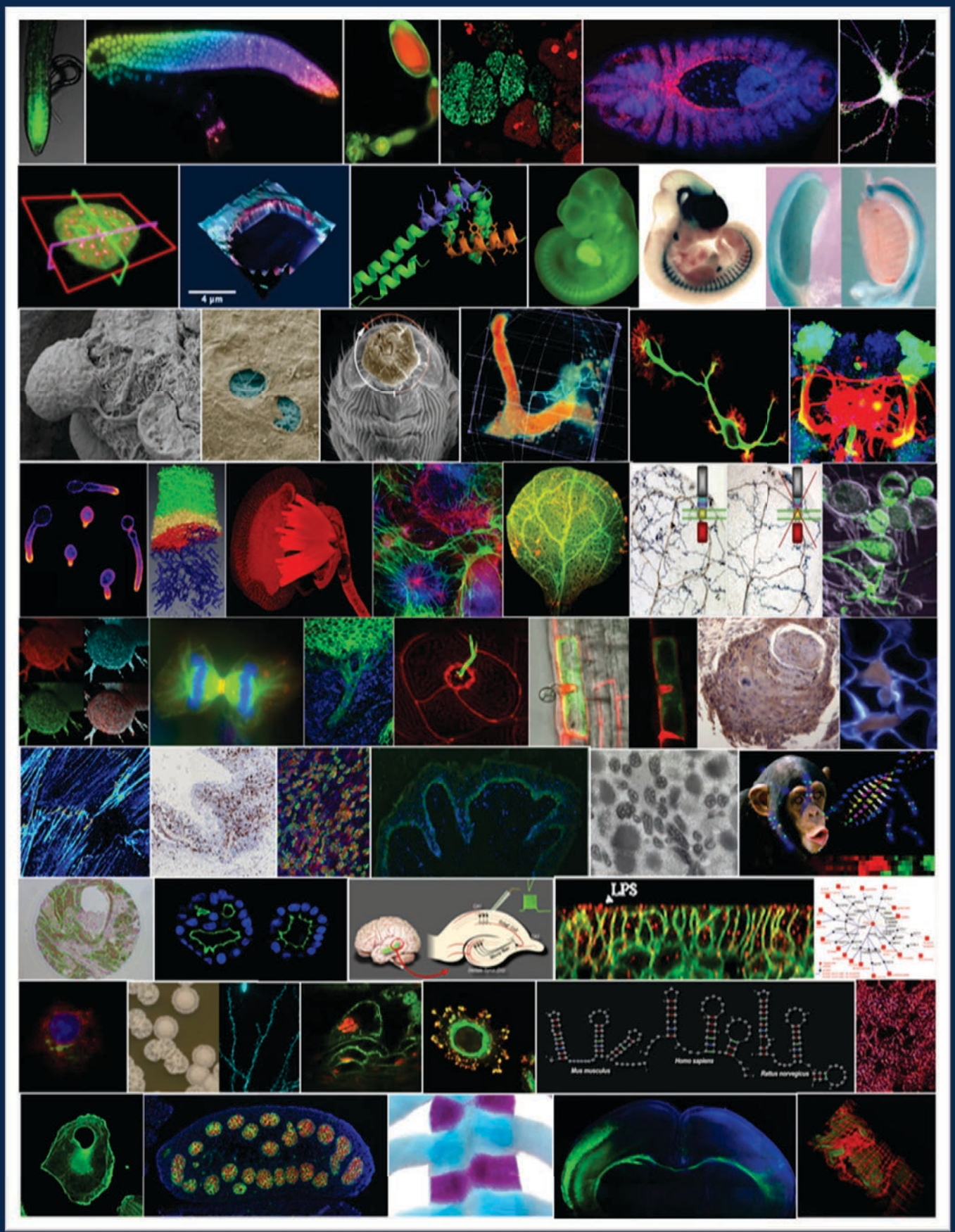
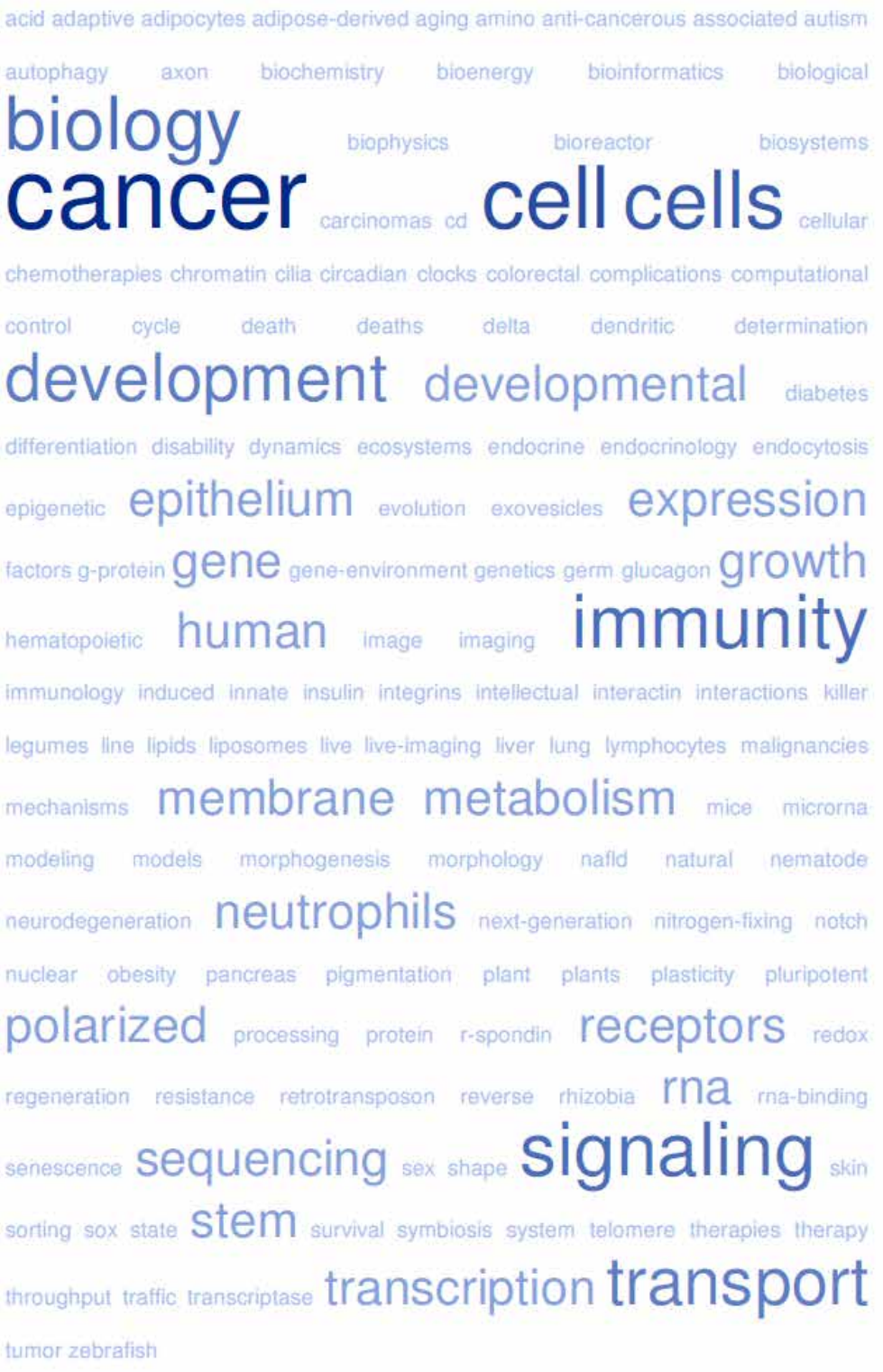
# INTERNATIONAL PhD PROGRAM

## Network for Innovation on Signal Transduction Pathways in Life Sciences




**OPEN DAYS May 31st and June 21st, 2016**
**Valrose Campus, Nice, France**




**Front cover: Composite of images from 30 research groups**

Photomontage created by M. Avella. Photo copyrights © SIGNALIFE 2013 by Abad, Arkowitz, Attard, Barbry, Bardoni, Bassilana, Besse, Braendle, Burel, Chaboissier, Chakrabanhu, Chassot, Collombat, Cseh, Descombes, Favery, Feral, Franco, Frendo, Fürthauer, Gaggioli, Gatti, Hofman, Hok, Hueber, Lalli, Lemichez, Luton, Magnaldo, Medioni, Meneguzzi, Marie, Martin, Nahon, Noselli, Panabières, Pegard, Poirié, Robichon, Rousset, Schedl, Studer, Thérond, Trabucchi, Virolle, V.O-Schilling

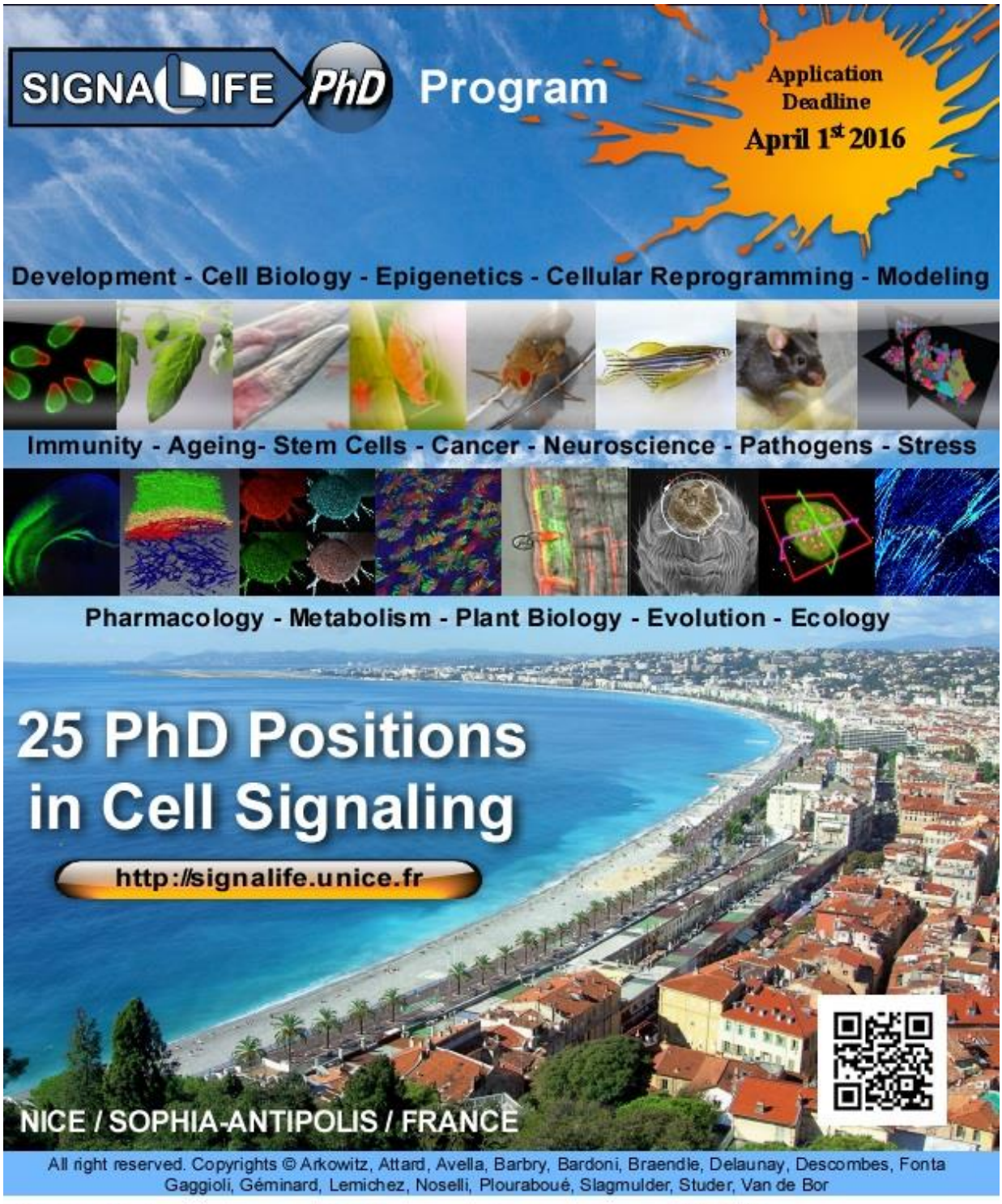
All rights reserved


# Labex SIGNALIFE - Nice France

*Network for Innovation on Signal Transduction Pathways in Life Sciences*

Labex SIGNALIFE - Institut de Biologie Valrose - Centre de Biochimie -
Université Nice Sophia Antipolis - Parc Valrose - 06108 NICE cedex 2 – France

