosis in a cohort mainly composed of morbidly obese European women patients with NAFLD undergoing bariatric surgery.
   Anty R, Marjoux S, Iannelli A, Patouraux S, Schneck AS, Bonnafous S, Gire C, Amzolini A, Ben-Amor I, Saint-Paul MC, Mariné-Barjoan E, Pariente A, Gugenheim J, Gual P, Tran A.
   (2012) **J of Hepatology** 57, 1090-6.
2. Identification of Adipose Tissue Dendritic Cells Correlated With Obesity-Associated Insulin-Resistance and Inducing Th17 Responses in Mice and Patients.
   Bertola A*, Ciucci T*, (*co-first authors) Rousseau D, Bourlier V, Duffaut C, Bonnafous S, Blin-Wakkach C, Anty R, Iannelli A, Gugenheim J, Tran A, Bouloumié A, Gual P$, Wakkach A$ ($ co-last authors).
   (2012) **Diabetes** 61, 2238-47
4. Elevated expression of osteopontin may be related to adipose tissue macrophage accumulation and liver steatosis in morbid obesity.
   Bertola, A., Deveaux V, Bonnafous S, Rousseau D, Anty R, Wakkach A, Dahman M, Tordjman J, Clement K, McQuaid SE, Frayn KN, Huet PM, Gugenheim J, Lotersztajn S, Le Marchand-Brustel Y, Tran A, and Gual P
   (2009) **Diabetes** 58, 125-33
5. Increased adipose tissue expression of hepcidin in severe obesity is independent from diabetes and NASH.
   Bekri, S*, Gual P* (Co first authors), Anty R, Luciani N, Dahman M, Ramesh B, Iannelli A, Staccini-Myx A, Casanova D, Ben Amor I, Saint-Paul MC, Huet PM, Sadoul JL, Gugenheim J, Srai SK, Tran A and Le Marchand-Brustel Y.
   (2006) **Gastroenterology** 131, 788-96

Awards

2003 : Prix de Recherche Clinique Insitut Roche de l'obésité « Rôle de l'IL6 dans les complications de l'obésité ». P. Gual

HOFMAN Paul

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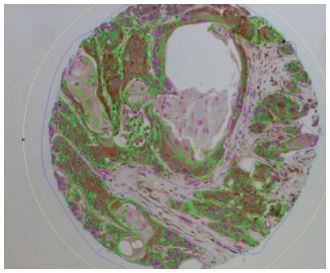
Carcinogenesis related chronic active inflammation



Crosstalk between neutrophil and lung cancer tumor

Epidemiological and histological data highlight that an intense and repeated neutrophil infiltration over a long period time is strongly linked to a high risk of carcinoma onset. However, even though different mechanisms claim to explain the onset of carcinogenesis in response to repeated neutrophil transepithelial migration and/or neutrophil epithelial contact. The pathophysiological of this process is complex and its understanding remains obscure. Within a tumour, cancer cells are surrounded by an inflammatory microenvironment containing different cell subtypes including polymorphonuclear leukocytes (PMNL, i.e. neutrophils). Accumulating evidence strongly suggests that cancer cells attract inflammatory cells, in particular PMNL, and might subvert their function to promote tumour cell proliferation, resistance again cell death and metastasis. However, the relationship between cytokines, epithelial cells and PMNL, and the consequence of such cell-cell interactions on regulation of downstream events (in particular, miRNA regulation and/or protein expression) has been poorly investigated, in particular during the critical transition from a chronic "active" inflammatory lesion to a carcinoma.

Our project is divided into the following objectives: i) to characterize the role of the microenvironment on PMNL maturation (aim 1), ii) to characterize the involvement of PMNL in tumour initiation (aim 2), and in tumour progression and dissemination (aim 3).

Selected Publications

1. Diagnostic value of immunohistochemistry for the detection of the BRAFV600E mutation in primary lung adenocarcinoma Caucasian patients.
   Ilie M, Long E, Hofman V, Dadone B, Marquette CH, Mouroux J, Vignaud JM, Begueret H, Merlio JP, Capper D, von Deimling A, Emile JF, Hofman P. (2013) **Ann Oncol** 24, 742-748
2. ALK-gene rearrangement: a comparative analysis on circulating tumour cells and tumour tissue from patients with lung adenocarcinoma.
   Ilie M, Long E, Butori C, Hofman V, Coelle C, Mauro V, Zahaf K, Marquette CH, Mouroux J, Paterlini-Bréchot P, Hofman P (2012) **Ann Oncol** 23, 2907-2911
3. Predictive clinical outcome of the intratumoral CD66b-positive neutrophil-to-CD8-positive T-cell ratio in patients with resectable nonsmall cell lung cancer.
   Ilie M, Hofman V, Ortholan C, Bonnetaud C, Coëlle C, Mouroux J and Hofman P.
   (2012) **Cancer** 118, 1726-1737
4. A synonymous variant in IRGM alters a binding site for miR-196 and causes deregulation of IRGM-dependent xenophagy in Crohn's disease.
   Brest P, Lapaquette P, Souidi M, Lebrigand K, Cesaro A, Vouret-Craviari V, Mari B, Barbry P, Mosnier JF, Hébuterne X, Harel-Bellan A, Mograbi B, Darfeuille-Michaud A, Hofman P
   (2011) **Nat Genet** 43, 242-254
5. Preoperative circulating tumor cell detection using the isolation by size of epithelial tumor cell method for patients with lung cancer is a new prognostic biomarker.
   Hofman V, Bonnetaud C, Ilie MI, Vielh P, Vignaud JM, Fléjou JF, Lantuejoul S, Piaton E, Mourad N, Butori C, Selva E, Poudenx M, Sibon S, Kelhef S, Vénissac N, Jais JP, Mouroux J, Molina TJ, Hofman P
   (2011) **Clin Cancer Res** 17, 827-835

Awards

2012: Shangai Clinical Cancer Center Prize 2012

HUEBER Anne-Odile

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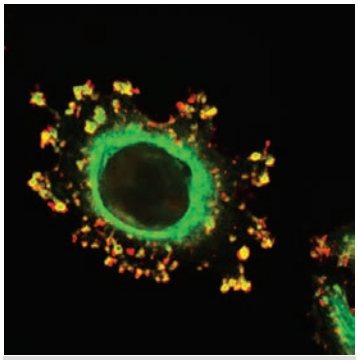
institut Valrose Biologie

Death receptors signaling and cancer therapy



Balance between life and death in colorectal cancer cell line

Alterations in the control of cell survival and death contribute to the pathogenesis of many human diseases. In particular, the dysfunction in the signaling cascade leading to the programmed cell death has been shown a key factor in the development of many types of cancer. Since the last ten years the lab is focus on the understanding of the role of the one of this apoptotic pathways, the one triggered by Fas upon its engagement by its ligand (FasL). Results in our laboratory show that triggering Fas signaling by sublethal doses of FasL can activate proteins with known survival functions (Akt and MAPK), and induce colorectal cancer (CRC) cell proliferation. Also, the evidence of Fas/FasL contribution in CRC metastasis is emerging. A multifaceted scenario has also been presented where CRC cells not only employ the anti-apoptotic and proliferative capacity of the Fas/FasL signaling for local growth but also utilize FasL to induce apotosis in hepatocytes to facilitate the liver metastasis. In addition, invasion of CRC cells and liver metastasis promoted by activating Fas with FasL have been shown dependent on oncogenic K-Ras. This thus links the Fas/FasL non-apoptotic signaling to major colorectal carcinogenesis pathways. Despite the fact that Fas signaling plasticity is central to the balance of life and death decision of the cell, the regulation of this versatility remains obscure. The PhD project will be part of the general focus on the lab: the understanding at a molecular level the versatility of Fas and its importance in the tumoral initiation and progression processes and thus the development of effective CRC therapies.

Selected Publications

1. Vesicles released by activated T cells induce both Fas-mediated RIP-dependent apoptotic and Fas-independent non-apoptotic cell deaths
   Koncz, G., Hancz, A., Chakrabandhu, K., Gogolak, P., Kerekes, K., Rajnavolgyi, E. and Hueber, AO.
   (2012) **Journal of Immunology** 189(6), 2815-2823
2. Palmitoylation of the TRAIL receptor DR4 confers an efficient TRAIL-induced cell death signaling
   Rossin, A., Derouet, M, Abdel Sater, F; and Hueber, A-O.
   (2010) **Biochemical J.** 419(1), 185-194.
3. The Extracellular Juxtamembrane Motif of Fas is Required for Fas-Glycosphingolipid Interaction and Fas-induced Cell Death
   Chakrabandhu, K., Huault, S., Garmy, N., Stebbe, E., Mailfert, S., Marguet, D., Fantini, J, and Hueber, A-O
   (2008) **Cell Death&Differentiation** 15(12), 1824-1837
4. The CD95 receptor: apoptosis revisited
   Marcus E. Peter, Ralph C. Budd, Julie Desbarats, Stephen M. Hedrick, Anne-Odile Hueber, M. Karen Newell, Laurie B. Owen, Richard M. Pope, Juerg Tschopp, Harald Wajant, David Wallach, Robert H., Wiltrout, Martin Zörnig, and David H. Lynch
   (2007) **Cell** 129(3), 447-450
5. Fas palmitoylation is required for efficient Fas-induced cell death
   K. Chabrandhu#, Z. Hérincs#, S. Huault, D. Britta, P. Ling, F. Conchonnaud, D. Marguet, H-T He, and A-O Hueber
   (2007) **The EMBO J.** 26(1), 209-220

Awards

2002: Cancerology Price Raymond Rosen

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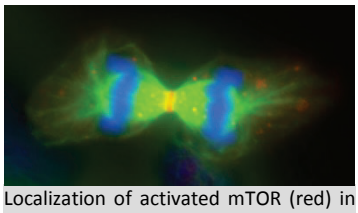
Regulatory mechanisms of gene expression in physiopathology



Localization of activated mTOR (red) in the midbody of telophase adrenocortical cancer mitotic cells. Green, beta-tubulin; blue, DAPI.

We use an approach that integrates molecular and cell biology, genomics, animal models and clinical investigations to advance our understanding of the mechanisms of gene expression regulation in health and disease, with a special focus in the development, function and pathology of the adrenal cortex.

Selected Publications

1. Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenocortical tumors.
   Custódio G, Parise GA, Kiesel FN, Komechen H, Sabbaga CC, Rosati R, Grisa L, Parise IZS, Pianovski MAD, Fiori CMCM, Ledesma JA, Barbosa JRS, Figueiredo FRO, Sade ER, Ibañez H, Arram SBI, Stinghen ST, Mengarelli LR, Figueiredo MMO, Carvalho DC, Avilla SGA, Woiski TD, Poncio LC, Lima GFR, Pontarolo R, Lalli E, Zhou Y, Zambetti GP, Ribeiro RC, Figueiredo BC.
   (2013) **J Clin Oncol** in press
2. Dkk3 is a component of the genetic circuitry regulating aldosterone biosynthesis in the adrenal cortex.
   El Wakil A, Bandulik S, Guy N, Bendahhou S, Zennaro M-C, Niehrs C, Mari B, Warth R, Barhanin J, Lalli E.
   (2012) **Hum Mol Genet (cover capture)** 21, 4922-4929
3. Increased Steroidogenic Factor-1 dosage triggers adrenocortical cell proliferation and cancer.
) Doghman M, Karpova T, Rodrigues GA, Arhatte M, De Moura J, Cavalli LR, Virolle V, Barbry P, Zambetti GP, Figueiredo BC, Heckert LL, Lalli E.
   (2007) **Mol Endocrinol** 21, 2968-2987
4. X-linked adrenal hypoplasia congenita is caused by abnormal nuclear localization of the DAX-1 protein.
   Lehmann SG*, Lalli E*, Sassone-Corsi P. (*Equal contribution)
   (2002) **Proc Natl Acad Sci USA (cover capture)** 99, 8225-8230
5. DNA binding and transcriptional repression by DAX-1 blocks steroidogenesis.
   Zazopoulos E*, Lalli E*, Stocco DM, Sassone-Corsi P. (*Equal contribution)
   (1997) **Nature** 390, 311-315

Awards

2008: »Cancer » prize of the French Academy of Medicine
2005: »Jayle » prize of the French Academy of Sciences

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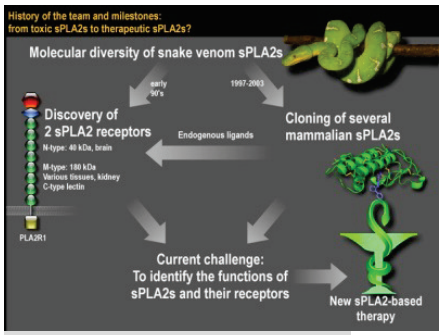
Molecular physiopathology of phospholipases A2 and their mediators



Milestones of the team and current challenges

Our team works on secreted phospholipases A2 (PLA2s), an emerging family of enzymes that hydrolyze phospholipids. Our recent work has led to the identification of novel biological functions of sPLA2s in both physiological and disease conditions including reproduction, inflammation, atherosclerosis, cancer and a rare human kidney disease.