PhD.signalife@unice.fr Phone : +33 (0) 4 92 07 69 98 http://signalife.unice.fr




All right reserved. Copyrights © Arkowitz, Attard, Avella, Barbry, Bardoni, Braendle, Delaunay, Descombes, Fonta Gaggioli, Géminard, Lemichez, Noselli, Plouraboué, Slagmulder, Studer, Van de Bor

# TABLE OF CONTENT

# 1. 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.

## 1.1. 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 in modern Cell Signaling using state-of-the-art techniques and approaches. Research towards a PhD degree can be carried out in any of the 49 different SIGNALIFE research groups[1], 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.**

## 1.2. Thesis research

Selected students will carry out the PhD research project they have been selected for in the laboratory of one of the 41 participating teams of the 2016 Program[1].

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.

[1] *Please note that 25 PhD positions are available by 41 participating labs in 2016 (see below, section 3.4, for details)*

## 1.3. 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

### 1.3.1. 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 | | |

### 1.3.2. 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.

### 1.3.3. 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.

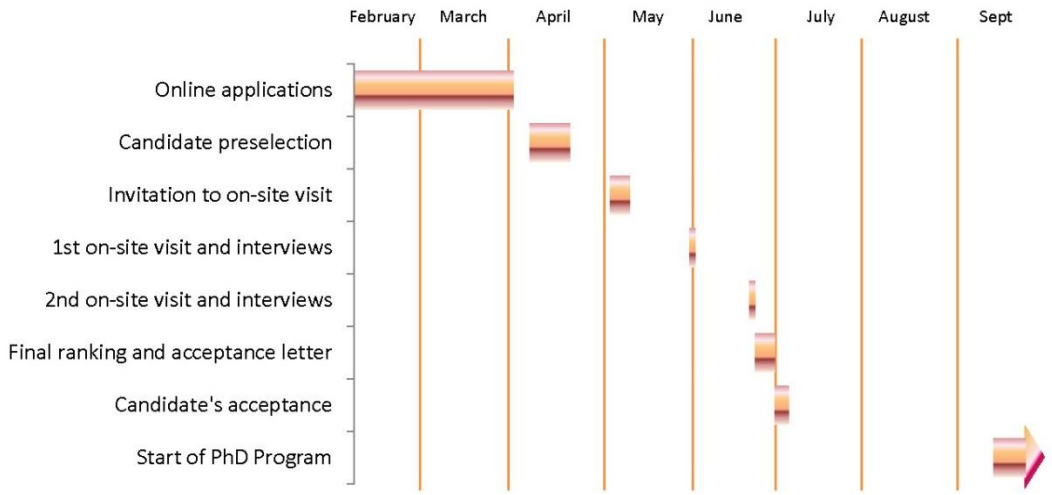
***Career counseling:*** Career counseling will be provided by professional counselors (either Dr. A. Forde, Careers Adviser for Life Science, Cambridge University Careers Service or S. Blackford, Career Counselor and Coach). Thesis project management and career guidance will be provided by either Dr. 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.

## 1.4. International SIGNALIFE International PhD Milestones:

- Applications open until **April 1st, 2016**
- Pre-selection of applicants: **April 2016**
- Invitation to visit the University of Nice: **May 3rd to May 9th, 2016**
- 1st Candidate's on-site visit and interview for final selection: **May 31st and June 1st, 2016**
- 2nd Candidate's on-site visit and interview for final selection: **June 21nd and 22rd, 2016**
- Final ranking and acceptance letter: **End of June 2016**.
- Student's acceptance: **Beginning of July 2016**.
- Start of PhD Program: **September 19th, 2016**.




## 1.5. 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.

# 2. LABEX SIGNALIFE

## 2.1. 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).

## 2.2. 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.

## 2.3. Organization

SIGNALIFE is coordinated by Dr. Stéphane Noselli, CNRS Directeur de Recherche and 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 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.

# 3. RESEARCH

## 3.1. French Research Institutions involved in the Labex SIGNALIFE

### 3.1.1. 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

### 3.1.2. 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).

### 3.1.3. 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.

### 3.1.4. 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.

**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.**

### 3.1.5. Partnership with Nice University Hospital

The *Centre Hospitalier Universitaire de Nice* (CHUN) is a public health institution jointly operated by the French Ministry of Health, and the Ministry of Higher Education and Research.
CHUN's three core missions are high-quality patient care (diagnostics, prevention, and education), good teaching standards (medical and paramedical training), and world-class research and innovation (advancing medical and pharmaceutical sciences).
Since the initial establishment of the School of Medicine in 1973, the hospital has been integrated into the university structure (CHU). Each year, it trains approximately 1,000 students and junior doctors in medicine and odontology, while at the same time offering training for health nurses, midwives, auxiliary nurses, ambulance drivers, and physiotherapists.
Within CHUN's eighteen research centres, the focus is on four key areas: cancer; circulation, metabolism and nutrition; immunology, haematology and pneumatology; and genetics and development. Others areas, such as neuroscience and health technology, are constantly developing thanks to the presence of highly-skilled dedicated teams.

### 3.1.6. Partnership with Antoine Lacassagne Cancer Center

The Nice Cancer Center, Centre Antoine-Lacassagne, was created in 1961. It belongs to the UNICANCER Cancer Center Federation gathering the 18 French cancer centers, which are private institutes dedicated to the public health service. The CAL has been certified without any reservations by the Public Health Authorities (HAS) in 2012. The Centre Antoine Lacassagne (CAL) has a dual mission, first to ensure medical services for cancer patients, and second to develop clinical and translational research with the aim to improve patient management at different levels (diagnosis, treatment *etc.*).
CAL treats more than 5000 patients each year. It is equipped with the **latest technology, in particular for radiotherapy** with two Cyclotrons and 3 IMRT machines, making the CAL one of the best-equipped centers in France. The CAL has recently developed two highly specialized medical platforms, one dedicated to the management of head and neck pathologies and the breast cancer Clinique. The CAL is also very active in the **clinical and translational research**, with more than 15% of patients included in clinical trials.
The CAL is organized with a *Département de Recherche Clinique, Innovations et Statistiques* and a Laboratory platform mainly **dedicated to personalized medicine**. This platform includes a Pathology unit and an Oncopharmacology unit, both belonging to the Molecular and Genetic Platform of the French National Cancer Institute (INCa). In the near future, the CAL will have an Early phase trial unit dedicated to clinical evaluation of new drugs and protocols.

### 3.1.7. 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.

## 3.2. 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.

## 3.3. Six Research Institutes

**SIGNALIFE**

**Network for Innovation on Signal Transduction Pathways in Life Sciences**

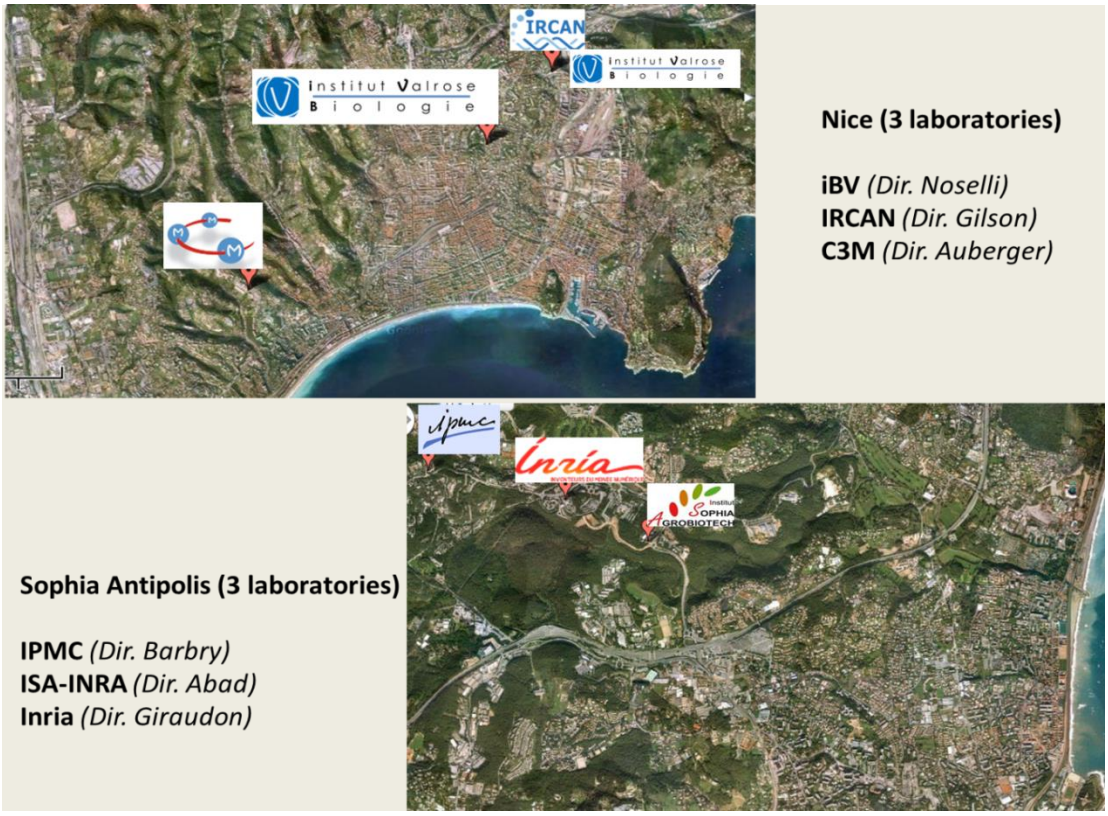
| *Partner 1* | *Partner 2* | *Partner 3* | *Partner 4* | *Partner 5* | *Partner 6* |
|---|---|---|---|---|---|
| **iBV** | **IPMC** | **C3M** | **IRCAN** | **ISA** | **INRIA** |
| Institut de Biologie Valrose | Institut de Pharmacologie Moléculaire et Cellulaire | Centre Méditerranéen de Médecine Moléculaire | Institute for Research on Cancer and Aging of Nice | Institut Sophia Agrobiotech | Sophia Antipolis-Méditerranéen Research Centre |

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



### 3.3.1. 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

### 3.3.2. 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/

### 3.3.3. 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

### 3.3.4. 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/

### 3.3.5. 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

### 3.3.6. 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

## 3.4. Fourty nine Research Groups

### 3.4.1. Notice about welcoming teams for 2016 PhD Students wave

**After acceptance in the program, students will carry out his/her thesis research starting in September 2016, specifically among the proposed 25 research (PhD) subjects by the 41 following teams:**

Antonny, Auberger, Ballotti, Barbry, Bardoni, Besse, Braendle, Chaboissier, Collombat, Cristofari, Dani, Delaunay, Descombes, Féral, Frendo, Fürthauer, Gilson, Glaichenhaus, Gouzé, Gual/Tran, Hofman, Lalli, Lémichez, Léopold, Liti, Luton /Franco, Magnaldo/Meneguzzi, Marie, Martin, Noselli, Panabières, Poirié, Rassoulzadegan, Robichon, Schedl, Tanti/Cormont, Tartare-Deckert, Thérond, Trabucchi, Van Obberghen, Van Obberghen-Schilling

### 3.4.2. General list and keywords for the 49 Labex teams

Abad Pierre **Plant nematode interactions**
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**
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**
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**
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**
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**
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**
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***
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**

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**
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**
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**
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**
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**
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**
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)**
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**
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**
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**
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**
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**
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)**
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**

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**

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**

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**

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**

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**

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***

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**

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**

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**

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**

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**

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)**
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***
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**
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)**
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**
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*
Robichon Alain **Genome Plasticity and Environment**
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**
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**
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**
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**
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**
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**
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**
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**

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.*

### 3.4.3. Detailed description of 25 SIGNALIFE PhD projects in 2016

# Project id: 1-ANTONNY/LEMICHEZ

**"Polyunsaturated fatty acids and membrane mechanics in bacterial infection"**

**KEYWORDS:** Omega-3 and 6 phospholipids, transendothelial cell tunnels, membrane mechanics, acyltransferases, actin cytoskeleton, membrane fusion

**PI 1 (Labex SIGNALIFE team):** **ANTONNY, Bruno**
Institute: *IPMC*
Email: antonny@ipmc.cnrs.fr , Phone: +33 (0)4 93 95 77 74
Website: https://www.ipmc.cnrs.fr/cgi-bin/ipmcx.cgi

**PI 2 (Labex SIGNALIFE team):** **LEMICHEZ, Emmanuel**
Institute: *C3M*
Email: lemichez@unice.fr , Phone: +33 (0)4 89 06 42 61
Website: http://www.unice.fr/c3m/FR/Equipe6.html

**PHD PROJECT SUMMARY:**

The general effect of polyunsaturated acyl chain composition of phospholipids on membrane mechanics is yet poorly defined except for a few cases such as touch sensitivity and endocytosis. In the latter case, the findings of Pinot et al., 2014 Science established that incorporation of polyunsaturated fatty acids (PUFA) renders the membrane more amenable to deformation by pulling forces and accelerates the rate of endocytosis (Pinot et al., 2014). In order to better define the role of polyunsaturation of acyl chains on membrane mechanics, we propose to explore their impact on membrane deformations triggered by toxins of pathogenic bacteria. In addition to fundamental contributions in a better understanding of the membrane architecture, our study may help to identify new key elements of infectious processes.

Infectious processes rely on the capacity of microbes to promote large-scale deformations of cellular membranes. In order to prevent acute and chronic infections there is an urge at developing compounds decoupling cell colonization by membrane-bound bacteria from cell invasion and bacterial dissemination. Here, we propose to study the importance of PUFA composition on a newly described mechanism of dissemination of Staphylococcus aureus through the endothelium barrier. Here, dissemination relies on the capacity of secreted toxins to promote the opening of large transcellular holes in endothelial cells, referred to as transendothelial cell macroaperture (TEMs) Tunnels (Lemichez et al., 2012). This process is a biological form of liquid dewetting, in which the plasma membrane tension provides the driving force of opening and enlargement of holes, a phenomenon that is resisted by a line tension distributed along the edge of TEMs. This will be investigated in human umbilical vein endothelial cells (HUVECs), which have a defined composition in PUFA incorporated in phospholipids (Héliès-Toussaint et al., 2006). This cellular system also offers the possibility to change the phospholipid content in PUFA by defined diets and will be also used for gene-editing by RNAi/CRISPR-CAS9-based methods. Scientific questions will be addressed by interdisciplinary approaches including cell biology and in vitro reconstitution assays.

In conclusion, our proposal aims at defining new general concepts on PUFA and membrane mechanics and implication in the control of endothelium barrier function in physiology and during infection.

The PhD student will be directly supervised by Dr Hélène Barelli and will get general input from E Lemichez, B Antonny and their collaborators.

**RELATED PUBLICATIONS:**

1. Pinot, M., Vanni, S., Pagnotta, S., Lacas-Gervais, S., Payet, L. A., Ferreira, T., Gautier, R., Goud, B., Antonny, B., and Barelli, H. (2014). Lipid cell biology. Polyunsaturated phospholipids facilitate membrane deformation and fission by endocytic proteins. Science 345, 693-697.

2. Lemichez, E., Gonzalez-Rodriguez, D., Bassereau, P., and Brochard-Wyart, F. (2012). Transcellular tunnel dynamics: Control of cellular dewetting by actomyosin contractility and I-BAR proteins. Biol Cell 105, 109-117.

3. Héliès-Toussaint, C., Gambert, S., Roller, P., Tricot, S., Lacour, B., and Grynberg, A. (2006). Lipid metabolism in human endothelial cells. Biochim Biophys Acta 1761, 765-774.

# Project id: 4-BESSE

**"Cellular and functional characterization of new regulators of neuronal RNA/protein particles"**

**KEYWORDS:** RNA transport, ribonucleoprotein (RNP) complexes, axon remodeling, Drosophila, multi-method approach

**PI (Labex SIGNALIFE team):** **BESSE, Florence**
Institute: *iBV*
Email: besse@unice.fr , Phone: +33 (0)4 92 07 64 34
Website: http://ibv.unice.fr/FR/equipe/besse.php

**PHD PROJECT SUMMARY:**

Over the past decade, several observations have highlighted important connections between protein aggregation, RNA biology, and age-related degenerative diseases. Indeed, a conspicuous feature associated with the progression of many neurodegenerative diseases is the accumulation of aggregates of RNA binding proteins and associated RNAs. As proposed recently, these pathological RNA-protein aggregates may sequester RNA binding proteins as well as RNA regulatory factors, resulting in altered RNA homeostasis and cellular dysfunction. In this context, it is thus crucial to understand how both normal and pathological RNA-protein (RNP) complexes are assembled, disassembled, and cleared.

We are using *Drosophila* CNS neurons as a model system to i) characterize the mechanisms underlying the formation and the polarized transport of axonal RNP complexes during neuronal development, and ii) test the function of these complexes in the context of a living brain. Our lab has recently identified the conserved RNA binding protein Imp as a core component of RNP granules transported to growing axons. Furthermore, we have shown that Imp is essential for the genetically-programmed remodeling of axons that occurs during brain maturation (Medioni et al., 2014).

To identify factors that control the assembly, the turnover and/or the axonal transport of Imp granules, we have performed two complementary experiments. First, we have biochemically purified Imp granules from brain lysates, and analyzed their protein content by Mass Spectrometry. 70 partners reliably associating with Imp, and potentially regulating Imp complex properties were identified. Second, we have initiated a high throughput microscopy-based screen to search for genes that control Imp granule assembly and clearance in cultured cells. With this screen, we will identify hits (and possibly pathways) affecting the number, size and/or morphology of Imp granules.

The objective of the proposed PhD project will be to characterize at the molecular and functional level the role of promissing candidates identified with these approaches. This will imply testing the in vivo role of candidates in axon remodeling and axonal transport of Imp, as well as performing in vitro test to understand if and how these candidates regulate the dynamics, composition or chemico-physical properties of Imp granules.

With this work, the candidate will characterize the function of new regulators of RNP biogenesis, as wells as factors essential for RNP disassembly or clearance.

**RELATED PUBLICATIONS:**

1. Marchetti G., Reichardt I., Knoblich J. and Besse F. (2014) The TRIM-NHL protein Brat promotes axon maintenance by repressing *src64B* expression. ***J. Neurosci,*** 34(41): 13855-64.
2. Medioni C., Ramialison M., Ephrussi A. and Besse F. (2014). Imp promotes axonal remodeling by regulating *profilin* mRNA during *Drosophila* brain development**.** ***Current Biol.,*** 24(7):793-800.
3. Besse F. and Ephrussi A. (2008). Translational control of localized mRNA: restricting protein synthesis in space and time. ***Nat Rev Mol Cell. Biol.,*** 9(12):971-80.

# Project id: 5-MARTIN

"Role of the sumoylation process in intellectual disability"

**KEYWORDS:** Sumoylation, neuron, synapse, fragile X syndrome, FMRP

**PI (Labex SIGNALIFE team):** **MARTIN, Stéphane**
Institute: *IPMC*
Email: martin@ipmc.cnrs.fr, Phone: +33 (0)4 93 95 34 61
Website: https://www.ipmc.cnrs.fr/cgi-bin/ipmcx.cgi

**PHD PROJECT SUMMARY:**

Intellectual disability (ID) is the most common cause of handicap in children and represents a major social and economic problem worldwide. Fragile X Syndrome (FXS) is the most frequent X-linked inherited cause of ID. It results from the transcriptional silencing of the FMR1 gene and consequently to the loss of function of its product, the Fragile X Mental Retardation Protein (FMRP). The absence of FMRP in neurons leads to an abnormal immature neuronal morphology with increased spine length and density. FMRP is therefore playing a central role in neuronal development. FMRP is a mobile RNA-binding protein that participates in the transport of many specific target mRNAs and their local translation. However, the molecular mechanisms underlying the physiological regulation of FMRP-mediated mRNA trafficking, translation and subsequent protein synthesis are still largely unknown. We recently discovered that FMRP is sumoylated in vivo.

Sumoylation is a post-translational modification that consists in the covalent conjugation of the small protein SUMO to specific lysine residues of substrate proteins. Sumoylation was originally thought to target nuclear proteins but it is now clear that it also has important extranuclear roles and regulates the function of many proteins including several molecules involved in many neurological disorders (1,2). Thus, our findings lead to fundamental questions: How is sumoylation impacting on the functional properties of FMRP? What are the physiological consequences of FMRP sumoylation in the brain?

To answer these questions, the selected PhD student will use state-of-the-art biochemical and live imaging techniques to:

1- Assess the role of sumoylation in the activity-dependent transport of FMRP in neurons.

2- Characterize the impact of missense Fragile X mutations on FMRP sumoylation and subsequently on FMRP function.

This project is completely innovative and we are uniquely placed to undertake the work proposed since we have a unique expertise in neuronal sumoylation (3-5), live cell-imaging (5-6) and a wealth of preliminary data demonstrating the feasibility of the project.

**RELATED PUBLICATIONS:**

1. Martin S., Wilkinson K., Nishimune A. and Henley J.M. (2007) Nature Rev Neuroscience 8, 948-59.
2. Gwizdek C., Cassé F. and Martin S. (2013) NeuroMolecular Medicine 15, 677-691.
3. Loriol C., Parisot J., Poupon G., Gwizdek C. and Martin S. (2012) PLoS ONE 7, e33757.
4. Loriol C., Khayachi A., Poupon G., Gwizdek C. and Martin S. (2013) Biol Cell 105, 30-45.
5. Loriol C. et al. (2014) Nature Communications 5:5113.
6. Cassé F. & Martin S. (2015) Frontiers in Cell Neuroscience 9:367.
7. Martin S., Nishimune A., Mellor J. and Henley J.M. (2007) Nature 447, 321 - 5.
8. Richter J.D., Bassell G.J., Klann E. (2015) Nat Rev Neurosci. 16:595-605.