Our current objective is to further depict the biological roles and mechanisms of action of sPLA2 in the above biological events and to identify novel functions for sPLA2s by using a combination of in vitro and in vivo experimental approaches. We are also working on the molecular properties of sPLA2s and PLA2R1 and the discovery of novel sPLA2 inhibitors using a combined approach based on biochemistry, bioinformatics and structural biology. Our work may pave the way to novel therapeutic avenues by targeting sPLA2s.

Selected Publications

1. Group X secreted phospholipase A2 limits the development of atherosclerosis in LDL receptor-null mice
   Ait-Oufella H, Herbin O, Lahoute C, Coatrieux C, Loyer X, Joffre J, Laurans L, Ramkhelawon R, Blanc-Brude O, Karabina SA, Girard CA, Payré C, Yamamoto K, Binder CJ, Murakami M, Tedgui A, Lambeau G.(co-last and corresponding author), Mallat Z.
   (2013) **Arterioscler. Thromb. Vasc. Biol.** 33, 466-473
2. Group X secreted phospholipase A2 proenzyme is matured by a furin-like proprotein convertase and releases arachidonic acid inside of human HEK293 cells
   Jemel I, Ii H, Oslund RC, Payre C, Dabert-Gay AS, Douguet D, Chargui K, Scarzello S, Gelb MH, Lambeau G
   (2011) **J. Biol. Chem.** 286, 36509-36521
3. Group X phospholipase A2 is released during sperm acrosome reaction and controls fertility outcome in mice
   Escoffier J, Jemel I, Tanemoto, A, Taketomi Y, Payré C, Coatrieux C, Sato H, Yamamoto K, Masuda S, Pernet-Gallay K, Pierre V, Hara S, Murakami M, De Waard M, Lambeau G (co-last author)Arnoult C
   (2010) **J. Clin. Invest.** 120, 1415-1428
4. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy
   Beck LH Jr, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, Klein JB, Salant DJ
   (2009) **N. Engl. J. Med.** 361, 11-21
5. Biochemistry and Physiology of Mammalian Secreted Phospholipases A2
   Lambeau G (co-last and corresponding author) and Gelb MH
   (2008) **Annu. Rev. Biochem.** 77, 495-520

Awards

2013: Louisiana State University Neuroscience Center of Excellence Award Lecture
2006: Pierre Desnuelle Prize Award of the French Academy of Sciences, Molecular and Cellular Biology section
1995: CNRS Bronze Medal

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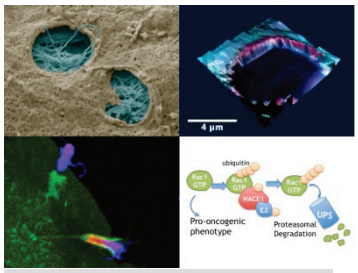
Microbial toxins in host pathogen interactions



Cellular effects of toxins targeting Rho GTPases

Rac1 and the other Rho proteins are small GTPases, which control all actin cytoskeleton dependent processes, such as adhesion, migration, cytokinesis and phagocytosis and are targeted by numerous bacterial virulence factors.
Our studies on the CNF1 toxin of uropathogenic E. coli have revealed a new mode of regulation of active Rac1 by ubiquitin-mediated proteasomal degradation. We have also defined the importance of the Rac1 signaling axis in the control of anti-microbial responses in addition to cell migration and cell invasion by pathogenic bacteria. We found that HACE1 catalyzes the ubiquitylation of the active form of Rac1 with major consequences on Rac1-dependent cell signaling and actin reorganization. Previous studies had established that the down-modulation of HACE1 triggers spontaneous late-onset cancer and kidney tumors in children. Our studies are aimed at clarifying the function of HACE1/Rac1 signaling axis in infection and cancer.
We are also studying the dynamic of large transcellular tunnels (TEM) in endothelial cells induced by cAMP- and RhoA-targeting toxins. Time-lapse video analysis has revealed that these tunnels open and close in less than 10 minutes, a dynamic controlled by a subset of I-BAR containing proteins (MIM and ABBA) that are endowed with the property to sense the curvature of membranes. We study other proteins involved in TEM dynamics.

Selected Publications

1. The E3 ubiquitin-ligase HACE1 catalyzes the ubiquitylation of active Rac1.
   Torrino S, Visvikis O, Doye A, Boyer L, Stefani C, Munro P, Bertoglio J, Gacon G, Mettouchi A and Lemichez E
   (2011) **Dev Cell** 21, 959-65
2. cAMP signaling by anthrax edema toxin induces transendothelial cell tunnels, which are resealed by MIM via Arp2/3-driven actin polymerization
   Maddugoda MP, Stefani C, Gonzalez-Rodriguez D, Saarikangas J, Torrino S, Janel S, Munro P, Doye A, Prodon F, Aurrand-Lions M, Goossens PL, Lafont F, Bassereau P, Lappalainen P, Brochard F and Lemichez E
   (2011) **Cell Host & Microbe** 10, 464-474
3. Pathogen-derived effectors trigger protective immunity via activation of the Rac2 enzyme and the IMD or Rip kinase signaling pathway.
   Boyer L, Magoc L, Dejardin S, Cappillino M, Paquette N, Hinault C, Charriere GM, Ip WK, Fracchia S, Hennessy E, Erturk-Hasdemir D, Reichhart JM, Silverman N, Lacy-Hulbert A and Stuart LM
   (2011) **Immunity** 35, 536-549
4. Escherichia coli producing CNF1 toxin hijacks Tollip to trigger Rac1-dependent cell invasion
   Visvikis O, Boyer L, Torrino S, Doye A, Lemonnier M, Lorès P, Rolando M, Flatau G, Mettouchi A, Bouvard D, Veiga E, Gacon G, Cossart P and Lemichez E
   (2011) **Traffic** 12, 579-590
5. Laminin-binding integrins induce Dll4 expression and Notch signaling in endothelial cells.
   Estrach S, Cailleteau L, Franco CA, Gerhardt H, Stefani C, Lemichez E, Gagnoux-Palacios L, Meneguzzi G and Mettouchi A.
   (2011) **Circ Res** 109, 172-182

Awards

1997: Human Frontier Science Program

LEOPOLD Pierre

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Genetics and Physiology of Growth in *Drosophila*

Individuals develop and reach final sizes according to both local (genetic) and environmental (for ex. nutrition) cues.

Animal growth is a complex process, linked to the developmental program in order to form adults with proper size and proportions. Genetics is an important determinant of growth. In addition, organisms use adaptative responses allowing modulating the size of individuals according to environmental cues, among which nutrition. Therefore, a sophisticated crosstalk between local and global cues is at play for the ultimate determination of individual size.
Our projects use Drosophila Genetics, Physiology and Cell Biology approaches to decipher the coupling between the environment and the developmental program that determines the final size of an organism. Our specific aims are the following:
1- understanding how insulin/IGF signaling is modulated by nutrition, and in particular identifying the humoral connection between the tissues involved in sensing the nutrients and those producing insulin-like peptides.
2- understanding the molecular basis for growth arrest and the coordination between tissue growth and the developmental timing.
3- Understanding the mechanisms allowing nutrient sensing in the brain and identifying the neuronal pathways controlling feeding according to nutritional cues.
4- Understanding the modulation of simple innate behaviors such as temperature or light preference by developmental cues.

Selected Publications

1. Secreted peptide Dilp8 coordinates Drosophila tissue growth with developmental timing
   Colombani, J. Andersen, D. S. Leopold, P.
   (2012) **Science** 336, 582-5
2. The steroid hormone Ecdysone controls systemic growth by repressing dMyc function in Drosophila fat cells.
   Delanoue, R. Slaidina, M. Léopold, P.
   (2010) **Dev. Cell** 18, 1012-1021
3. A Drosophila insulin-like peptide promotes growth during nonfeeding states
   Slaidina, M. Delanoue, R. Gronke, S. Partridge, L. Leopold, P.
   (2009) **Dev. Cell** 17, 874-84
4. Remote control of insulin secretion by fat cells in Drosophila
   Geminard, C. Rulifson, E. J. Leopold, P.
   (2009) **Cell Metab.** 10, 199-207
5. Drosophila and the genetics of the internal milieu
   Leopold, P. Perrimon, N.
   (2007) **Nature** 450, 186-188

Awards

2011: Research Prize Inserm
2010: ERC Advanced grant Award
2009: French Academy Prize
2008: Elected EMBO Member

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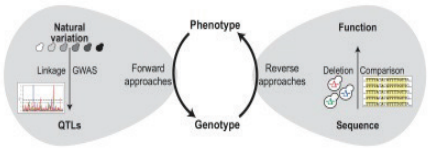
Population genomics and complex traits



Different routes from genotype to phenotype. Complementary forward and reverse genetic approaches to understanding cellular traits

Most human traits, including many diseases, are regulated by multiple interacting quantitative trait loci (QTLs). Dissecting the genetic mechanisms underlying this phenotypic variation is a major challenge. In our lab, we use the budding yeast, S. cerevisiae, as model to dissect the genetic architecture of multiple traits related to ageing and cancer. We are currently co-leading a major resequencing effort that aims to release high quality genomes for 1002 natural S. cerevisiae strains. This large sample size of full genome sequences coupled to high-throughput phenotyping will provide powerful opportunities for genome wide association studies. The PhD candidate will exploit yeast natural variation to investigate cell signaling pathways. For example, we previously found that widespread natural sequence variation in RAS signalling pathways contribute to quantitative differences in ageing and general stress response. We will use population genomics datasets to understand how the RAS signalling pathway vary and become misregulated in some diverged lineages. This project is suitable for a person either with computational biology background or wet lab experience. In conclusion, we aim to elucidate essential aspects of individual variation among yeast strains with the major goal of understanding the genetic mechanisms underlying complex traits and human diseases.