# Project id: 7-NOSELLI/FÜRTHAUER

"Function of the Myosin 1C/D system in Drosophila and Zebrafish Left/Right asymmetry"

**KEYWORDS:** Left-Right asymmetry, Zebrafish,Drosophila, MyosinI, Actin cytoskeleton

**PI 1 (Labex SIGNALIFE team): NOSELLI, Stéphane**
Institute: *iBV*
Email: noselli@unice.fr , Phone: +33 (0)4 92 07 64 33
Website: http://ibv.unice.fr/EN/equipe/noselli.php

**PI 2 (Labex SIGNALIFE team): FÜRTHAUER, Maximilian**
Institute: *iBV*
Email: furthauer@unice.fr , Phone: +33 (0)4 92 07 64 39
Website: http://ibv.unice.fr/EN/equipe/furthauer.php

## PHD PROJECT SUMMARY:

**Left-Right (LR) asymmetry** or laterality, is essential for the correct asymmetric morphogenesis and function of visceral organs (heart, liver, spleen, gut, brain etc..). Clinical studies indicate that approx. 1/10,000 humans suffer from LR defects (*situs inversus*, heterotaxia, and isomerism) leading to a number of complex congenital heart defects, misrotation of the intestine, spontaneous miscarriage, asplenia, etc.. Additionally, LR asymmetry defects, which can originate from ciliopathies, are often associated with polycystic renal disease, Kartagener and Ivemark syndromes, and others.

Our PhD project will use the joint expertise of two labs working with *Drosophila* (Noselli) and Zebrafish (Fürthauer) to study the **role of a conserved group of Myosins in establishing LR asymmetry**.The Noselli laboratory has pioneered the study of LR asymmetry in *Drosophila* through the identification of the unconventional **Myosin 1D (Myo1D) as a unique dextral determinant**. Myo1D is highly conserved in vertebrates up to humans. The action of Myo1D is itself negatively regulated by the closely related Myosin 1C (Myo1C), establishing the **Myosin 1C/D system as a master regulator of *Drosophila* LR asymmetry**. The Noselli and Fürthauer labs have started a collaboration to analyze the function of the Myosin 1C/D system in Zebrafish and obtained very interesting preliminary results indicating that the function of this LR pathway is evolutionarily conserved. The objective of this PhD project at the interface between cellular and developmental biology, is to functionally dissect the contribution of the Myosin 1C/D system to the establishment of zebrafish LR asymmetry. Comparative studies using the two model systems (*Drosophila*, Zebrafish) will allow establishing Myosin 1C/D function in LR asymmetry evolution.

The overall aim of our research project is to take advantage of complementary methodologies from both model systems (genetic, cellular, molecular, imaging and modelling approaches) to determine the function of Myosin 1C/D, its spatial and temporal requirements, identify its partners and targets. The interaction of the Myosin 1C/D system with known LR pathways (nodal, cilia, actin cytoskeleton) will also be studied, leading to an integrated model of LR asymmetry establishment.

The selected candidate will benefit from the use of a number of tools that the Fürthauer lab has started to establish to manipulate Zebrafish Myosin 1C/D function. A unique feature of this project is that the constant interactions between the two partner teams will generate new insights using two different model systems, offering the opportunity to acquire expertise in the use of two of the most widely used animal model systems. Importantly, this will permit directly and rapidly testing the molecular mechanisms governing LR asymmetry and which aspects of Myosin 1C/D function have been evolutionarily conserved.

## RELATED PUBLICATIONS:

1. Spéder P, Adám G, Noselli S. Type ID unconventional myosin controls left-right asymmetry in Drosophila. *Nature* 2006, 440(7085):803-7.
2. Petzoldt AG, Coutelis JB, Géminard C, Spéder P, Suzanne M, Cerezo D, Noselli S. DE-Cadherin regulates unconventional Myosin ID and Myosin IC in Drosophila left-right asymmetry establishment. *Development* 2012, 139(10):1874-84.
3. Gonzales-Morales N., Géminard C., Coutelis JB., Cerezo D. & Noselli S. (2015). The atypical cadherin Dachsous controls Left-Right asymmetry in Drosophila. Developmental Cell, 33:675-689.Héliès-Toussaint, C., Gambert, S., Roller, P., Tricot, S., Lacour, B., and Grynberg, A. (2006). Lipid metabolism in human endothelial cells. Biochim Biophys Acta 1761, 765-774.

# Project id: 8-THÉROND/LUTON

"Role of vesicular trafficking and actin remodeling in cell-cell interactions"

**KEYWORDS:** Epithelial morphogenesis, vesicular trafficking, actin cytoskeleton, cell-cell interaction, EFA6/Arf6

**PI1 (Labex SIGNALIFE team): THÉROND, Pascal**
Institute: *iBV*
Email: therond@unice.fr , Phone: +33 (0)4 92 07 64 46
Website: http://ibv.unice.fr/EN/equipe/therond.php

**PI2 (Labex SIGNALIFE team): LUTON, Frédéric**
Institute: *IPMC*
Email: luton@ipmc.cnrs.fr , Phone: +33 (0)4 93 95 77 70
Website: https://www.ipmc.cnrs.fr/cgi-bin/ipmcx.cgi

**PHD PROJECT SUMMARY:**

Extracellular signals, like secreted molecules with morphogenetic activity are indispensable not only during embryonic development but also in adult life. Morphogens regulate cell fate, tissue reorganization, stem cell differentiation and tissue homeostasis in a well-controlled manner in time and space. However, the cellular mechanism in place to control secretion and transport of these signals still need to be solved.

Our laboratory is focusing on one particular morphogen molecule, called Hedgehog. We use *Drosophila melanogaster* as a model system to study aspects of Hedgehog secretion and signaling both in short-, and long-ranges. Recently, the laboratory of Dr. P. Thérond obtained evidences that specialized cell surface domains, apical and basal, are necessary for the establishment of short and long range signal of Hedgehog (Ayers et al., Dev Cell 2010; Matusek et al., Nature 2014; D'Angelo et al., Dev. Cell 2015).

The goal of this project is to investigate the role of vesicular trafficking and actin remodeling factors in this process. The formation of apical and basal cell surface domains relies on vesicular trafficking (recycling pathways for example) and on specialized actin filaments. To specifically affect cell surface domains we plan to knock-down regulators of trafficking such as small G proteins, regulators of actin polymerization and of cellular extensions and analyze its consequence on Hedgehog secretion. Factors that coordinate vesicular trafficking with actin remodeling will be particularly studied especially the exchange factor EFA6, its cognate small G protein Arf6 and several of their effectors which control epithelial morphogenesis (Luton et al., MBoC 2004; Thèard et al., EMBO J. 2010; Zangari et al., Cancer Res. 2014).

For this project we will use cell biology and genetic technics as well as live imaging methodology to investigate the cell architecture and dynamics of Hedgehog release and spreading. Super resolution microscopy and ultrastructure analysis will also be used to analyze the aforementioned apical and basal membrane domains.

This PhD project is a collaborative work under the joint supervision of the laboratories of Drs. Thérond (IBV) and Luton (IPMC). The PhD position will be located in the laboratory of Dr. Thérond. Interested candidates should have knowledge in genetics, cell biology and optic microscopy (confocal/spinning disc). The PhD position is funded for 3.5 years in duration. Candidates can be nationals of any country.

**RELATED PUBLICATIONS:**

1. Tamas Matusek, Franz Wendler, Sophie Polès, Sandrine Pizette, Gisela D'Angelo, Maximilian Fürthauer and Pascal P. Thérond. The ESCRT Machinery Regulates the Secretion and Long-Range Activity of Hedgehog. ***Nature*** 2014 Dec 4;516(7529): 99-103.

2. Gisela D'Angelo, Tamàs Matusek, Sandrine Pizette and Pascal P. Thérond. Endocytosis of Hedgehog through Dispatched Regulates Long-Range Signaling. ***Developmental Cell*** 2015 Feb. 9 ; 32, 290-303.

3. Zangari J, Partisani M, Bertucci F, Milanini J, Bidaut G, Berruyer-Pouyet C, Finetti P, Long E, Brau F, Cabaud O, Chetaille B, Birnbaum D, Lopez M, Hofman P, Franco M, Luton F. EFA6B antagonizes breast cancer. ***Cancer Res.*** 2014 Oct 1;74(19):5493-506

# Project id: 9-BRAENDLE/LÉOPOLD

"Molecular and evolutionary genetics of cell-organ size relationships "

**KEYWORDS:** allometry, evolution, size control, Drosophila, C. elegans

**PI 1 (Labex SIGNALIFE team):** **BRAENDLE, Christian**
Institute: *iBV*
Email: braendle@unice.fr , Phone: +33 (0)4 92 07 68 97
Website: http://www.braendlelab.net

**PI 2 (Labex SIGNALIFE team):** **LÉOPOLD, Pierre**
Institute: *iBV*
Email: Pierre.LEOPOLD@unice.fr , Phone: +33 (0)4 92 07 64 05
Website: http://ibv.unice.fr/EN/equipe/leopold.php

**PHD PROJECT SUMMARY:**

Molecular mechanisms that coordinate size relationships among different cell types and organs are fundamental for organismal growth and fitness, yet still poorly understood. Moreover, it remains unclear how mechanisms governing such allometry have evolutionarily diverged among distant taxa or among genotypes of the same species. This project addresses these questions using an integrative – molecular and quantitative genetic – approach and taking take advantage of two genetic model organisms, the fruit fly (*Drosophila melanogaster*) and the nematode (*C. elegans*).

The specific objectives of the projects are:

1. Developmental genetic analysis of size relationships among different cell types and organs in *C. elegans*. Comparative analysis of size control mechanisms in *C. elegans* versus *D. melanogaster*.

2. Mapping of natural genetic variation in cell-organ size relationships in *C. elegans* and/or *D. melanogaster* using Genome-Wide Association Study and QTL (Quantitative Trait Locus) mapping using *C. elegans* F2 Recombinant Inbred lines.

3. Molecular characterization of candidate gene variants affecting size relationships (results of objective 2) using complementation analysis, RNAi, transgenesis and targeted genome editing (CRISPR-Cas9).

This interdisciplinary project will be jointly coordinated and supervised by Christian Braendle and Pierre Léopold at the Institute of Biology Valrose, Nice.

**RELATED PUBLICATIONS:**

1. Colombani, J., Andersen, D.S., Boulan, L., Boone, E., Romero, N., Virolle, V., Texada, M., and Leopold, P. (2015). Drosophila Lgr3 Couples Organ Growth with Maturation and Ensures Developmental Stability. Curr.Biol. 25, 2723-2729.
2. Poullet N, Vielle A, Gimond C, Ferrari C & Braendle C 2015 Evolutionarily divergent thermal sensitivity of germline development and fertility in hermaphroditic Caenorhabditis nematodes. Evolution & Development 17: 380-397.
3. Colombani, J., D. S. Andersen, and P. Leopold. 2012. Secreted peptide Dilp8 coordinates Drosophila tissue growth with developmental timing. Science 336:582-585.

# Project id: 10-COLLOMBAT

"Induction of pancreatic beta-cell neogenesis"

**KEYWORDS:** Diabetes, Regeneration, Pancreas, beta-cells

**PI (Labex SIGNALIFE team):** **COLLOMBAT, Patrick**
Institute: *iBV*
Email: collombat@unice.fr , Phone: +33 (0)492076416
Website: http://collombat.com

**PHD PROJECT SUMMARY:**

We are looking for a highly motivated and enthusiastic student to join our research team on a project in the combined fields of mouse genetics, Diabetes, and cell reprogramming.