Selected Publications

1. High quality de novo sequencing and assembly of the Saccharomyces arboricolus genome
   1. Liti G, Nguyen Ba AN, Blythe M, Müller CA, Bergström A, Cubillos FA, Dafhnis-Calas F, Khoshraftar S, Malla S, Mehta N, Siow CC, Warringer J, Moses AM, Louis EJ and Nieduszynski CA
   (2013) **BMC Genomics** 14(1), 1-14
2. Advances in quantitative trait analysis in yeast.
   Liti G and Louis EJ
   (2012) **PLoS Genetics.** 8(8), e1002912., 1-7
3. Revealing the genetic structure of a trait by sequencing a population under selection.
   Parts L, Cubillos FA, Warringer J, Jain K, Salinas F, Bumpstead SJ, Molin M, Zia A, Simpson JT, Quail MA, Moses AM, Louis EJ, Durbin R and Liti G
   (2011) **Genome Research** 21(7), 1131-8
4. Assessing the Complex Architecture of polygenic traits in yeast
   Cubillos FA, Billi E, Zörgö E, Parts L, Fargier P, Omholt S, Blomberg A, Warringer J, Louis EJ and Liti G.
   (2011) **Molecular Ecology** 20(7), 1401-13
5. Population genomics of domestic and wild yeasts.
   Liti G, Carter DM, Moses AM, Warringer J, Parts L, James SA, Davey RP, Roberts IN, Burt A, Koufopanou V, Tsai IJ, Bergman CM, Bensasson D, O'Kelly MJT, van Oudenaarden A, Barton DBH, Bailes E, Nguyen Ba AN, Jones M, Quail MA, Goodhead I, Sims S, Smith F, Blomberg A, Durbin R and Louis EJ
   (2009) **Nature** 19; 458(7236), 337-41

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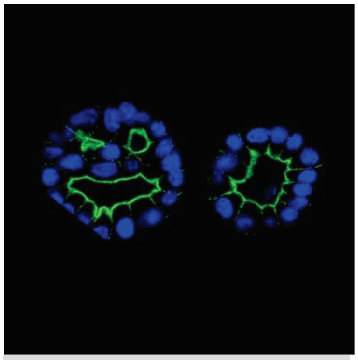
Arf proteins, cell morphology and membrane transport



Acini of breast cancer cell line in 3D cell culture system

A fundamental question in cell biology is to understand how epithelial cells organize collectively as monolayers, multilayers, tubules or acinis to form a large variety of organs such as lungs, intestine, kidney, mammary glands, etc. It is also of interest in the biology of epithelial cancers since primary tumor development is associated with the loss of the epithelial collective organization and the establishment in cell motility and invasive properties. By combining in vitro reconstitution of epithelial organization using 3D cell culture systems, analyses of human tumor specimen and clinical data we are addressing the role of the small G protein Arf6 and its exchange factor EFA6 (Exchange Factor for Arf6) in breast cancer development. We are currently focusing our studies on a particular breast cancer subtype for which no specific treatment is available. Future directions of this project include the characterization of EFA6/Arf6 associated signaling pathways, which are deregulated in breast cancer development, the search for specific pharmacological compounds directed against in-house identified targets and new breast cancer animal models.

Selected Publications

1. Arf6 negatively controls the rapid recycling of the beta2 adrenergic receptor
   Macia, E., Partisani, M., Paleotti, O., Luton, F. and Franco, M.
   (2012) **J. Cell Science** 125, 4026-35
2. USP9x-mediated deubiquitination of EFA6 regulates de novo tight junction assembly
   Theard, D., Labarrade, F., Partisani, M., Milanini, J., Sakagami, H., Fon, E. A.,Wood, S.A., Franco, M., and Luton F.
   (2010) **Embo J.** 29, 1499-509
3. EFA6 facilitates the assembly of the tight junction by coordinating an Arf6-dependent and-independent pathway
   Klein, S., Partisani M., Franco, M. and Luton, F.
   (2008) **J. Biol. Chem.** 283, 30129-30138
4. The PH domain of the Arf6-specific exchange factor EFA6 localizes to the plasma membrane by interacting with PI(4,5)P2 and F-actin
   Macia, E., Partisani M., Favard, C., Mortier, E., Zimmermann, P., Carlier, M.F., Gounon, P., Luton, F. and Franco, M.
   (2008) **J. Biol. Chem.** 283, 19836-19844

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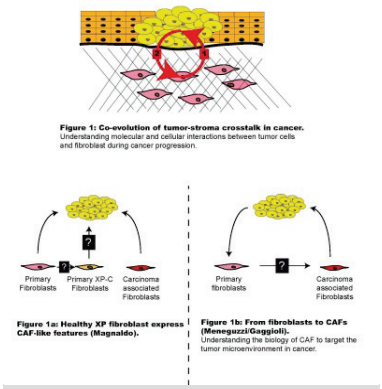
Genetics and epigenetics in the ephysiopathology of epithelial cancers



Co-evolution of tumor-stroma crosstalk in cancer

Epithelial cancers arise with age, among which, squamous cell carcinomas (SSCs) are by far the most common and generally lethal in human. Invasiveness of SCCs depends on reciprocal signaling between the tumor cells and their microenvironment (figure 1). In primary tumors, cancer cells are immersed in a complex microenvironment network including fibroblasts. Malignant eptithelial secrete cytokines and growth factors that activate fibroblasts towards acquisition of the Carcinoma Associated Fibrolast (CAF) phenotype. In turn, CAF promote carcinoma cells invasion and malignancy. Our main objective is to unravel molecular pathways bridging epithelial to stroma cells in the context of carcinogenesis.
By innovative experimental settings of cancer modeling in vitro and vivo, we aim at determining the signaling pathways associated with epithelial carcinogenesis/stroma activation and, subsequently, initiate suitable therapeutic routes. We have developed two complementary system models, based on either i-) healthy skin cells isolated from rare patients suffering from the cancer prone genetic syndrome Xerodema pigmentosum (T. Magnaldo), or ii-) cancer associated fibroblasts and cancer cell lines established from human sporadic tumors (C. Gaggiolli).

Selected Publications

1. Preclinical corrective gene transfer in xeroderma pigmentosum human skin stem cells.
   Warrick E, Garcia M, Chagnoleau C, Chevallier O, Bergoglio V, Sartori D, Mavilio F, Angulo JF, Avril MF, Sarasin A, Larcher F, Del Rio M, Bernerd F, Magnaldo T. 2012
   (2012) **Mol Ther** 20, 798-807
2. PTCH1 +/- dermal fibroblasts isolated from healthy skin of Gorlin syndrome patients exhibit features of carcinoma associated fibroblasts.
   Overexpression of matrix metalloproteinase 1 in dermal fibroblasts from DNA repair-deficient/cancer-prone xeroderma pigmentosum group C patients.
   (2008) **Oncogene** 27, 5223-5232
3. Confluence switch signaling regulates ECM composition and the plasmin proteolytic cascade in keratinocytes
   Botta A, Delteil F, Mettouchi A, Vieira A, Estrach S, Négroni L, Stefani C, Lemichez E, Meneguzzi G, Gagnoux-Palacios L
   (2012) **J Cell Sci.** 125, 4241-4252
4. ROCK and JAK1 signaling cooperate to control actomyosin contractility in tumor cells and stroma
   Sanz-Moreno V, Gaggioli C, Yeo M, Albrengues J, Wallberg F, Viros A, Hooper S, Mitter R, Féral CC, Cook M, Larkin J, Marais R, Meneguzzi G, Sahai E, Marshall CJ
   (2011) **Cancer Cell** 20, 229-245
5. Fibroblast-led collective invasion of carcinoma cells with differing roles for RhoGTPases in leading and following cells
   Gaggioli C, Hooper S, Hidalgo-Carcedo C, Grosse R, Marshall JF, Harrington K, Sahai E
   (2007) **Nat Cell Biol** 9, 1392-1400

Awards

1999: Annual Congress of Dermatological Research (Magnaldo)
2007: European Society of Dermatological Research (Magnaldo)
2005: Prix jeune chercheur 2005 fondation Bettencourt-Schueller

MARIE Hélène

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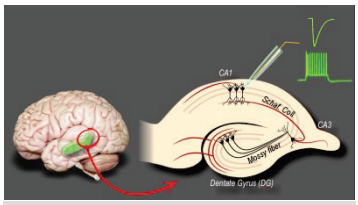
Molecular Mechanisms of Neuronal Plasticity in Health and Disease



Electrophysiological recordings of hippocampal neurons from acute slices of Alzheimer's disease mice to investigate neuronal dysfunction

Memory is a fundamental brain function allowing an individual to adapt to his environment, to create his own and unique history. Identifying the cellular and molecular mechanisms that govern this process is one of the great challenges facing the neuroscientific community. Our team is working to elucidate these mechanisms and how they become defective in memory disorders such as in Alzheimer's disease. Some of our recent work focused on the role of the transcription factor CREB in the molecular mechanisms of memory. We studied the implication of CREB by coupling behavioral, biochemical and electrophysiological analyses. We developed in vivo viral-mediated expression of specific proteins to evaluate their implication in memory processes.

We also study transgenic mouse models of Alzheimer's disease to characterize defects in synaptic plasticity of the hippocampus, a structure primarily affected in this disease. Using electrophysiology, we record hippocampal glutamatergic neurons to characterize in depth their functional deficits. We complete our functional analysis with a biochemical analysis of the hippocampus. We also evaluate the memory deficits of these models by behavioral studies. Finally, based on our results, we test new therapeutic strategies that are designed to prevent or delay this loss.

Selected Publications

1. CREB is necessary for synaptic maintenance and learning-induced changes of the AMPA receptor GluA1 subunit.
   Middei S, Houeland G, Cavallucci V, Ammassari-Teule M, D'Amelio M, and Marie H.
   (2013) **Hippocampus** 23, 488-499
2. Computational modeling of the effects of amyloid-beta on release probability at hippocampal synapses.
   Romani A, Marchetti C, Bianchi D, Leinekugel X, Poirazi P, Migliore M, Marie H.
   (2013) **Front. Comp. Neurosci.** 7, 1-7
3. Hippocampal synaptic plasticity in Alzheimer's disease: what have we learned so far from transgenic models?
   Marchetti C, Marie H.
   (2011) **Rev Neurosci.** 22, 373-402
4. Caspase-3 triggers early synaptic dysfunction in a mouse model of Alzheimer's Disease.
   D'Amelio M, Cavallucci V., Middei S., Marchetti C., Pacioni S., Ferri A., Diamantini A., De Zio D., Carrara P., Battistini L., Moreno S., Bacci A., Ammassari-Teule M., Marie H., Cecconi F.
   (2011) **Nat Neurosci.** 14, 69-76
5. Chronic NGF deprivation results in mild deficits in hippocampal CA1, but severe deficits in dentate gyrus glutamatergic synaptic plasticity
   Houeland G., Romani A., Marchetti C., Amato G., Capsoni S., Cattaneo A., Marie H.
   (2010) **J. Neurosci.** 30, 13089-13094

Awards

2010: Young Investigator ATIP-AVENIR Award (France)
2009: New Investigator Alzheimer Association Grantee (USA)
2007: NARSAD Young Investigator Award (USA)

MARTIN Stéphane

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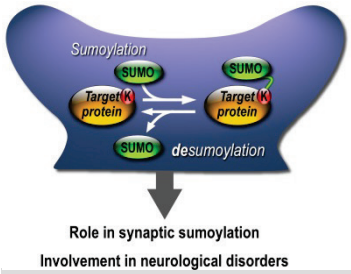
Activity-dependent dynamics and roles of synaptic sumoylation



Investigating the function and dysfunction of synaptic sumoylation

Sumoylation is a covalent and reversible enzymatic process that involves the conjugation of a small protein called SUMO to specific lysine residues of target proteins. Sumoylation was initially thought to target nuclear proteins where it is an essential regulator of their function. However, we discovered that multiple synaptic proteins are substrates for sumoylation (Martin et al., 2007, Nature). This raised the possibility that sumoylation, like other post-translational modifications (phosphorylation, ubiquitination…) play important roles in brain function. Intriguingly, among identified SUMO substrates are several proteins directly linked to neurological disorders.

Our focus is now on synaptic sumoylation, a key posttranslational modification for many proteins including some involved in brain disorders. Using biochemical and state-of-the-art imaging techniques we are investigating the regulatory mechanisms of the SUMO pathway and functionally characterizing novel sumoylated proteins involved in intellectual disabilities.

The wide range of state-of-the-art expertise available (proteomic, animal and imaging facilities) within the IPMC as well as the proximity of the Labex groups provide exceptional added values to our projects and we are confident that we will make real and meaningful advances in this competitive field of Neuroscience.

Selected Publications

1. Activity-dependent regulation of the sumoylation machinery in rat hippocampal neurons.
   Loriol C, Khayachi A, Poupon G, Gwizdek C and Martin S.
   (2013) **Biol Cell** 105, 30-45
2. Developmental regulation and spatiotemporal redistribution of the sumoylation machinery in the rat Central Nervous System.
   Loriol C, Parisot J, Poupon G, Gwizdek C and Martin S.
   (2012) **PLoS ONE** 7, e33757
3. Emerging extranuclear roles for protein sumoylation in neuronal function and dysfunction.
   Martin S, Wilkinson K, Nishimune A and Henley JM.
   (2007) **Nature Reviews Neuroscience** 8, 948-959
4. Sumoylation Regulates Kainate Receptor Mediated Synaptic Transmission.
   Martin S, Nishimune A, Mellor J and Henley JM.
   (2007) **Nature** 447, 321-325

Awards

2012: ATIP+ CNRS
2009: Bettencourt-Schueller Foundation Prize
2008: ATIP CNRS

NAHON Jean-Louis

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Group Leader IPMC
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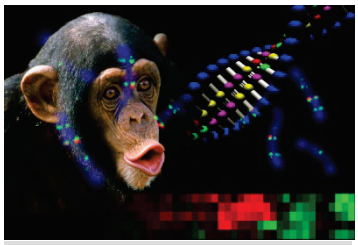
Genomics and Evolution in Neuroendocrinology (GENE)



Evolution, structure and function of the primate-specific genes. From gene sequencing (DNA helix) til functional characterization (biochip)

Diseases linked to energy intake-storage disequilibria are a major challenge for human health care. We are investigating the structural evolution, regulation and functions of genes involved in the central control of energy balance in mammals. Our favorite model concerns a peptide called “melanin-concentrating hormone” (MCH). Two relevant exemples of our research projects are presented below.