The major research focus of our group is Type 1 Diabetes research, which is characterized by a selective loss of insulin-producing beta-cells. Despite actual therapies, type 1 diabetic patients still display a shortened life expectancy and an altered quality of life. We therefore aim at developing alternative approaches. Towards this goal, using the mouse as a model, we recently demonstrated that specific pancreatic cells can be regenerated and converted into insulin-producing cells by the ectopic expression of a single gene, Pax4. These cells are functional and can reverse several times the consequences of chemically-induced diabetes in vivo.

More recently, in a collaborative project regrouping INSERM, Harvard, the MIT, and the Max-Planck institute (under the direction of the PI), we identified a compound inducing similar beta-cell regeneration processes (patented and licensed with NovoNordisk). The successful candidate will be directly involved in the characterisation of this compound and alternative ones using the mouse and human islets as models.

The successful candidate would hold a Master degree in Molecular/Cellular/Developmental Biology or a similar field. Interest or previous experience in mouse handling, diabetes would be a plus. Working language in the group and the department is English and therefore good English communication skills are essential. We expect high motivation and commitment, a competitive scientific productivity and ability to work under pressure.

**RELATED PUBLICATIONS:**

1. Courtney M, et al. **PLoS Genet.** 2013. Oct;9(10): e1003934
2. Al-Hasani K, et al**.** Adult duct-lining cells can reprogram into β-like cells able to counter repeated cycles of toxin-induced diabetes. **Dev Cell.** 2013. 26(1):86-100
3. Collombat P, et al. The misexpression of Pax4 in the mouse pancreas induces the conversion of progenitor cells into alpha- and subsequently beta-cells. **Cell**. 2009; 138(3): 449-62

## Project id:

# 12-RASSOULZADEGAN/ROBICHON

**"RNA-mediated epigenetic heredity: site-specific methylation by Dnmt2 in paramutation and telomere length transgenerational controls "**

**KEYWORDS:** RNA/DNA hybrid, methylation, telomere, epigenetic, heredity, quadruplex

**PI (Labex SIGNALIFE team):** **RASSOULZADEGAN, Minoo**
Institute*: iBV*
Email: minoo@unice.fr , Phone: +33 (0)4 92 07 64 12
Website: http://ibv.unice.fr/EN/equipe/rassoulzadegan.php

**PI 2 (Labex SIGNALIFE team):** **ROBICHON, Alain**
Institute: *ISA/INRA*
Email: Alain.Robichon@sophia.inra.fr, Phone: 33 (0)4 92 38 64 19
Website: http://www6.paca.inra.fr/institut-sophia-agrobiotech_eng/Research-teams/GEP

**PHD PROJECT SUMMARY:**

The transmission of a number of complex phenotypes and diseases strongly suggests the possibility of epigenetic non-Mendelian heredity. To validate the concept, we propose two model systems that could provide robust experimental assays to search rules and mechanisms of transmission of the variations. In a murine model, we have identified sperm RNA as the transgenerational vector, as previously determined for several cases of paramutation, and recently, for acquired metabolic and psychic disorder. We intend to develop a collaborative approach in which one of our laboratories (MR) will develop *in vivo* analysis to better define the role of non coding RNAs and its modifications (Dnmt2-dependent methyltransferase) in the establishment and transmission of the characters (telomere lengthening) in mouse. The AR laboratory will in parallel develop in the fly (*Drosophila melanogaster*) new "paramutation-like" phenotypes for advanced genetic analysis of this type of heredity and biochemical analysis of the site-specific methylation catalyzed by Dnmt2. The current working hypothesis is that any RNA that presents sequence motifs compatible with base pairing according to the Hoogsteen rules and consequently capable to engage in a triplex structure might direct the action of Dmnt2.

**RELATED PUBLICATIONS:**

1. M. Rassoulzadegan *et al.*, *Nature* 441, 469 (2006).
2. J. Kiani *et al.*, *PLoS genetics* 9, e1003498 (2013).
3. Aviv Dombrovsky, Laury Arthaud, Terence N. Ledger, Sophie Tares and Alain Robichon. Genome Res. 2009 Nov;19(11):2052-63.
4. Claude Pasquier, Mathilde Clément, Aviv Dombrovsky, Stéphanie Penaud, Martine Da Rocha, Corinne Rancurel, Neil Ledger, Maria Capovilla, Alain Robichon. PLoS ONE 2014 9(12):e115022

# Project id: 15-FRENDO/POIRIÉ

**"Cross-talk between aphid facultative symbiosis and plant nitrogen fixation symbiosis in the *Acyrthosiphon pisum* - *Medicago truncatula* interaction "**

**KEYWORDS:** Symbiosis, insect-symbionts-plant interaction, biological nitrogen fixation, pea aphid, plant defense

**PI1 (Labex SIGNALIFE team): FRENDO, Pierre**
Institute: *ISA*
Email: Pierre.FRENDO@unice.fr , Phone: +33 (0)4 92 38 66 38
Website: http://www6.paca.inra.fr/institut-sophia-agrobiotech_eng/Research-teams/SYMBIOSE

**PI2 (Labex SIGNALIFE team): POIRIÉ, Marylène**
Institute: *ISA*
Email: poirie@sophia.inra.fr , Phone: +33 (0)4 92 38 64 09
Website: http://www6.paca.inra.fr/institut-sophia-agrobiotech/Equipes-ISA/ESIM

## PHD PROJECT SUMMARY:

The field of microbial symbiosis has achieved astonishing advances demonstrating that symbionts play a crucial role in shaping the host phenotype and drive its adaptation to the environment. In this context, the cross-talk between different interacting species and their respective symbionts adds a level of complexity that still remains to be considered. The project will explore this new field focusing on the interaction between a leguminous plant and a leguminous-dependant aphid species.

Legumes live a well-described symbiosis with bacteria that increases the availability of nitrogen. *Medicago truncatula*, a small self-fertile annual plant, is one legume model organism. It is attacked by the pea aphid *Acyrthosiphon pisum* (the aphid model) that feeds on several legumes (e.g. pea, alfalfa, broad bean), and is thus a major agronomic pest. Aphids have evolved as sap-feeding insects thanks to their trophic association with an obligatory bacterium, and the pea aphid also hosts eight different facultative symbionts that strongly influence its phenotype (e.g. pathogen resistance, immune components). Interestingly, this species is structured into host races adapted to different legume plants, and particular facultative symbionts are strongly associated with aphids feeding on certain plants (Peccoud and Simon 2012). Finally, there has been recent evidence in sap-feeding insects of symbiont circulation in sap and plant-mediated symbiont transfer (Caspi-Fluger, 2012; Gonella et al., 2015).

The PhD project will question whether and how the presence of different facultative symbionts in the pea aphid and the nitrogen fixing symbiosis (NFS) modulate the legume-aphid interaction and vice-versa. Using aphid lines of the same genetic background harboring different symbionts, we will i) evaluate the influence of the NFS on aphid and symbionts traits and of each facultative symbiont on the NFS efficiency (plant growth, primary metabolism) ii) identify *Medicago* defense pathways to aphids and the possible changes with different aphid facultative symbionts. Having evaluated the importance of aphid and plant microbial partners in the outcome of the interaction, we will focus on identification of their cellular and molecular bases (effectors, signalling pathways) in the different partners.

Functional aspects of symbiosis are generally considered at the species level. Here, we will evaluate the multitrophic, direct and indirect effects of the species association with various bacterial symbionts. Identifying biotic factors that may interfere in the field with NFS efficiency will also be highly relevant for sustainable agronomy.

*Available tools*: Aphid lines of identical genetic background with different facultative symbionts (collab. JC Simon, Rennes). Genomes available (*Medicago*, pea aphid, all symbionts). Genetic transformation tools (Medicago), RNAi (aphid).

*Main approaches*: Plant genetics, transcriptomics, metabolomics, insect/plant cell biology, microbiology.

## RELATED PUBLICATIONS:

1. Puppo A, Pauly N, Boscari A, Mandon K, Brouquisse R. (2013) Hydrogen peroxide and nitric oxide: key regulators of the legume – Rhizobium and mycorrhizal symbioses. Antioxidant and Redox Signaling. 18(16):2202-2219.
2. Schmitz A, Anselme C, Ravallec M, Rebuf C, Simon J-C, Gatti J-L, Poirié M (2012) The cellular immune response of the pea aphid to foreign intrusion and symbiotic challenge. PLoS One 7(7): e42114.
3. Foyer CH, Verral SR, Hancock RD (2015) Systematic analysis of phloem-feeding-insect-induced transcriptional reprogramming in Arabidopsis highlights common features and reveals distinct responses to specialist and generalist insects. J. Exp. Bot 66(2): 495-512.

# Project id: 16-KELLER

**"Functional Analysis of a Receptor-Like Kinase in Arabidopsis thaliana: Characterization of the Role of Individual Domains in Plant-Microbe Interactions "**

**KEYWORDS:** plant-pathogen interactions, disease susceptibility, molecular reprogramming, receptor-mediated signaling, functional complementation

**PI (Labex SIGNALIFE team):** **KELLER, Harald (PANABIÈRES, Franck)**
Institute: *ISA*
Email: keller@sophia.inra.fr , Phone: +33 (0)4 92 38 65 94
Website: http://www6.paca.inra.fr/institut-sophia-agrobiotech_eng/Research-teams/IPO/Team-members/KELLER-Harald

## PHD PROJECT SUMMARY:

Oomycetes are extremely devastating filamentous pathogens that impact ecosystems and agriculture. Our research aims at characterizing the molecular mechanisms that govern the establishment of disease in host plants. To sense the environment, plant cells possess more than 200 plasma membrane receptors, which are composed of extracellular leucine-rich repeats (LRRs) and an intrinsic, intracellular kinase domain. These receptors are characteristic for plant cells, but absent from higher animals. We previously identified the Arabidopsis receptor "Impaired Oomycete Susceptibility 1" (IOS1), which contributes to the infection success of pathogenic oomycetes, such as *Hyaloperonospora arabidopsidis* and *Phytophthora parasitica* (Hok *et al.*, 2011). In addition to LRRs, the extracellular region of IOS1 possesses a domain, which shares similarities with malectin from animals. Malectins bind carbohydrates and participate in monitoring the glycosylation state of proteins during their transit in the endoplasmic reticulum (ER). IOS1 ligands might thus be both carbohydrates and proteins. Upon oomycete infection, IOS1 negatively regulates a hormone signaling pathway, which is governed by abscisic acid (ABA) (Hok *et al.*, 2014).

**The main aims of the proposed PhD project are:**

**1.** To characterize the role of the extracellular domain for plant defense and ABA signaling.

By using different domains of the receptor for functional complementation assays of a knock-out mutant. Many lines are already available in the laboratory for analysis.

By producing recombinant domains for carbohydrate-binding assays and co-immunoprecipitation experiments (see below). This work might identify potential oligosaccharide and protein ligands.

**2.** To identify IOS1 protein partners that are required for signal transduction:

By characterizing the function of protein candidates that were already identified in the laboratory.

By immunoprecipitation experiments and *in planta* interaction assays.

The project exploits multidisciplinary approaches (plant pathology and physiology, functional genomics and transcriptomics, genetics, and microbiology, biochemistry, molecular and cellular biology). The student will benefit from a wide range of tools and genetic resources that are available in the host laboratory, and from dedicated platforms for biochemistry and cellular biology that are hosted by the institute.