1. Central regulation of neuroendocrine functions

Two MCH receptors (MCHR1 and MCHR2) have been found in humans whereas only MCHR1 has been identified in rodents. In order to study MCH signaling in an animal model mimicking the human situation we have generated a transgenic mouse model expressing human MCHR2 (KI-hMCHR2 mouse). We are currently analyzing the expression profile and phenotypes of homozygotic KI-hMCHR2 mice.

2. Genomics and Evolution

By combining Molecular Biology, Phylogenetic and Bioinformatic techniques we have proposed an original scenario for the emergence in Hominoid lineage of two “chimaeric” genes, named PMCHL1 and PMCHL2. These “chimaeric” genes display differential expression in the human brain. One of our major objectives is to unravel their functional relevance in higher Primates. We are also investigating putative association between expression of the “primate-specific” genes and etiology of metabolic disorders and neurodegenerative diseases.

Selected Publications

1. Melanin-concentrating hormone regulates beat frequency of ependymal cilia and ventricular volume.
   Conductier G*, Brau F*, Viola A*, Langlet F, Ramkuma N, Dehouck B, Lemaire T, Chapot R, Lucas L, Rovère C, Maitre P, Hosseiny S, Petit-Paitel A, Adamantidis A, Lakaye B, Risold PY, Prévot V**, Meste O**, Nahon JL**§, Guyon A**§
   (2013) **Nature Neurosci** doi: 10.1038/nn.3401, 1-3
2. Variations in circulating inflammatory factors are related to changes in calorie and carbohydrate intakes early in the course of surgery-induced weight reduction.
   Dalmas E, Rouault C, Abdennour M, Rovere C, Rizkalla S, Bar-Hen A, Nahon JL, Bouillot JL, Guerre-Millo M, Clément K, Poitou C. (2011) **Am J Clin Nutr.** 94, 450-458
3. Genes regulated in MPTP-treated macaques and human Parkinson’s disease suggest a common signature in prefrontal cortex.
   Storvik M*, Arguel M.-J.*, Schmieder S., Delerue-Audegond A., Li Q., Qin C., Vital A., Bioulac B., Bross C.E., Wong G., Nahon JL **, Bezard E. ** (2010) **Neurobiol. Dis.** 38, 386-394
4. Glucose inhibition persists in hypothalamic neurons lacking tandem-pore K+ channels.
   Guyon A, Tardy MP, Rovère C, Nahon JL**, Barhanin J**, Lesage F. **
   (2009) **J Neurosci.** 29, 2528-2533
5. Birth of two chimeric genes in the Hominidae lineage
   Courseaux A. and Nahon J.L
   (2001) **Science (Human Genome Issue)** 291, 1293-1297

Awards

2012: Prime d’Excellence Scientifique -CNRS (JLN)
2012: Danone Research Award (GC)
2010: Société Française de Nutrition (GC)
2009: Prix de la Société de Neuroendocrinologie (GC)

NOSELLI Stéphane

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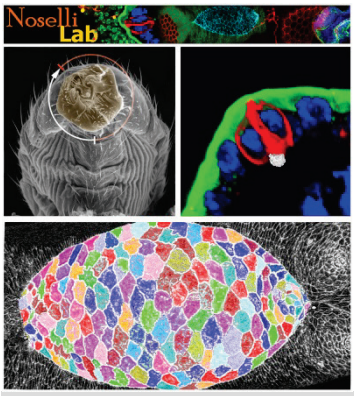
institut Valrose Biologie

Epithelial morphogenesis and left-right asymmetry in *Drosophila*



Epithelial morphogenesis, cell migration and left-right asymmetry in Drosophila

Using Drosophila, our team made several original contributions leading to the emergence of new fields (Dorsal closure, JNK, Jak/Stat, novel roles of ECM, L/R asymmetry). The diversity of biological questions studied provides an exciting scientific environment, with more than 40 students and post-docs trained.

JNK, Dorsal Closure (DC), reprogramming: our team identified the physiological role of the conserved JNK pathway, controlling epithelial morphogenesis during DC and cell reprogramming to release tissue tension. Current work characterizes novel JNK target genes and the mechanisms of cell reprogramming.

Extracellular matrix, Jak/Stat, cell invasion: we co-discovered the Drosophila Jak/Stat receptor and its role in cell migration during oogenesis. Our current results reveal a novel and complex assembly of basement membrane BM, redefining its role in tissue homeostasis and signaling. We also reveal a novel role of specific blood cells in matrix formation important for stem cell niche control.

Left-Right asymmetry: we established Drosophila as a L/R model, through the identification of the conserved Myosin ID gene (MyoID). Recent work showed a coupling between L/R patterning and apoptosis, and identified HOX/Abd-B as a 'master' gene controlling L/R asymmetry. Our current work studies the coupling of L/R and PCP patterning as well as characterizing novel L/R asymmetry genes.

Selected Publications

1. Drosophila Left/Right asymmetry establishment is controlled by the Hox gene Abdominal-B
   Coutelis JB, Géminard C, Spéder P, Suzanne M, Petzoldt A and Noselli S.
   (2013) **Dev Cell** 24, 89-97
2. Coupling of apoptosis and L/R patterning controls stepwise organ looping
   Suzanne, M., Petzoldt, A.G., Spéder, P., Coutelis, J.B., Steller, H. and Noselli, S
   (2010) **Curr Biol** 20, 1173-1178
3. JNK signalling controls remodelling of the segment boundary through cell reprogramming during Drosophila morphogenesis
   Gettings M, Serman F, Rousset R, Bagnerini P, Almeida L, Noselli S.
   (2010) **PLoS Biol** 8, 1000390
4. Type ID unconventional myosin controls left-right asymmetry in Drosophila
   Spéder*, P., Adam*, G. & Noselli, S
   (2006) **Nature** 440, 803-807
5. hemipterous encodes a novel Drosophila MAP kinase kinase, required for epithelial cell sheet movement
   Glise, B., Bourbon, H., and Noselli, S
   (1995) **Cell** 83, 451-461

Awards

2013: Grand Prix Mottart, Académie des Sciences
2008: CNRS Silver Medal
2011: EMBO Young Investigator Program (EMBO YIP)
1999: ATIP CNRS, Developmental Biology
1998: CNRS Bronze Medal

PANABIERES Franck

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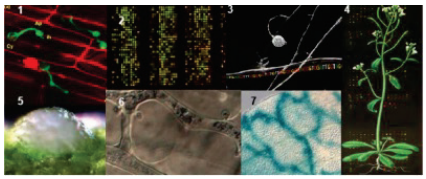
Plant oomycete interactions



Research is conducted on both plant and pathogen, using a multi-faceted approach from cell biology to functional genomics and biochemistry

Oomycetes are eukaryotic microorganisms that include severe plant pathogens, and then constitute a major threat to agriculture and environment worldwide.Despite similar physiological and ecological traits shared with fungi, oomycetes display phylogenetic affinities with diatoms and brown algae among Chromalveolates, that include dinoflagellates and several animal pathogens (Plasmodium, Toxoplasma, Theileria…). As a consequence of this taxonomical position, most traditional fungicide molecules are generally poorly efficient, because they have been developed against true pathogenic fungi. In addition, adaptive potential of oomycetes in response to their environment leads to a rapid breakdown of varietal resistances. So, the development of integrated management strategies that would be more efficient and environmentally friendly implies a better knowledge on the mechanisms that govern oomycete physiology and pathogenicity .
In this context, our team constructs multidisciplinary strategies to decipher the molecular dialog occurring between the oomycete pathogen and its plant host. We develop functional genomics approaches that rely on complete oomycete and plant genomes. They allow defining the interaction transcriptome from both partners and identifying key regulators, as well as identifying molecules that stimulate plant innate defense mechanisms.

Selected Publications

1. The Phytophthora parasitica RXLR effector Penetration-Specific Effector 1 favours Arabidopsis thaliana infection by interfering with auxin physiology.
   Evangelisti E, Govetto B, Minet-Kebdani N, Kuhn ML, Attard A, Ponchet M, Panabières F, Gourgues M
   (2013) **New Phytol** Apr 17. doi: 10.1111/nph.12270. , [Epub ahead of print].
2. Ecosystem screening approach for pathogen-associated microorganisms affecting host disease
   Galiana E, Mura C, Marais A. Industri B, Arbiol G, Ponchet M
   (2011) **App Environ Microbiol** 77, 6069-6075
3. An Arabidopsis (malectin-like) leucine-rich repeat receptor-like kinase contributes to downy mildew disease.
   Hok S, Danchin EG, Allasia V, Panabières F, Attard A, Keller H
   (2011) **Plant Cell Environ** 34, 1944-1957
4. The immediate activation of defense responses in Arabidopsis roots is not sufficient to prevent Phytophthora parasitica infection.
   Attard A, Gourgues M, Callemeyn-Torre N, Keller H
   (2010) **New Phytol** 187, 449-460
5. Cellular and molecular characterization of Phytophthora parasitica appressorium mediated penetration.
   Kebdani N, Pieuchot L, Deleury E, Panabières F, Le Berre JY, Gourgues M
   (2010) **New Phytol** 185, 248-257

POIRIE Marylène

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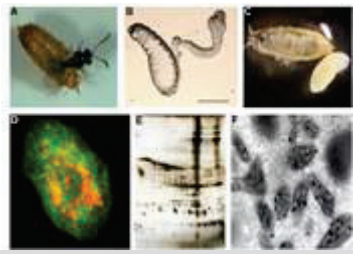
Evolution and Specificity of Multitrophic Interactions (ESIM)



L. boulardi wasp: emerging adult (A) larvae (C) venom gland (B). RhoGAP toxin in host hemocytes (D) on venom vesicles (F). 2D of venom (E).

The team mainly focuses on the immune interactions between insects hosts (Drosophila species) and their parasitoid wasps (Hymenoptera) as a model of immune suppressive eukaryotic parasites. We aim to characterize at the molecular and cellular level both the molecules/mechanisms involved in parasitoid virulence and those responsible for host resistance, as well as to identify the bases of the specificity of the interaction. Resistance may be linked with signaling networks involved in hemocyte proliferation/differentiation. Parasitoid virulence is achieved through injection of venom components, notably extra-cellular RhoGAPs toxins that are internalized inside host hemocytes and target Rac proteins. The transport of the RhoGAPs inside hemocytes through recently identified venom vesicles (venosomes) and the nature of the involved receptors is one of our main subject area. Evolutionary aspects of these interactions lie also at the heart of the research undertaken.
We also recently developed research on the immune components in a new insect model, the pea aphid. Thanks to its clonal reproduction and long-lasting symbioses with bacteria, this model allows us to finely address the question of how symbionts can shape the immunity of their host, in the context of the link between immunity and metabolism.

Selected Publications

1. Tracing back the nascence of a new sex determination pathway to the ancestor of bees and ants.
   Schmieder S, Colinet C and Poirié M.
   (2012) **Nat. Commun.** 3, 895
2. Extracellular superoxide dismutase in insects: characterization, function and inter-specific variation in parasitoid wasps' venom.
   Colinet D, Cazes D, Belghazi M, Gatti JL, Poirié M.
   (2011) **J Biol Chem** 286(46), 40110-21
3. Colinet D., Schmitz A., Cazes D., Gatti JL, Poirié M. The origin of intraspecific variation of virulence in an eukaryotic immune suppressive parasite.
   Colinet D, Schmitz A, Cazes D, Gatti JL, Poirié M.
   (2010) **PLoS Pathog** 6(11) , e1001206.
4. Variation of Leptopilina boulardi success in Drosophila hosts: what is inside the black box?
   Dubuffet A, Colinet D, Anselme C, Dupas S, Carton Y and Poirié M.
   (2009) **Adv Parasitol** 70, 148-188
5. Convergent use of RhoGAP toxins by eukaryotic parasites and bacterial pathogens.
   Colinet D, Schmitz A, Depoix D, Crochard D and Poirié M.
   (2007) **PloS Pathog** 3(12), e203

Awards

2009: Prize of the French National Academy of Sciences in Integrative Sciences – Balachowski prize of Entomology
2009-2011: "Jeune Equipe INRA " - thème "Immune interactions between insect hosts and insect parasitoids : molecular, cellular and evolutionary aspects"

RASSOULZADEGAN Minoo

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RNA-mediated epigenetic heredity

10 days old, Kit mutants and paramutants progenies (background n Agouti mouse strain).

Our laboratory established the first mouse models of an epigenetic heredity distinct from the Mendelian rules. Small noncoding (snc) RNA molecules with sequence homology to the transcript were shown to act as transgenerational signals leading to the establishment of the modified phenotypes. Several of the observed variants reproduce human pathologies with a clear familial distribution but without a Mendelian determinant identified, such as heart hypertrophy and a form of diabetes. The modified phenotypes independently observed for three loci, Kit, Sox9 and Cdk9 result from a transcriptional modulation of the locus activity. Our current work aims at the establishment of the molecular mechanisms of the variation using two types of models, the early embryo in which paramutation is triggered by microinjection of the signalling RNA and identification of the vectors in transmission of the acquired characters, in which we have demonstrated a response to the same sncRNA identical to that observed in paramutation. The analysis focuses on the following parts of the signalling cascade: a requirement for cytosine methylation in the inducing sncRNAs by the RNA methyltransferase Dnmt2. We are also exploring the possibility of RNA-signalling and transgenerational maintenance of other phenotypes including comportmental variations for which evidence of paternal inheritance has been established.

Selected Publications

1. RNA-Mediated Epigenetic Heredity Requires the Cytosine Methyltransferase Dnmt2.
   Kiani J, Grandjean V, Liebers R, Tuorto F, Ghanbarian H, Lyko F, Cuzin F, Rassoulzadegan M.
   (2013) **PLoS Genet.** May;9(5): e1003498.
2. Novel small noncoding RNAs in mouse spermatozoa, zygotes and early embryos.
   Kawano M, Kawaji H, Grandjean V, Kiani J, Rassoulzadegan M.
   (2012) **PLoS One.** ; 7 (9), e44542.
3. The miR-124-Sox9 paramutation: RNA-mediated epigenetic control of embryonic and adult growth.
   Grandjean V, Gounon P, Wagner N, Martin L, Wagner KD, Bernex F, Cuzin F, Rassoulzadegan M.
   (2009) **Development.** Nov;136(21), 3647-55.
4. RNA induction and inheritance of epigenetic cardiac hypertrophy in the mouse.
   Wagner KD, Wagner N, Ghanbarian H, Grandjean V, Gounon P, Cuzin F, Rassoulzadegan M.
   (2008) **Dev Cell.** Jun;14(6), 962-9.
5. RNA-mediated non-mendelian inheritance of an epigenetic change in the mouse.
   Rassoulzadegan M, Grandjean V, Gounon P, Vincent S, Gillot I, Cuzin F.
   (2006) **Nature.** May 25;441(7092): 469-74.

Awards

2011: Prix Doyen Lepine de la ville de Nice
2009: Elected EMBO Member
1987: Prix FRM (Biologie Moléculaire)
1985: Prix Lacassagne

RICCI Jean-Ehrland

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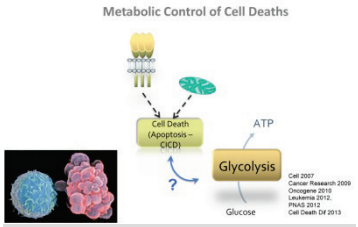
Metabolic control of cell deaths



We are investigating how targeting glucose metabolism can enhance cell death (apoptotic and a non-apoptotic forms of death called CICD)

The main drawback of chemotherapies is their lack of specificity toward cancer cells. In addition cancer cells are very diverse. However they are sharing a few commune features including escape from cell death and a particular metabolism (so-called the Warburg effect).

In our team we aim to understand how the modulation of cancer cell metabolism could improve therapies (increase cell death) and modulate anticancer immune response. We demonstrated that the inhibition of glucose metabolism can not only enhances the chemotherapeutic toxicity but it can also allow the immune system to react against the tumor (leading to an anti-cancer immune response that participates in a long term protection of the patient against the tumor). In collaboration with chemists, we are now developing original glycolytic inhibitors to enhance this effect and increase its specificity. In parallel we observed that out of the 10 glycolytic enzymes needed for glucose metabolism, one (GAPDH) is very particular as it can help the cell to escape non apoptotic from of death. We are deciphering its mechanisms of action.

Our research is conducted in cell lines, pre-clinical models as with patient samples (in close relation with the clinical service of Nice and Monaco hospitals).

Selected Publications

1. GAPDH binds active Akt leading to Bcl-xL increase and escape from caspase-independent cell death.
   1. Jacquin M.A., Chiche J., Zunino B., Bénéteau M., Meynet O., Pradelli L.A. Marchetti S., Cornille A., Carles M. and J-E Ricci.
   (2013) **Cell Death Differ** in press, in press
2. The combination of glycoysis inhibition with chemotherapy results in an antitumor immune response.
   2. Bénéteau M., Zunino B., Jacquin M.A., Chiche J., Meynet O., Pradelli L.A., Marchetti S., Cornille A., Carles M. and J-E Ricci.
   (2012) **Proc Natl Acad Sci U S A.** 109, 20071-6
3. Cancer metabolism: current perspectives and future directions.
   4. Munoz-Pinedo C, El Mjiyad N and J-E Ricci
   (2012) **Cell Death and Disease** 3, e248
4. Glycolysis inhibition targets Mcl-1 to restore sensitivity of lymphoma cells to ABT-737-induced apoptosis.
   3. Meynet O., Bénéteau M., Jacquin M.A., Pradelli L.A., Cornille A., Carles M. and J-E Ricci.
   (2012) **Leukemia** 26, 1145-7
5. Glycolysis inhibition sensitizes tumor cells to death receptors-induced apoptosis by AMP kinase activation leading to Mcl-1 block in translation.
   10. Pradelli, L.A., M. Beneteau, C. Chauvin, M.A. Jacquin, S. Marchetti, C. Munoz-Pinedo, P. Auberger, M. Pende, and J.E. Ricci.
   (2010) **Oncogene** 29, 1641-52

Awards

2012: Award “Arloing, Courmont” from Pasteur Institute in Lyon, France;
2010: Award from the 7th EU Workshop on Cell Death;
2006: Awarded of the INSERM/AVENIR program

ROBICHON Alain

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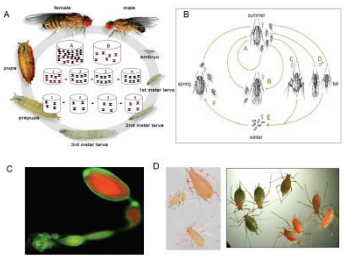
Genome Plasticity and Environment



Epigenetic variation in drosophila m.(A) and aphid A pisum (B-D)

Up to recently, the dogma postulates that evolution and genome plasticity are written in the genetic code. In contrast, many recent reports describe that identical genomes might lead to different heritable characters depending on environmental factors, thus opposing genetic determinism and epigenetic response. Surprisingly and of considerable interest, we found that the A. pisum that alternates clonality and sexuality, generates a repertoire of phenotypic variants. We recently found solid evidence for a role of methylation of the aphid genome in the regulation of environmentally induced phenotypes. We are interested in investigating the potential of stable epigenetic marks that might contribute to lasting and heritable phenotypes. Our objective is to determine whether patterns of DNA methylation might be heritable across clonality and also whether this heritability might pass the sexual barrier to be transmitted in the newly emerged clonal generations the next spring. Our team is particularly interested to investigate the mechanisms of the epigenetic regulation of adaptive traits of insects in fluctuating environment. Using genetic and biochemical tools the aim of our project consists in analyzing the covalent modifications of DNA, their functional roles and their heritable transmission that confers the passage of an acquired phenotype to the next generations in clonality context.

Selected Publications

1. Profiling the repertoire of phenotypes influenced by environmental cues that occur during asexual reproduction
   Dombrovsky A., Arthaud L., Ledger T.N., Tares S. and Robichon A..
   (2009) **Genome Res** 19(11), 2052-63.
2. Genome Sequence of the Pea Aphid Acyrthosiphon pisum
   The International Aphid Genomics Consortium
   (2010) **PLoS Biol.** 8(2), e1000313.
3. Light- induced electron transfer and ATP synthesis in a carotene synthesizing insect
   Valmalette J.C., Dombrovsky A., Brat P., Christian Mertz C., Capovilla M., Alain Robichon A.
   (2012) **Scientific Reports** 2, article number 579/ doi : 10.1038/srep00579
4. Analysis of carotenoid compounds in aphids by Raman imaging and mass spectrometry.
   Bratt, P., Valmalette, J. C., Mertz, C., de Sousa, G., Dombrovsky, A., Capovilla, M., and Robichon, A.
   (2012) **Nature Protocol Exchange** none, doi:10.1038/protex.2012.047
5. Photosynthesis-like process found in insects
   Lougheed K.
   (2012) **Nature News** 11214, doi:10.1038/nature.2012.11214

SCHEDL Andreas

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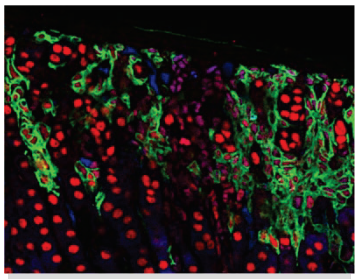
institut Valrose Biologie

Molecular programs controlling development and tissue homeostasis



Lineage tracing analysis identifies a novel stem/progenitor cell population in adult mice.

Tissue repair in most organs is guaranteed through resident stem/progenitor cells. Stem cells are essential for organ renewal and lack of activation or depletion of the stem cell pool can lead to progressive organ failure. In contrast overactivation of stem cells and their transiently proliferating derivatives can cause overgrowth and cancer. Understanding stem cell biology is therefore of very high importance from both a biological and a medical point of view.

Development and tissue maintenance are highly interrelated processes and molecular programs driving development and differentiation are also triggered when stem cells become activated to replace damaged or lost cells. In our research program we try to understand the transcriptional control underlying tissue development, define stem/progenitor cells in the adult organism and determine the signaling pathways involved in their maintenance and activation. As a model of choice we use the mouse, as its physiology largely reflects that of the human body and as it allows easy manipulation of its genome using transgenic and gene-targeting techniques.