## RELATED PUBLICATIONS:

1. Hok S, Danchin EG, Allasia V, Panabières F, Attard A, and Keller H (2011). An Arabidopsis (malectin-like) leucine-rich repeat receptor-like kinase contributes to downy mildew disease. *Plant Cell Environ.* 34, 1944-1957.
2. Hok S, Allasia V, Andrio E, Naessens E, Ribes E, Panabières F, Attard A, Ris N, Clément M, Barlet X, Marco Y, Grill E, Eichmann R, Weis C, Hückelhoven R, Ammon A, Ludwig-Müller J, Voll LM, and Keller H (2014). The receptor kinase IMPAIRED OOMYCETE SUSCEPTIBILITY1 attenuates abscisic acid responses in Arabidopsis. *Plant Physiol.* 166, 1506-1518.
3. Rodiuc N, Barlet X, Hok S, Perfus-Barbeoch L, Allasia V, Engler G, Séassau A, Marteu N, de Almeida-Engler J, Panabières F, Abad P, Kemmerling B, Marco Y, Favery B, and Keller H (2016). Evolutionarily distant pathogens require the Arabidopsis phytosulfokine signalling pathway to establish disease. Plant Cell Environ. in press.

# Project id: SCHEDL/CHABOISSIER

**"Signaling pathways driving steroid organ development and repair "**

**PI1 (Labex SIGNALIFE team): SCHEDL, Andreas**
Institute: *iBV*
Email: schedl@unice.fr , Phone: +33 (0)4 92 07 64 01
Website: http://ibv.unice.fr/EN/equipe/schedl.php

**PI2 (Labex SIGNALIFE team): CHABOISSIER, Marie-Christine**
Institute: iBV
Email: chaboiss@unice.fr , Phone: +33 (0)4 92 07 64 51
Website: http://ibv.unice.fr/EN/equipe/chaboissier.php

**PHD PROJECT SUMMARY:**

Adrenal glands and gonads are two important endocrine organs that arise from the same primordium (adreno-gonadal primordium=AGP). Our groups have in the past made major contributions to decipher the molecular programs underlying sex determination (Chaboissier) and adrenal development (Schedl). By contrast the pathways determining the processes underlying renewal and repair of these organs are poorly understood. Repair of organs during normal homeostasis or after damage involves the activation of cellular signaling programs that ensure proliferation and differentiation of progenitor/stem cells. One key pathway in this activation is WNT/β-catenin signaling. Regulation of β-catenin signaling occurs on multiple levels including both positive and negative modulators. Of particular importance for the development of steroidogenic organs appear to be the signaling molecules Wnt4 and Rspo1/3. Aim of the present project is to determine how these factors influence cell renewal, determine cell lineage relationships and develop conditions that allow growth of progenitors in vitro.

*1. Lineage tracing of Wnt4 expressing cells*

A Wnt4-CreERT2 allele will be created using a CRISPR/CAS9 mediated approach and mice crossed with the mTmG reporter strain. Lineage tracing will be performed following tamoxifen injection at different time points and variable chase times. This analysis will provide important insights into lineage relationships as well as cell turnover in both adrenals and gonads.

*2. Determining the role of Rspondins in steroidogenic maintenance*

We have already established an important role for Rspo1 and Rspo3 in steroidogenic organ development. It will be now important to determine the precise cell types that they act on, as well as to define their molecular targets. To achieve this goal a combination of reporter mice, gain and loss of function models and a range of molecular analyses will be employed.

*3. Establishing culture conditions for adrenal progenitors*

We and other labs have established important roles for signaling pathways in the growth and maintenance of adrenal progenitors. We will use this information to establish culture conditions of identified progenitor cells either alone or in combination with other cell types (organoids).

# Project id: 17-AUBERGER/BALLOTTI

**"Mechanisms of resistance to targeted therapies in melanoma and myeloid malignancies Preclinical characterization and validation of innovative compounds"**

**KEYWORDS:** Melanoma, Myelodysplastic syndroms, AMPK, targeted therapy, innovative compounds

**PI 1 (Labex SIGNALIFE team): AUBERGER, Patrick**
Institute: *Team 2,U1065, C3M*
Email: auberger@unice.fr , Phone: +33 (0)4 89 06 43 11
Website: http://www.unice.fr/c3m/index.php/research-teams/patrick-auberger/

**PI 2 (Labex SIGNALIFE team): BALLOTTI, Robert**
Institute: *Team 1, U1065, C3M*
Email: robert.ballotti@unice.fr , Phone: +33 (0)4 89 06 43 33
Website: http://www.unice.fr/c3m/index.php/research-teams/robert-ballotti/

**PHD PROJECT SUMMARY:**

Melanoma and MyeloDysplatic Syndromes (MDS) are two deadly cancer entities which frequently develop resistance to classical antitumor treatments. Regarding melanoma B-Raf inhibitors have demonstrated an improvement in both overall and progression free survivals. Unfortunately, despite encouraging responses with this inhibitor, relapse consistently occurs within months following initiation of treatment. MDS is a heterogeneous stem cell disease characterized by ineffective hematopoiesis leading to pancytopenias. The leading treatment for MDS patients is 5-Azacytidine or Vidaza® which significantly improves overall survival compared to conventional therapies. As in the case of melanoma, most of patients eventually relapse within months. Therefore, in both cancers, there is an urgent need to identify and target new pathways to overcome resistance.

The two teams involved in the present project have longstanding collaborations in the field of cancer. More precisely, we have shown that Adenosine Monophosphate Kinase (AMPK) activators such as biguanides and nucleoside derivatives caused growth arrest and cell death in melanoma and MDS, respectively (1-4). AMPK is a major regulator of cell metabolism that acts as an intracellular fuel sensor in all eukaryotic cells. AMPK regulates cellular energy, homeostasis in response to energy stress. Beyond regulation of energy metabolism, AMPK is now emerging as a promising drug target for anticancer therapies. In this context and in collaboration with the Institut de Chimie de Nice (UMR CNRS 7272) the two participating teams have developed innovative compounds that specifically target the AMPK pathway. Preliminary results indicate that both family of compounds induces AMPK activation and cell death, but by slightly different mechanisms (Apoptosis, Autophagic Cell Death or both).

In this context, the work lines of the proposed project are:

1- To confirm the efficiency of both series of compounds on melanoma and MDS
2- To decipher their mechanisms of action *in vitro* using sensitive and resistant melanoma and MDS cell lines and tumoral primary cells from melanoma and MDS patients
3- To validate the efficiency of these compounds in xenografted athymic mice models of melanoma an MDS

Targeting the AMPK pathway is a promising and novel option in cancer therapy. We hope that the proposed project should improve the management of patients suffering melanoma and MDS and resistant to targeted therapies (B-Raf inhibitors and Vidaza®).

**RELATED PUBLICATIONS:**

**Cell Death and Disease**-2011, **Oncotarget** -2012, **Mol. and Cell. Therapeutics**-2013, **Curr Pharm Des**-2013, **Oncotarget**-2014, **Pigment Cell and Melanoma Research**-2015. **Patents** - **S. Rocchi, R. Ballotti, T. Tomic,** (Biguanide compounds, 2010, PCT/EP2O1 1/002268) -**G. Robert, R. Benhida, P. Auberger** (Nucleoside analogues, 2011. WO PATENT : WO/2012/143624).

# Project id: 18-BARDONI/LALLI

"New genes and pathways involved in autism spectrum disorder"

**KEYWORDS:** Autism, intellectual disability, transcription factors, gene expression, transcriptional regulation

**PI 1 (Labex SIGNALIFE team):** **BARDONI, Barbara**
Institute: *IPMC*
Email: Bardoni@ipmc.cnrs.fr , Phone: +33 (0)4 93 95 77 66
Website: https://www.ipmc.cnrs.fr/cgi-bin/ipmcx.cgi

**PI 2 (Labex SIGNALIFE team):** **LALLI, Enzo**
Institute: *IPMC*
Email: ninino@ipmc.cnrs.fr , Phone: +33 (0)4 93 95 77 55
Website: https://www.ipmc.cnrs.fr/cgi-bin/ipmcx.cgi

**PHD PROJECT SUMMARY:**

Intellectual disability (ID) and autism spectrum disorders (ASD) represent a serious and widespread public health problem. Both disorders have in common alterations in brain circuits and anatomical structures, such as synaptic transmission and dendritic spine morphology. Even if both ID and ASD are characterized by the heterogeneity of their genetic and molecular bases, recent studies have indicated significant enrichment for the expression of several categories of genes in ID/ASD while mutations in an increasing number of genes have been shown to be a cause for both disorders. An example is the Fragile X Mental retardation gene, FMR1, whose silencing causes the Fragile X syndrome, the most common form of intellectual disability and autism, which is also characterized by physical hallmarks.
By screening of patients affected by autism and intellectual disability we identified several variants in a set of genes and we validated one of them, present in a gene coding for a transcription factor, as a new potentially pathogenic mutation. This protein is known to be involved in several signalling pathways in testis, adrenal gland and adipocytes but was never characterized in neurons. We plan to develop cell and animal models to identify the cascade of events donwstream this mutated gene during neurodevelopment in order to understand the molecular and cellular causes of altered behavior and cognitive functions.
Techniques: genomics, molecular biology, cell biology, immunohistochemistry.

**RELATED PUBLICATIONS:**

1. Doghman M, Figueiredo BC, Volante M, Papotti M, Lalli E. (2013) Integrative analysis of SF-1 transcription factor dosage impact on genome-wide binding and gene expression regulation. Nucl. Acids Res. 41: 8896-8907
2. Abekhoukh S, Bardoni B (2014) – CYFIP family proteins between autism and intellectual disability: links with Fragile X syndrome. Front Cell Neurosci., doi: 10.3389/fncel.2014.00081
3. Maurin T, Melko M, Abekhoukh S, Khalfallah O, Davidovic L, Jarjat M, D'Antoni S, Catania MV, Moine H, Bechara E, Bardoni B. (2015) The FMRP/GRK4 mRNA interaction uncovers a new mode of binding of the Fragile X Mental Retardation Protein in cerebellum. Nucl Acids Res., 43: 8540-50.

# Project id: 19-CRISTOFARI/FÉRAL

"Deciphering muscular stem cell alterations in FSHD muscular dystrophy patients"

**KEYWORDS:** muscle adult stem cells, mechanotransduction, genetic instability, epigenetics, CRISPR/Cas9

**PI (Labex SIGNALIFE team):** **CRISTOFARI, Gaël**
Institute: *IRCAN*
Email: Gael.Cristofari@unice.fr , Phone: +33 (0)4 93 37 70 87
Website: http://www.ircan.org/

**PI 2 (Labex SIGNALIFE team):** **FÉRAL, Chloé**
Institute: *IRCAN*
Email: Chloe.Feral@unice.fr , Phone: +33 (0)4 93 37 76 18
Website: http://www.ircan.org/

**PHD PROJECT SUMMARY:**

Fascioscapulohumeral muscular dystrophy (FSHD) is one of the most common degenerative myopathies. It is associated with chromatin relaxation of the D4Z4 macrosatellite array (decreased repressive histone marks and DNA hypomethylation). This phenomenon eventually leads to the pathogenic expression of the DUX4 retropseudogene encoded by the D4Z4 unit itself. DUX4 is a transcription factor and its expression profoundly alters muscle cell gene expression programs. Although the most prevalent form of this disease (FSHD1) results from the reduction of the number of D4Z4 repeats, a second form of the disease (FSHD2) has been recently identified, in which the number of D4Z4 repeats is unchanged, but an epigenetic regulator, SMCHD1, is mutated. However, the molecular, cellular and physiological alterations directly responsible for disease initiation and progression remain unclear, in particular in muscle stem cells.