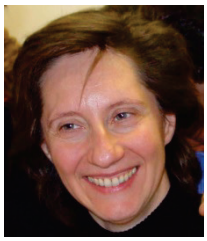
Selected Publications

1. SOX9 Controls Epithelial Branching by Activating RET Effector Genes during Kidney Development
   Reginensi A, Clarkson M, NeirijnckY, Lu B, Ohyama T, Groves AK, Sock E, Wegner M, Costantini F, Chaboissie MC, Schedl A
   (2011) **Hum. Mol. Genet.** 20, 1143-1153
2. Renal abnormalities and their developmental origin.
   Schedl A
   (2007) **Nature Rev. Genet.** 8, 791-802
3. Coronary vessel development requires activation of the TrkB neurotrophin receptor by the Wilms' tumor transcription factor Wt1
   Wagner N., Wagner KD., Theres H., Englert C., Schedl A*. and Scholz H
   (2005) **Geners & Dev** 19, 2631-2642
4. Sox9 induces testis development in XX transgenic mice
   Vidal VP, Chaboissier MC, de Rooij DG, Schedl A
   (2001) **Nat. Genet.** 28, 216-217
5. Two alternatively spliced isoforms of WT1 have distinct functions during sex determination and nephron formation.
   Hammes A, Guo J, Lutsch G, Landrock D, Ziegler A, Gubler MC, Schedl A
   (2001) **Cell** 106, 319-329

Awards

2009: Award of the French kidney foundation (Fondation du Rein)
2003: Avenir (INSERM, France
2002: Philippe Leverhulme Prize (UK)
2001: EMBO Young Investigator Programme

STUDER Michèle



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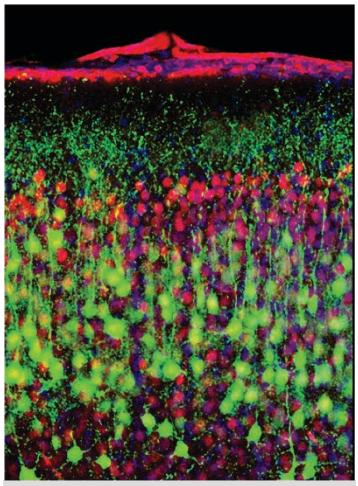
institut Valrose Biologie

Genetics of mouse cortical development



In utero electroproration of EGFP at E14.5 and taken at P8 showing the soma and dendrites of upper layer neurons of the mouse cortex.

The major aim of our research is to elucidate the key mechanisms of neurogenesis in the developing and post-natal mouse cerebral cortex. During corticogenesis, the remarkable array of different neuronal cell types is generated from a population of multipotent stem and progenitor cells following a precise spatial and temporal pattern, before being assembled in areal- and laminar-specific maps and circuits. We are interested in understanding the cellular and molecular mechanisms by which these different neuronal cell types are temporally and spatially regulated through the action of defined regionalized and coordinated differentiation programs.

We found that a family of nuclear receptors is required in balancing the neocortex into motor and sensory areas, in controlling the generation and specification of corticospinal motor neurons, in axonal outgrowth, in neuronal migration, and in cortical interneuron migration and cell-type specification.

By combining several in vivo and in vitro molecular and cellular approaches, including mouse genetics, in utero elctroporation, biochemical assays, neural stem cell cultures, but also morphological and behavioural analyses, we aim to contribute in dissecting signalling pathways and molecular cascades involved in cortical neuronal cell-type specification and establishment of functional cortical circuits during mouse brain development.

Selected Publications

1. The nuclear receptors COUP-TF: a long lasting experience in forebrain assembly.
   Alfano C., Kawssar H., Magrinelli E. and Studer M.
   (2013) **Cell Mol Life Sci.** Mar 23., [Epub ahead of print]
2. COUP-TFI promotes radial migration and proper morphology of callosal neurons by repressing Rnd2 expression.
   6. Alfano C., Viola L., Heng J.I.T., Pirozzi M., Clarkson M., Flore G., De Maio A., Schedl A., Guillemot F. and Studer M.
   (2011) **Development** 138, 4685-4697
3. Loss of COUP-TFI alters the balance between caudal ganglionic eminence- and medial ganglionic eminence-derived interneurons and results in resistance to epilepsy.
   Lodato S., Tomassy Srubek G., De Leonibus E., Uzcategui Y.G., Andolfi G., Armentano M., Touzot A., Gaztelu J. M., Arlotta P., Menendez de la Prida L. and Studer M.
   (2011) **J Neurosci.** 31(12), 4650-4662
4. Area-specific temporal control of corticospinal motor neuron differentiation by COUP-TFI.
   Tomassy Srubek G., De Leonibus E., Jabaudon D., Lodato S., Alfano C., Mele A., Macklis J.D. and Studer M.
   (2010) **PNAS** 107(8), 3576-3581
5. COUP-TFI regulates the balance of cortical patterning between frontal/motor and sensory areas.
   Armentano M., Chou S. J., Srubek Tomassy G., Leingärtner A., O'Leary D.D.M. and Studer M.
   (2007) **Nat Neurosci.** 10, 1277-1286

Awards

2011: Equipe labélisée FRM
2009: ANR Senior Chaire d'Excellence
1997: MRC (Medical Research Council) Career Development Award

TANTI Jean-François/CORMONT Mireille

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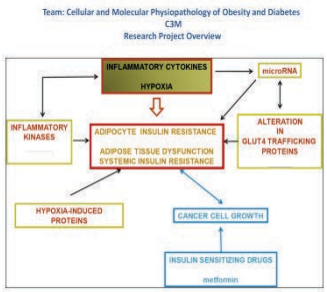
Cellular and Molecular Physiopathology of Obesity and Diabetes



Our team by using cells and animal models deciphers the mechanisms linking adipose tissue dysfunction to insulin resistance and tumor growth

Inflammatory and hypoxic stresses as well as senescence develop in AT during obesity. Activation of stress-sensing pathways in obese AT alters insulin signaling and the trafficking of the glucose transporter Glut4 decreasing the metabolic functions of adipocytes leading to insulin resistance and type 2 diabetes development. Further adipose tissue stresses maybe involved in obesity–related carcinogenesis. Our team by using cells and animal models deciphers the dysfunction of adipose tissue metabolism linked to obesity and diabetes.
Our objectives are:
1. To identify the cellular and molecular mechanisms involved in insulin resistance induced by AT inflammatory and hypoxic stresses. We study:
• The implication of RabGTPase in Glut4 trafficking and in the regulation of the gluco-lipidic metabolism.
• The implication of microRNAs in the control of the metabolic functions of adipocytes and their deregulations in obesity.
• The implication of stress kinases in adipose tissue inflammation and insulin resistance.
• The implication of hypoxia in adipocyte insulin resistance.
2. To understand the pathophysiological mechanisms responsible for the association between obesity and cancer. We study:
• The effect of insulin sensitizing drugs on tumor development
Our goal is to identify new therapeutic targets for the treatment of obesity-associated pathologies.

Selected Publications

1. Regulated in development and DNA damage responses -1 (REDD1) protein contributes to insulin signaling pathway in adipocytes.
   Regazzetti C, Dumas K, Le Marchand-Brustel Y, Peraldi P, Tanti JF, Giorgetti-Peraldi S.
   (2012) **PLoS One.** 12, e52154
2. Metformin, independent of AMPK, induces mTOR inhibition and cell-cycle arrest through REDD1.
   Ben Sahra I, Regazzetti C, Robert G, Laurent K, Le Marchand-Brustel Y, Auberger P, Tanti JF, Giorgetti-Peraldi S, Bost F.
   (2011) **Cancer Res** 71, 4366-4372
3. Deficiency in the extracellular signal-regulated kinase 1 (ERK1) protects leptin-deficient mice from insulin resistance without affecting obesity.
   Jager J, Corcelle V, Grémeaux T, Laurent K, Waget A, Pagès G, Binétruy B, Le Marchand-Brustel Y, Burcelin R, Bost F, Tanti JF.
   (2011) **Diabetologia** 54, 180-189
4. Tpl2 kinase is upregulated in adipose tissue in obesity and may mediate interleukin-1beta and tumor necrosis factor-{alpha} effects on extracellular signal-regulated kinase activation and lipolysis.
   Jager J, Grémeaux T, Gonzalez T, Bonnafous S, Debard C, Laville M, Vidal H, Tran A, Gual P, Le Marchand-Brustel Y, Cormont M, Tanti JF.
   (2010) **Diabetes** 59, 61-70
5. Involvement of TNF-alpha in abnormal adipocyte and muscle sortilin expression in obese mice and humans.
   Kaddai V, Jager J, Gonzalez T, Najem-Lendom R, Bonnafous S, Tran A, Le Marchand-Brustel Y, Gual P, Tanti JF, Cormont M.
   (2009) **Diabetologia** 52, 932-940

TARTARE-DECKERT Sophie

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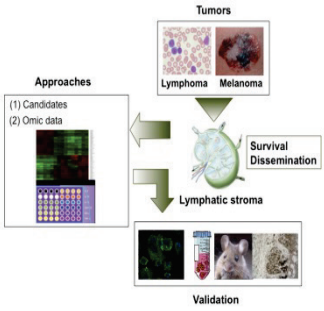
Microenvironment, Signaling and Cancer



Research workflow of team "MicroCan"

Our laboratory is interested in the crosstalk between cancer cells and stroma within the lymph node microenvironment in two models, melanoma, an aggressive form of skin cancers and lymphoma. The lymph node is the first locus of expansion for invasive melanoma and a pipeline for distant metastasis as well as one niche of malignant B-cells. During these past years, our team achieved important discoveries such as the identification of secreted factors from the microenvironment that promote Epithelial to Mesenchymal Transition (EMT) and inactivate p53 in melanoma. The team also contributed to characterization of survival pathways that operate in normal and pathological leukocytes. Ongoing projects are pursuing our observations using relevant pre-clinical models and aim at deciphering how lymphatic stromal cells impact on tumor survival. We are performing candidate gene and unbiased screen approaches for new microenvironment mediators of therapeutic response. In addition, we are exploring pathways operating within melanomas that enable them to invade lymphatics and to execute various steps of metastasis. Our work will bring a more comprehensive view of tumor-stroma communications and better understanding of melanoma and lymphoma malignancies. Our findings might have potential clinical implications for identification of novel biomarkers, potential targets and management of diseases.

Selected Publications

1. A novel FRET flow cytometry method for detection of actin dynamics on resting and activated T cell
   Larbret F, Dubois N, Brau F, Guillemot E, Mahiddime K, Tartare-Deckert S, Verhasselt V and Deckert M.
   (2013) **J Leuk Biol** In press
2. The epithelial-mesenchymal transition (EMT) regulatory factor Slug (SNAI2) is a downstream target of SPARC and AKT in promoting melanoma cell invasion
   Fenouille N, Tichet M, Dufies M, Pottier A, Mogha A, Soo J K, Rocchi S, Malavialle A, Khammari A, Lacour J-P, Galibert MD, Ballotti R, Deckert M and Tartare-Deckert S.
   (2012) **PLoS One** 7, e40378
3. SPARC functions as an anti-stress factor by inactivating p53 through Akt-mediated MDM2 phosphorylation to promote melanoma cell survival
   Fenouille N, Puissant A, Tichet M, Zimniak G, Abbe P, Mallavialle A, Rocchi, S., Ortonne JP, Deckert M, Ballotti R, and Tartare-Deckert S.
   (2011) **Oncogene** 30, 4887-900
4. Permanent activation of the Fyn/Erk axis mediates Imatinib resistance in Chronic Myelogenous Leukemia cells through increased expression of intracellular SPARC
   Fenouille N, Puissant A, Dufies M, Robert G, Jacquel A, Ohanna M, Deckert M, Pasquet JM, Mahon FX, Cassuto JP, Raynaud S, Tartare-Deckert* S and Auberger* P.
   (2010) **Cancer Res** 70, 9659-9670
5. Spleen tyrosine kinase functions as a tumor suppressor in melanoma cells by inducing senescence-like growth arrest
   Bailet O, Fenouille N, Abbe P, Robert G, Rocchi S, Gonthier N, Denoyelle C, Ticchioni, M. Ortonne, JP, Ballotti, R, Deckert M and Tartare-Deckert S.
   (2009) **Cancer Res** 69, 2748-2756

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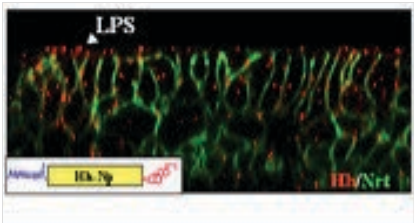
Secretion and Signaling of Morphogens in *Drosophila* development



Confocal Z section showing Hedgehog (in red) aggregates (LPS) enriched at the apical side of embryonic epithelial cells (baso-lateral membrane)

We focus our studies on two molecules, the secreted cholesterol-modified Hedgehog (Hh) and Wingless (Wg) proteins, key molecules that control the pattern formation of multicellular organisms.
We use genetic, biochemical and dynamic imaging approaches in Drosophila to identify and characterize molecules that modulate the cellular responses to Hh and Wg. We identified a protein module which governs proteolysis and access to the nucleus of the Ci/Gli transcription factor that mediates Hh signal (Robbins et al., Cell 1997; Ruel et al., NCB 2003). Moreover, our work highlighted the importance of the proteoglycans, of the extra-cellular matrix, in the internalization of the ligand-receptor complex for Hh signaling and Wg trafficking (Gallet et al., Dev. Cell 2008). Recently we developed new dynamic imaging tools to understand how the extra-cellular gradient of Hh is converted into an intra-cellular gradient of Ci/Gli activity (Ranieri et al., Dev. Cell 2012 and unpublished data).
Our current research interests also include the spreading of Hh in the epitheliums (Briscoe and Thérond, Nat Rev Mol Cell Biol, 2013). We showed that the cholesterol adduct on Hh is necessary for its controlled planar spreading. We showed that the spread of Hh into the extracellular space is contingent upon its assembly in large soluble multimers and glypican activity (Gallet et al., Dev. Cell, 2003). We pioneered the concept that overall morphogen gradient is a cellular summation of pools secreted by different routes (apical and basolateral) and favor the existence of several carriers for Hh transportation (Ayers et al., Dev. Cell, 2010). We are currently isolating these different carriers and identifying the cellular machinery involved in Hh and Wg secretion.