The project proposed here aims at exploring the link between SMCHD1 mutations, DUX4 expression and muscular dystrophy. More specifically, we plan to:

1. define the genetic and phenotypical profiles of FSHD cells compared to wild-type cells (SMCHD1 mutations, size of D4Z4 array, D4Z4 methylation profile, DUX4 expression, genetic and chromosomal instability, differentiation in culture mimicking muscle microenvironment, mechanical tissue properties, regenerative capacity in xenograft mouse models);
2. test the reversibility of the identified genetic, epigenetic and phenotypic alterations upon SMCHD1 rescue, in particular in muscle stem cells, through genome engineering approaches.

This research program will be established through a collaborative work between the laboratories of Chloé Féral and Gaël Cristofari, who will co-supervise the PhD thesis. The project will benefit from their respective expertise in tissue regeneration and mechanotransduction, and in genetics and epigenetics of DNA repeats, and from strong interactions with the neuromuscular disease department at the University Hospital of Nice (directed by Pr. Sabrina Sacconi). The candidate should have an excellent background in molecular and cellular biology, with a strong interest in human genetics. The working language is English.

**RELATED PUBLICATIONS:**

1. Blau HM, et al. Nat Med 21, 854-862 (2015).
2. Lemmers RJ, et al. Nat Genet 44, 1370-1374 (2012).
3. Lemmers RJ, et al. Science 329, 1650-1653 (2010).

# Project id: 20-DANI/MAGNALDO

**"Deciphering the network of interactions between dermal adipose stem cells, fibroblasts and epithelial cells"**

**KEYWORDS:** dermal adipose stem cells, fibroblasts, epithelial cells, skin, cancer, aging

**PI (Labex SIGNALIFE team):** **DANI, Christian**
Institute: *iBV*
Email: christian.dani@unice.fr , Phone: +33 (0)4 93 37 76 47
Website: http://ibv.unice.fr/EN/equipe/dani.php

**PI 2 (Labex SIGNALIFE team):** **MAGNALDO, Thierry**
Institute: *IRCAN*
Email: tmagnaldo@unice.fr , Phone: +33 (0)4 93 37 76 70
Website: http://www.ircan.org/

**PHD PROJECT SUMMARY:**

The proposed project associates the team of Christian Dani (IBV) and the team of Thierry Magnaldo (IRCAN). CD team focuses his research on mechanisms that orchestrate the differentiation of human mesenchymal stem cells in adipocytes. TM team is involved in cell-cell interactions upon aging and carcinogenesis using skin as a favorite study system.
Proper interactions between mesenchymal with epithelial cells are essential upon organogenesis, tissue maintenance and repair. These interactions are severely altered with age and more dramatically, cancer. The role of fibroblasts derived from mesenchymal stem cells (MSC) has been extensively studied in both aging and cancer. In contrast the role of adipocytes, another cell type derived from MSC, remains poorly understood. In skin, adipocytes reside in the deepest dermis, fibroblasts compose the intermediate compartment and epidermal keratinocytes form the superficial layer. Recent data revealed a common precursor for dermal fibroblasts and dermal adipocytes. One study in genetically engineered mice has suggested that adipocytes could be involved in the control of hair follicle stem cells, but where and how fibroblasts may convey/contribute to adipocyte-keratinocyte signaling has not been studied. The aim of the project is to study the influence of human adipocytes derived from dermal adipose stem cells on dermal fibroblasts and, in turn, the behavior of WT or pathologic epithelial cells. The study will be based on the development of 3D organotypic cultures and biochemical and molecular analyses. Deciphering the network of interactions between dermal adipose stem cells, fibroblasts and epithelial cells should further contribute to our basic knowledge on complex cellular interactions underlying homeostasis and pathological conditions and, hence, contribute to the improvement pharmacological treatments.

**RELATED PUBLICATIONS:**

1. Gache, Y., F. Brellier, E. Burty-Valin, S. Barnay, S. Scarzello, M. Ruat, N. Sevenet, M.-F. Avril and T. Magnaldo, T., Basal cell carcinoma in Gorlin's patients: a matter of fibroblasts-led protumoral microenvironment ? PLoS One. 2015 Dec 22;10(12):e0145369. doi: 10.1371/journal.pone.0145369. eCollection 2015.
2. Ravaud, C, Esteve, D, Villageois P, Bouloumie A, Dani C, Ladoux A Promotes Expansion of Adipose Progenitor Cells in Response to Changes in Distinct Microenvironmental Effectors. Stem Cells. 2015 Aug; 33(8):2564-73. doi: 10.1002/stem.2016. Epub 2015 May 13.

# Project id: 22-GILSON

"Role of the telomeric protein TRF2 in neuronal development and aging "

**KEYWORDS:** Telomere, Chromosome stability, Neurogenesis, Aging, Mouse model

**PI (Labex SIGNALIFE team):** **GILSON, Eric**
Institute: *IRCAN*
Email: Eric.Gilson@unice.fr , Phone: +33 (0)6 07 27 29 73
Website: http://www.ircan.org/

## PHD PROJECT SUMMARY:

**Introduction**

Most of the knowledge about the role of telomere during development and aging has been obtained from replicative cells. However, telomere biology may also play an important role in non-dividing cells by controlling tissue-specific programs of DNA damage sensitivity, differentiation, and adaptation to environmental changes. In this PhD project, we will address the functions of the shelterin telomere protein TRF2 in neuronal development and aging as well as whether these functions are modulated by developmental signaling pathways and telomere shortening.

**Objectives**

In addition to its key role in protecting telomeres from unwanted activation of the DNA damage response (DDR), the shelterin component TRF2 plays extratelomeric roles in transcriptional regulation particularly for genes expressed in neurons. Therefore, studying the coupling between telomere dynamics and neuronal-specific role of TRF2 emerges as a paradigm to understand how tissue-specific developmental programs are involved in aging.

**Methodologies**

To better understand the link between TRF2, neurogenesis and aging, the student will develop human cellular and mouse models in order to:

- determine the regulation and the role of TRF2 in human progenitor and mature neurons by siRNA screening.
- generate human neuronal progenitors harbouring different telomere lengths to assay TRF2 expression and functions in relationships with telomere length.
- study the outcome of TRF2 inhibition in progenitor and mature human neurons regarding stress response, telomere integrity, transcriptome and global chromatin structure.
- analyze developmental and aging phenotypes of mice conditionally invalidated for TERF2 in either neural stem cells/progenitors or in mature neurons (the mice are already available in the lab).
- provide a detailed molecular description of TRF2 function in the mouse models by high-throughput analysis in neuronal cells of transcriptome and global chromatin analysis.

**Collaborations**

F. Saudou (Grenoble Institute of Neurosciences, France); L. Rudolph (Leibniz Institute Jena,Germany); G. Garinis (Heraklion, Greece).

**Expected Results:**

- identification of the signaling pathways regulating TRF2 expression in neuronal cells during development and aging.
- understanding the role of TRF2 in neurogenesis
- establishing links between neuronal development and aging through telomere chromatin remodeling.

## RELATED PUBLICATIONS:

1. 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) The human TTAGGG Repeat Factors 1 and 2 bind to a subset of interstitial telomeric sequences and satellite repeats Cell Research, 21(7):1028-38
2. Biroccio A, Cherfils-Vicini J, Augereau A, …… Vivier E, Gilson E. TRF2 inhibits a cell-extrinsic pathway through which natural killer cells eliminate cancer cells. Nat Cell Biol. 2013 Jul;15(7):818-28.
3. Ye J, Renault VM, Jamet K, Gilson E. Transcriptional outcome of telomere signalling. Nat Rev Genet. 2014 Jul; 15(7):491-50

# Project id: 23-GLAICHENHAUS

**"Neuroendocrine regulation of antiviral innate immunity in mice and humans"**

**KEYWORDS:** Neuroimmunology, Innate immunity, Mucosal immunity, influenza virus

**PI (Labex SIGNALIFE team):** **GLAICHENHAUS, Nicolas**
Institute: *IPMC*
Email: nicolas.glaichenhaus@unice.fr , Phone: +33 (0)4 93 95 77 85; +33 (0)6 18 99 44 61
Website: http://www.ipmc.cnrs.fr

**PHD PROJECT SUMMARY:**

Studies in humans and animals have shown that both neural and endocrine signals regulate the activity of immune cells. Compared to controls, human individuals who were exposed to chronic psychological stress exhibited reduced immune responses to vaccines directed against seasonal influenza virus, hepatitis B, and pneumococcal pneumonia. Likewise, loneliness and neuroticism had a negative impact on vaccine-induced immune responses while social support and positive affect improved immunity. Other studies have shown that specific behaviors such as physical exercise, alcohol consumption, diet, smoking, and sleep deprivation could regulate vaccine-induced antibody responses in humans. Studies in animal models have confirmed that neural and endocrine signals could regulate immunity. Mice exposed to chronic stress as neonates exhibited altered immune responses when infected with the influenza type A virus (IAV). While the regulatory mechanisms that are at work in these various situations have only been partially elucidated, several studies have pointed to a critical role of the hypothalamicpituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), and of their main mediators - noradrenaline/adrenaline and glucocorticoids. However, it remains to be determined which immune cell types are targeted by these mediators, and how they modify their phenotypes. In preliminary experiments, we have shown that mice housed in an environment conducive to high levels of social, motor and sensory stimulation, referred to as "enriched environment" (EE), show increased resistance to IAV infection and disease compared to mice housed in a standard environment (SE). Two days after infection, Broncho Alveolar Lavages from EE mice contained higher amounts of type I interferon (IFN), lower levels of interleukin-1ß, and fewer neutrophils compared to SE mice. Further experiments suggested that the relative resistance of EE mice to IAV infection may reflect an altered ability of innate immune cells to respond to viral determinants. Following up on these experiments, we propose (1) to identify the nature of neural and endocrine signals that may promote resistance of EE mice to IAV disease; and (2) to elucidate how these signals regulate the production of pro-inflammatory and anti-viral cytokines in a mouse model of IAV infection. In an attempt to translate our findings in humans, we plan to identify whether and which psychosocial and behavioral factors regulate the production of cytokines in young adult humans. This latter study, which has already started, is nested within the Internet-based Students HeAlth Research Entreprise (www.i-Share.fr) longitudinal cohort and will take advantage of the recently described TruCulture system that has successfully been used to define the boundaries of a healthy immune response to various stimuli, including whole microbes and purified Pathogen-Associated Molecular Patterns (PAMPs) or synthetic analogs.