Selected Publications

1. The mechanisms of Hedgehog signaling and its roles in development and disease.
   Briscoe J. and Thérond P.(2013) **Review in Nat Rev Mol Cell Biol.** 14, 1-12
2. Distinct Phosphorylations on Kinesin Costal-2 Mediate Differential Hedgehog Signaling Strength.
   Ranieri, N., Ruel, L., Gallet, A., Raisin S., and Thérond P. (2012) **Developmental Cell** 22, 279-294
3. The long range Hedgehog Gradient Is Formed In the Apical Extracellular Space by the Glypican Dally and the Hydrolase Notum. Ayers K., Gallet A., Staccini-Lavenant L., and Thérond, P. (2010) **Developmental Cell** 18, 605–620
4. The Cellular Trafficking of the Glypican Dally-like Is Required for Full-Strength Hedgehog Signaling and Wingless Transcytosis. Gallet, A.,Staccini-Lavenant L. and Thérond P.(2008) **Developmental Cell** 14, 1-14
5. Phosphorylation of the atypical kinesin Costal2 by the kinase Fused induces the partial disassembly of the Smoothened-Fused-Costal2-Cubitus interruptus complex in Hedgehog signalling
   Ruel L., Gallet A., Raisin S., Truchi A., Lavenant L., Cervantes A. and Thérond P. (2007) **Development** 134, 3677-3689

Awards

2009: Victor Noury Prize from the French Academy of Science
2004: Marie Curie Host for Research Training
2001: EMBO Young Investigator Program award
1998: Recipient of the ATIPE Programme in Cell Biology from CNRS

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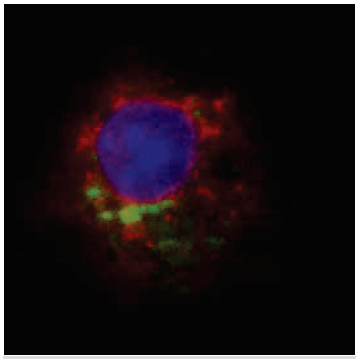
Control of gene expression



FISH detecting a small RNA (in green) expression in GW182-positive P-bodies (in red) of macrophage foam cells

Uncontrolled and chronic inflammation is nowadays considered a major component of many widely occurring diseases, including asthma, atherosclerosis and peripheral vascular disease, Alzheimer's disease, type 2 diabetes, and cancer. Innate immune and inflammatory response significantly contributes to onset, progression, tissue dysfunction, and ultimately organ failure in these diseases. The study of the mechanisms regulating the amplitude and the consecutive resolution of the inflammation may provide new insight into the pathogenesis of inflammatory diseases allowing the exploration of novel targets for the treatment and the prevention of many disorders.

We are investigating the molecular strategies used to generate genome-wide, integrated gene expression responses to the vast signaling network that regulates inflammatory response in macrophages. To achieve our goal we are using genetic, biochemical and biological approaches to define the gene expression strategies used by the human body in specific pathological contexts. Our work has revealed unexpected gene-specific strategies that link regulated gene responses to other cellular response programs, including cell signaling. Defining these strategies has suggested new approaches to diseases, including diabetes, arteriosclerosis, and several prevalent forms of cancer.

Selected Publications

1. Let-7b/c enhance the stability of a tissue-specific mRNA during mammalian organogenesis as part of a feedback loop involving KSRP.
   E. Repetto, P. Briata, N. Kuziner, B.D. Harfe, M.T. McManus, R. Gherzi, M.G. Rosenfeld, M. Trabucchi
   (2012) **Plos Genetics** 8, e1002823
2. DICER- and AGO3-dependent generation of retinoic acid-induced DR2 Alu RNAs regulates human stem cell proliferation.
   Q. Hu, B. Tanasa*, M. Trabucchi*, W. Li, J. Zhang, K.A. Ohgi, D.W. Rose, C.K. Glass, M.G. Rosenfeld
   (2012) **Nature structural & molecular biology** 19, 1168-1175
3. PI3K/AKT signaling determines a dynamic switch between distinct KSRP functions favoring skeletal myogenesis.
   P. Briata, W.J. Lin, M. Giovarelli, M. Pasero, C.F. Chou, M. Trabucchi, M.G. Rosenfeld, C.Y. Chen, R. Gherzi
   (2012) **Cell Death Differ** 19, 478-87
4. The RNA-binding Protein KSRP Promotes the Biogenesis of a Subset of miRNAs
   M. Trabucchi, P. Briata, M.F. Garcia-Mayoral, A.D. Haase, W. Filipowicz, A. Ramos, R. Gherzi, M.G. Rosenfeld
   (2009) **Nature** 459, 1010-1014.
5. LPS induces KH-type splicing regulatory protein-dependent processing of microRNA-155 precursors in macrophages
   T. Ruggiero*, M. Trabucchi*, F. De Santa, S. Zupo, B.D. Harfe, M.T. McManus, M.G. Rosenfeld, P. Briata, R. Gherzii
   (2009) **FASEB J** 23, 2898-2908

Awards

2011: AVENIR
2005: American-Italian Cancer Foundation award
2006: Italian Telethon foundation

VAN OBBERGHEN Emmanuel

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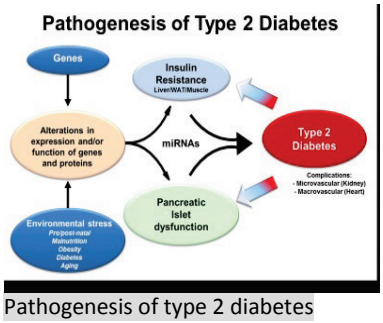
Aging and diabetes



Pathogenesis of type 2 diabetes

Diabetes and cardiovascular diseases increase with age and are tightly linked as diabetes predisposes to cardiac failure, and as cardiovascular complications cause the chief diabetic morbidity. Environmental/lifestyle and genetic factors participate in the defects of type 2 diabetes (T2D), which are insufficient insulin secretion and action. The risk of chronic diseases, such as T2D, in human adults is accounted for partly by environmental influences, particularly those occurring in utero. We hypothesize that under deleterious in utero conditions the altered miRNA control on gene regulation increases the risk of insulin resistance and T2D in adults. Hence, we study offsprings of pregnant rats exposed to an inappropriate diet or environment, predisposing to insulin resistance and T2D. Offsprings are studied for miRNAs misexpressed in the liver and pancreas and for their cardiac development.
As the age-related T2D increase involves pancreatic failure, we investigate whether a perturbed dialogue between beta cells and endothelial cells occurs. Finally, because both aging and diabetes favor myocardial infarction, myocardium repair is studied. Our multipronged approach will advance the understanding of the mechanisms underlying increased diabetes incidence during aging and offer key medical implications by fostering prevention strategies for T2D and its cardiovascular complications.

Selected Publications

1. microRNAs and metabolism crosstalk in energy homeostasis
   Dumortier O, Hinault C, Van Obberghen E
   (2013) **Cell Metabolism, in press**
2. Methylglyoxal impairs insulin signalling and insulin action on glucose-induced insulin secretion in the pancreatic beta cell line INS-1E
   Fiory F, Lombardi A, Miele C, Giudicelli J, Beguinot F, Van Obberghen E
   (2011) **Diabetologia** 54, 2941-2952
3. Peroxisome proliferator-activated receptor β/δ (PPAR β/δ) is highly expressed in liposarcoma and promotes migration and proliferation
   Wagner KD, Benchetrit M, Bianchini L, Michiels JF, Wagner N.
   (2011) **J Pathol** 224, 575-88
4. The podocyte protein nephrin is required for cardiac vessel formation. Hum Mol Genet
   Wagner N, Morrison H, Pagnotta S, Michiels JF, Schwab Y, Tryggvason K, Schedl A,Â Wagner KD.
   (2011) **Hum Mol Genet.** 20, 2182-94
5. miR-375 targets 3'-phosphoinositide-dependent protein kinase-1 and regulates glucose-induced biological responses in pancreatic beta-cells.
   El Ouaamari A, Baroukh N, Martens GA, Lebrun P, Pipeleers D, Van Obberghen E
   (2008) **Diabetes** 57, 2708-2717

Awards

2008: Jacobeus Lecture Award, NovoNordisk Foundation, Denmark
2007: Claude Bernard Award Lecture, European Association for the Study of Diabetes
2005: D. Hermann Award, Foundation for Cardiovascular Research, Institute of France
2000: Gold Medal G.B. Morgagni Prize, Faculty of Medicine, University of Padua, Italy
1985: Oskar Minkowski Award, European Association for the Study of Diabetes

VAN OBBERGHEN-SCHILLING Ellen

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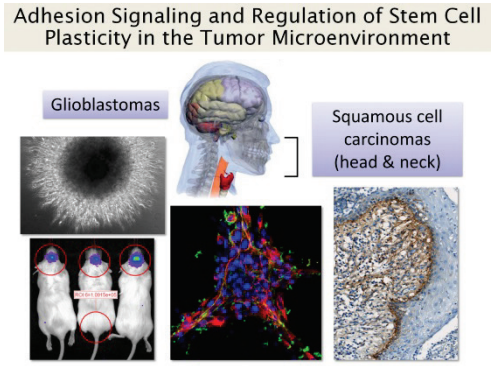
Adhesion Signaling and Regulation of Cell Plasticity in the Tumor Microenvironment



Understanding microenvironment-driven molecular pathways involved in tumor progression.

Our research is focused on adhesion-based signaling in head and neck cancer and glioblastomas. Ongoing projects address i) the molecular mechanismis underlying tumor-stroma interactions and their impact on tumor angiogenesis and invasion and ii) mechanisms that regulate the stem-cell state of cancer-initiating cells. The team has a history of productive interactions and collaborations with clinical partners. Projects rely on the integration of data derived from cellular and molecular analyses of cultured cells, orthotopic manipulations and analysis of human tumors.

Selected Publications

1. Tumorigenic Potential of miR-18A* in Glioma Initiating Cells Requires NOTCH-1 Signaling.
   Turchi L, Debruyne DN, Almairac F, Virolle V, Fareh M, Neirijnck Y, Burel-Vandenbos F, Paquis P, Junier MP, Van Obberghen-Schilling E, Chneiweiss H, Virolle T
   (2013) **Stem Cells**, in press
2. Contrasted outcomes to gefitinib on tumoral IGF1R expression in head and neck cancer patients receiving postoperative chemoradiation (GORTEC trial 2004-02).
   Thariat J, Bensadoun RJ, Etienne-Grimaldi MC, Grall D, Penault-Llorca F, Dassonville O, Bertucci F, Cayre A, De Raucourt D, Geoffrois L, Finetti P, Giraud P, Racadot S, Morinière S, Sudaka A, Van Obberghen-Schilling* E, Milano G* (*equal contribution)
   (2012) **Clin Cancer Res** 18, 5123-5133
3. The miR 302-367 cluster drastically affects self-renewal and infiltration properties of glioma-initiating cells through CXCR4 repression and consequent disruption of the SHH-GLI-NANOG network.
   Fareh M, Turchi L, Virolle V, Debruyne D, Almairac F, de-la-Forest Divonne S, Paquis P, Preynat-Seauve O, Krause KH, Chneiweiss H, Virolle T
   (2012) **Cell Death Differ** 19, 232-244
4. Fibronectin and tenascin-C: accomplices in vascular morphogenesis during development and tumor growth.
   Van Obberghen-Schilling E, Tucker RP, Saupe F, Gasser I, Cseh B, Orend G
   (2011) **Int J Dev Biol** 55, 511-525
5. Autocrine fibronectin directs matrix assembly and crosstalk between cell-matrix and cell-cell adhesion in vascular endothelial cells.
   Cseh B, Fernandez-Sauze S, Grall D, Schaub S, Doma E, Van Obberghen-Schilling E
   (2010) **J Cell Sci** 123, 3989-3999

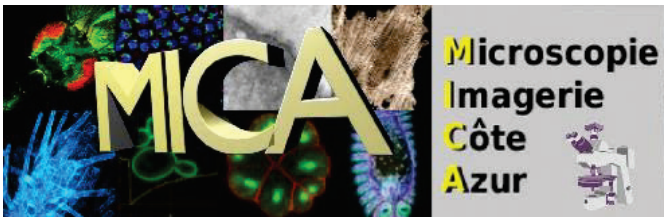
Awards

2001: INSERM Research Award in Physiology/Pathology
1996: Award Fondation pour la Recherche Médicale

5. LABEX FACILITIES AND EQUIPMENT

The SIGNALIFE Institutes have state-of-the-art technology platforms with open access for all local scientists:

- Imaging Facilities through the multi-site MICA Platform (http://www.mica-bio.fr/), provide access to optical microscopy including bright field and fluorescence microscopy, live cell microscopy (both wide-field and spinning disk confocal), TIRF and confocal scanning microscopy, laser-capture microdissection and electron microscopy, facilities for image analysis (deconvolution, 3D rendering and animation) and a number ofl flow cytometers and cell sorters.



- Functional Genomics Platform (http://www.genomique.info/) equipped with microarrays and Nest Generation sequencing facilities in Sophia-Antipolis and Nice associated with bioinformatics support.
- Proteomics facilities (http://www.capabio.fr/) located on 3 sites with multiple mass spectrometry and proteomics equipments.
- A Biobank, located in Nice Hospital provides high quality, ethically obtained biospecimens to support research and is closely associated with genotyping and a molecular pathology laboratory.
- Several histology platforms provide advice and training for histological studies
- Animal housing and experimental facilities for various animal models: mouse, zebrafish, *Drosophila*, nematodes, *Xenopus*, *etc*.

6. RESOURCES

6.1. Fellowship

The SIGNALIFE PhD thesis funding is for three years.

All students participating in the Program will receive a monthly salary of 2,000 € gross which includes social security. In addition each participant will receive an installation allowance of 1,700 € upon arrival.

6.2. PhD Program Officer

The arrival and installation of each student will be aided and accompanied by a dedicated PhD Program Officer, Konstanze Beck (see contacts), who will provide practical, administrative and scientific aid with respect to the institutions and local authorities (*i.e.* lodging, visa, social security, bank account, *etc.*).

6.3. Housing

The Campus of the University of Nice can provide aid with respect to on site student housing. Information can be found at the C.R.O.U.S. web site (http://www.crous-nice.fr/).
There are also numerous off-campus opportunities, for which the PhD Program Officer can provide assistance.

6.4. University restaurant

A student restaurant is located on the campus and provides lunch and dinner services, and is open on week-ends.
In addition, there are numerous other eating possibilities around the campus. All research laboratories located outside the university campus have their own restaurant open to students.

6.5. Library facilities

The University Library together with the Medicine Faculty Library provides an inter-University exchange service allowing ordering specific books and journals that are not accessible online.

6.6. Student Life

The OAE (Office of Student Life) has the distinction of being managed solely by students. It offers a one-stop shop for information relating to your daily life. It can help you in the realization of all community activities, whether cultural, humanitarian or athletic.
The Department of Culture offers a range of free activities for UNS students: cultural workshops, invitations to shows and concerts, cultural events, support of cultural projects, *etc.* The University Department of Physical Education and Athletics also offers numerous activities. Foreign students can visit the UNS Web site for practical questions.

http://unice.fr/international/portail-etudiants-etrangers/pratique

7. VALROSE

Valrose was the name of one of the finest properties in the Riviera. Today, it is the name of a university campus among the best locations in France, home of the University of Nice Sophia Antipolis headquarters and the Faculty of Sciences. This campus is adjacent to the residential communities of the Cimiez area. This 10 Ha domain was the property of the Russian community in the middle of the XIXth century. Despite the presence of new administrative and research buildings, it has kept its Second Empire style and remains a testimony of the past luxurious life of the French Riviera.

8. NICE

Nice has the advantage of an exceptional micro-climate which has contributed to its worldwide reknown for almost 200 years. Midday temperatures average 10-15°C in winter and 30°C degrees in summer, with rainfalls occurring in the mid-season months. This climate is ideal for a range of athletic as well as recreational activities including water sports, hiking and skiing with 3000 meter high mountains within 100km of Nice.

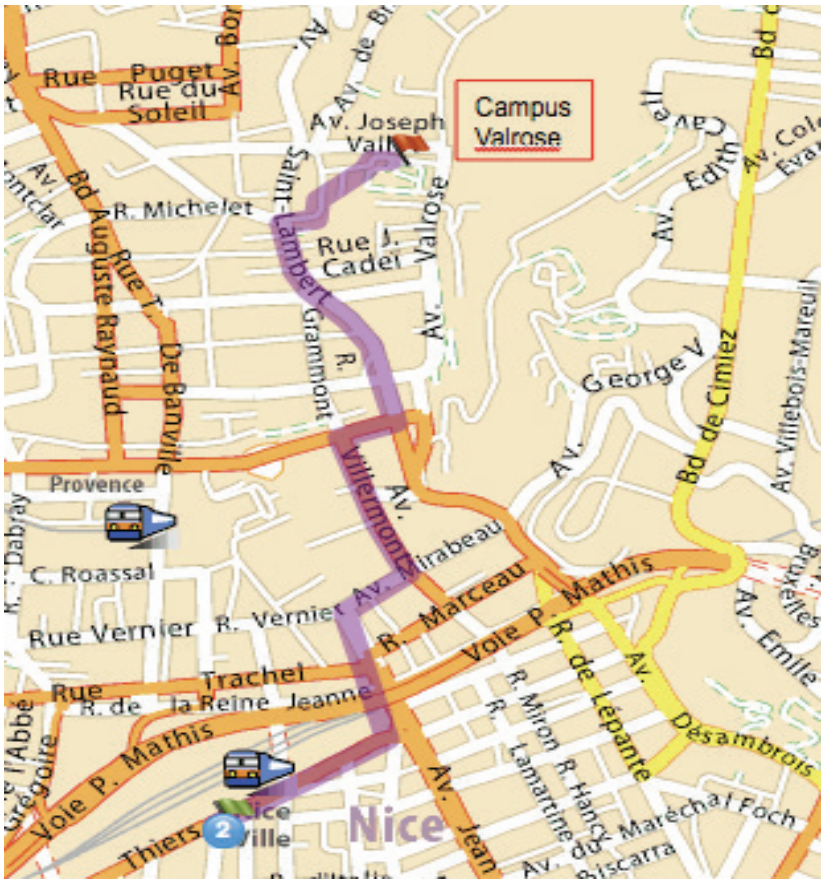
For further information on Nice and its surroundings: http://www.nicetourism.com/

9. DIRECTIONS to Valrose Campus

9.1. From the train station

By foot :

- Avenue Malausséna
- Avenue Borriglione
- Right turn on Av. Joseph Vallot



By tram :

- Tram Direction Las Planas
- Stop at Valrose University

9.2. From freeway (by car)

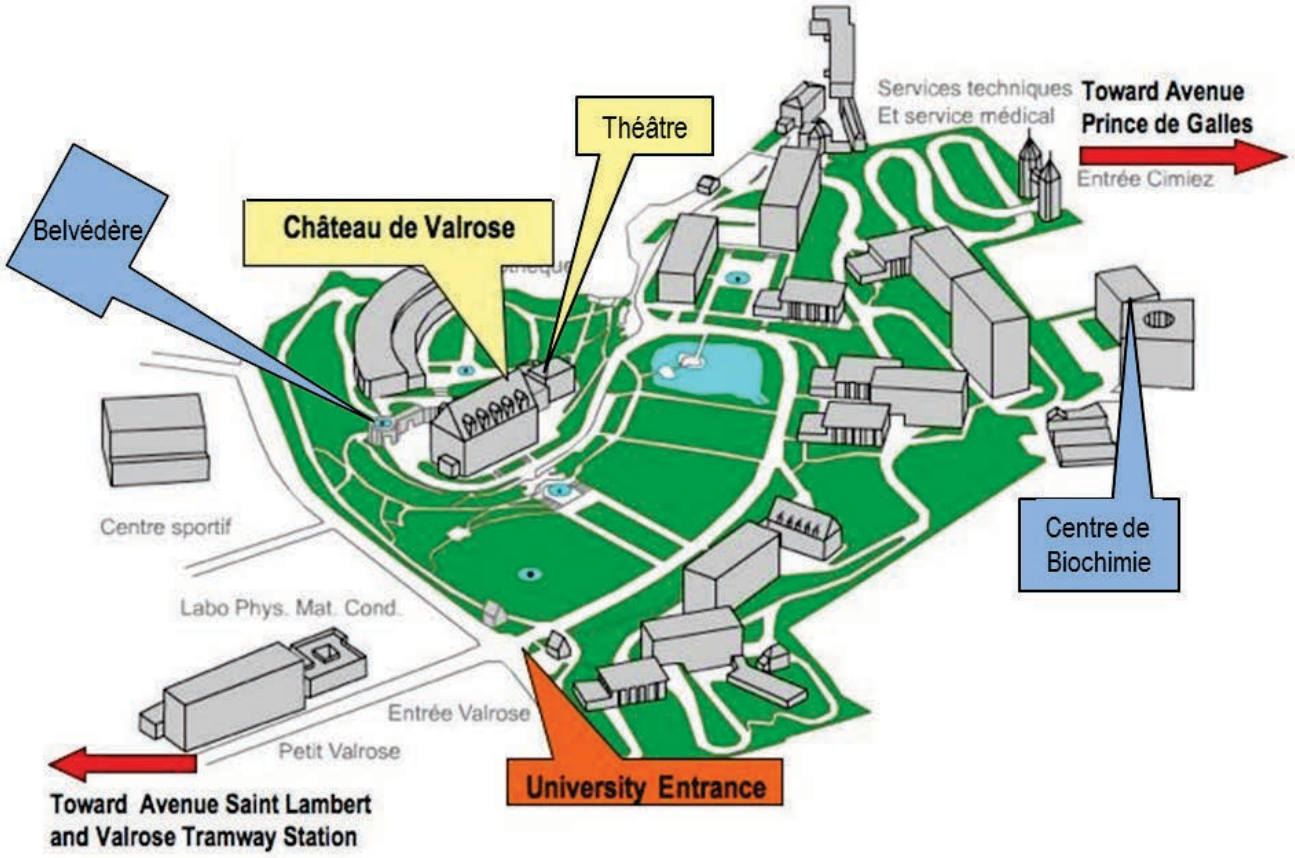
-Exit Nice Nord
-Boulevard Comte de Falicon
-Left turn on Avenue du Ray
-Boulevard Borriglione
-Left turn on Avenue Joseph Gallot

9.3. From Airport (by bus)

- Direct bus line 23 or 99
- Stop Vallot/Valrose: duration about 1h

9.4. Valrose Campus

Valrose Campus and room location for the on-site visit : open days of June 14th-15th, 2013.



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Back cover: **Identity photos of all SIGNALIFE group leaders**

Pamphlet produced in Nice, June 2013, M. Avella

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Anjuère


Chaboissier


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Cristofari


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Hueber


Lalli


Lambeau


Lemichez


Leopold


Liti


Luton


Franco


Magnaldo


Meneguzzi


Marie


Martin


Nahon


Noselli

Panabières

Poirié

Rassoulzadegan

Ricci

Robichon

Schedl

Studer

Tanti

Cormont

Tartare-Deckert

Thérond

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