**RELATED PUBLICATIONS:**

1. Irwin MR, Cole SW. 2011. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol 11: 625-32
2. Nithianantharajah J, Hannan AJ. 2006. Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nat Rev Neurosci 7: 697-709
3. Duffy D, Rouilly V, Libri V, Hasan M, Beitz B, David M, Urrutia A, Bisiaux A, Labrie ST, Dubois A, Boneca IG, Delval C, Thomas S, Rogge L, Schmolz M, Quintana-Murci L, Albert ML. 2014. Functional Analysis via Standardized Whole-Blood Stimulation Systems Defines the Boundaries of a Healthy Immune Response to Complex Stimuli. Immunity 40: 436-50

# Project id: 24-GUAL/DELAUNAY

**"KLF10: a potential actor in the liver complications of obesity"**

**KEYWORDS:** Obesity, Liver, Metabolism, Circadian Clock

**PI 1 (Labex SIGNALIFE team):** **GUAL, Philippe**
Institute: *INSERM U1065, C3M, Team 8*
Email: gual@unice.fr , Phone: +33 (0)4 89 06 43 23
Website: http://www.unice.fr/c3m/index.php/research-teams/philippe-gual-albert-tran/

**PI 2 (Labex SIGNALIFE team):** **DELAUNAY, Franck**
Institute: *CNRS UMR7277 INSERM U1091 - iBV*
Email: delaunay@unice.fr , Phone: +33 (0)4 92 07 68 38
Website: http://ibv.unice.fr/FR/equipe/delaunay.php

**PHD PROJECT SUMMARY:**

The incidence of obesity is rapidly increasing in many Western countries. This pandemic is associated with the development of type 2 diabetes and liver complications (Non Alcoholic Fatty Liver Diseases (NAFLD)). NAFLD is one of the three principal causes of cirrhosis and increases the risk of liver-related death and hepatocellular carcinoma. Despite this major public health concern, apart from lifestyle changes, treatment of NAFLD is still elusive as no large study has shown any efficacy for pharmacological treatment of NAFLD. NAFLD are frequently associated with visceral obesity and insulin resistance. However, the molecular mechanisms responsible for the development of NAFLD are still unclear. The Krüppel like transcription factor KLF10 is expressed in hepatocytes, immune cells and hepatic stellate cells and is involved in circadian clock, liver metabolism and TGF beta signaling. However, its role in the development and the severity of liver complications associated with obesity is still unknown. The two partners will share their expertise in the clinical and basic aspects of fatty liver disease (Philippe Gual), and circadian clock and metabolism (Franck Delaunay) to investigate the role of KLF10 in the progression of fatty liver disease. The project will benefit from the access to samples from a large cohort of patients, availability of a variety of techniques and approaches, animal models (general and cell specific KLF10 KO mice) and primary cultures of liver cells that will be shared by the two groups.
We will 1) evaluate in mice the consequence of general and hepatocyte specific deficiency of KLF10 in the development of insulin resistance and liver complications (from steatosis to fibrosis); 2) study *in vivo* and *in vitro* the role of KLF10 in hepatocyte metabolism, immune cells and stellate cells functions; and 3) evaluate the relevance of the hepatic KLF10 pathways in our cohort of obese patients with NAFLD (1008 patients).
This project should allow a better understanding of hepatic metabolism and NAFLD and leading to propose new therapeutic targets.

**RELATED PUBLICATIONS:**

1. Tran A, Gual P. Nonalcoholic steatohepatitis in morbidly obese patients. *Clin Res Hepatol Gastroenterol. 2013* Feb;37(1):17-29.
2. Anty R et al. 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. *J of Hepatology,* 2012, 57(5):1090-6. (I.F. 11.33)
3. Guillaumond F, Gréchez-Cassiau A, Subramaniam M, Brangolo S, Peteri-Brünback B, Staels B, Fiévet C, Spelsberg TC, Delaunay F, Teboul M. Kruppel-like factor KLF10 is a link between the circadian clock and metabolism in liver. *Mol Cell Biol*, 2010, 30(12):3059-70

# Project id: 26-HOFMAN/VAN OBBERGHEN

**"The role of miR-375 in perturbed metabolism and carcinogenesis of lung cancers"**

**KEYWORDS:** MiR-375, carcinogenesis, metabolism, lung carcinoma, signaling

**PI (Labex SIGNALIFE team):** **HOFMAN, Paul**
Institute: *IRCAN*
Email: hofman@unice.fr, Phone: +33 (0)4 92 03 87 49
Website: http://www.ircan.org/

**PI 2 (Labex SIGNALIFE team):** **VAN OBBERGHEN, Emmanuel**
Institute: *IRCAN*
Email: emmanuel.vanobbeghen@unice.fr, Phone: +33 (0)4 93 37 77 72
Website: http://www.ircan.org/

## PHD PROJECT SUMMARY:

MicroRNAs are evolutionary conserved small, approximately 22 nucleotide long, single stranded noncoding RNAs, which have been shown to modulate numerous biological processes by virtue of their action on posttranscriptional gene regulation. MiR-375 has emerged as a clear example of a multifunctional miRNA being involved in several important functions. While it was initially discovered in pancreatic islets as a modulator of insulin secretion, its action affects also pancreatic beta cell proliferation and islet development, lung surfactant secretion and tumorigenesis in general. In various types of cancer the expression of miR-375 has been shown to be altered. Importantly, low expression of miR-375 in squamous-cell carcinoma and high expression in adenocarcinoma of lung is an unfavorable prognostic factor for overall survival. At molecular level, this altered expression seems to affect the action of a series of molecules involved in control of cell growth including PDK1, IGF1-R and the essential autophagy protein *ATG7*. In addition, our preliminary data suggest that miR-375 might also participate in the perturbed cellular metabolism which is now considered as a key feature of cancer cells.
*The overall aim* of the proposed project is to identify the targets of miR-375 and to characterize its function in subtypes of lung cancer. Despite major advances in diagnostic procedures and therapeutic approaches lung cancer remains a leading cause of death world-wide and is increasing at staggering pace in several emerging countries partly due to augmenting pollution and tobacco use. Several factors are likely to contribute to the generally bad prognosis of lung cancer including heterogeneity and insufficient comprehension of the tumor biology.
*The specific aims* are the following: 1) Analysis of miR-375 expression in the different lung carcinoma subtypes, including small cell lung carcinoma cell carcinoma, adenocarcinoma and squamous cell carcinoma using qRT-PCR and in situ hybridization assays; 2) Identification of specific miR-375 target genes and altered signaling pathways by gain (miR-mimics) and loss of function (antagomiRs) experiments in different cell-lines derived from non-cancerous lung tissue and in cell-lines derived from cancerous lung tissue with different genomic alteration; 3) A particular emphasis will be put on the investigation of the contribution of missexpression of miR-375 on the altered cellular metabolisms (autophagy, mitochondrial and "Warburg" energy metabolisms...) of the lung tumors. 4) Investigation of the regulation of miR-375 expression by lung oncogenes (*KRAS, EGFR, ALK*…) and lung carcinogens (tobacco and air pollutants), followed by the identification of their underlying signaling.
From this basic and translational project, we anticipate gaining insight into how miR-375 expression levels can impact lung cancer patient outcome and incidence of distant metastasis through the exploration of its molecular mechanisms.

## RELATED PUBLICATIONS:

1. Lassalle S, Brest P, Barbry, P, Mari B, **Hofman P**. SEC23A targeting by miR-375 is a biomarker of the in vitro efficacy of vandetanib. Oncotarget 2016 in press
2. Dumortier O, Hinault C, Gautier N, Patouraux S, Casamento V, **Van Obberghen E**. Maternal protein restriction leads to pancreatic failure in offspring: role of misexpressed microRNA-375. Diabetes. 2014 Oct;63(10):3416-27.
3. Brest P, Lapaquette P, Souidi M, Lebrigand K, Cesaro A, Vouret-Craviari V, Mari B, Barbry , **Hofman P.** synonymous variant in IRGM alters a binding site for miR-196 and causes deregulation of IRGM-dependent xenophagy. Nat Genet. 2011 Mar;43(3):242-5

# Project id: 27-MARIE

**"Unravelling the physiopathological actions of the newly-discovered Aη peptides in the brain "**

**KEYWORDS:** Neuroscience, neurons, Alzheimer disease, synaptic plasticity, memory

**PI (Labex SIGNALIFE team):** **MARIE, Hélène**
Institute: *IPMC*
Email: marie@ipmc.cnrs.fr , Phone: +33 (0)4 93 95 34 40
Website: https://www.ipmc.cnrs.fr/cgi-bin/ipmcx.cgi

**PHD PROJECT SUMMARY:**

The amyloid precursor protein (APP) is highly expressed in neurons. Its cleavage into several distinct fragments is a meticulously regulated process, which occurs constitutively in the brain. Release of APP fragments in and around the synaptic cleft makes them ideally positioned to acutely influence synapse function. For decades, studies focused on the pathological effects of an APP fragment, amyloid-β (Aβ), on synapse function and cognition in the context of Alzheimer's disease. Yet, together with the German team of Dr. Haass, we recently reported the discovery of another secreted APP fragment, Aη, which also impacts neuronal function (Willem, Nature, 2015). Aη is secreted under physiological and pathological conditions, but little is known about its contribution to synapse function and cognition in the healthy adult brain and how it might contribute to Alzheimer's disease-related synapse dysfunction and memory impairment.

We propose a highly innovative PhD thesis at the forefront of Alzheimer's disease research that would focus on understanding the relationship between this new APP fragment Aη, neuronal function and cognition. To fulfil this goal, the PhD student would use a state-of-the-art multi-technical approach, including ex-vivo whole-cell electrophysiology, in vivo peptide injections, in vivo microdialysis, biochemistry and behavioral tasks. This work will therefore dissect out with unprecedented precision the physiopathological actions of Aη in the brain.

**RELATED PUBLICATIONS:**

1. Willem M, et al. (2015) η-*Secretase processing of APP inhibits neuronal activity in the hippocampus.* **Nature**, 526(7573):443-7.
2. Lanté F, et al. (2015) *Subchronic glucocorticoid receptor inhibition rescues early episodic memory and synaptic plasticity deficits in a mouse model of Alzheimer's disease.* **Neuropsychopharmacology.** 40:1772-81.
3. D'Amelio M, et al. (2011) *Caspase-3 triggers early synaptic dysfunction in a mouse model of Alzheimer's Disease.* **Nat Neurosci** 14:69-76.

# Project id: 28-TANTI/TRABUCCHI

**"Implication of small non-coding RNAs regulated by p53 in adipose tissue dysfunction and insulin resistance development"**

**KEYWORDS:** Insulin resistance, adipose tissue, non-coding RNA, p53, atherosclerosis

**PI 1 (Labex SIGNALIFE team): TANTI, Jean-François**
Institute: *C3M INSERM U1065*
Email: tanti@unice.fr, Phone: +33 4 89 06 42 37
Website: http://www.unice.fr/c3m/index.php/research-teams/jean-francois-tanti-mireille-cormont/

**PI 2 (Labex SIGNALIFE team): TRABUCCHI, Michele**
Institute: *C3M INSERM U1065*
Email: mtrabucchi@unice.fr, Phone: +33 4 89 06 42 52
Website: http://www.unice.fr/c3m/index.php/research-teams/michele-trabucchi/

## PHD PROJECT SUMMARY:

The project gathers two SIGNALIFE teams. Team 1 headed by Drs JF Tanti and M Cormont has a long lasting expertise in the pathophysiology of insulin resistance and Type 2 Diabetes. Team 2 headed by Dr M Trabucchi has a strong background in the field of small non-coding RNAs. The proposed project is at the interface between metabolic disorders and small RNA biology.

Insulin resistance is associated with obesity and is the major underlying cause of the susceptibility to Type 2 Diabetes (T2D) and cardiometabolic diseases, which are the most common causes of death in western world. In obese individuals, the expansion of adipose tissue (AT) induces a chronic low grade inflammatory state in AT, which is due to recruited immune cells, including macrophages. This would ultimately lead to the onset of insulin resistance and the increasing risk of T2D and cardiometabolic diseases. Recent data from team 1 (1) and others support a role for DNA damage and p53 pathway in AT dysfunctions and activation of inflammatory response in AT. Therefore, there is a clear need to identify the targets of p53 involved in the alterations of AT function and to study their role in insulin resistance. P53 is a transcription factor whose activation modulates gene expression programs, including non-coding RNA expression control. Importantly, Team 1 recently identified by RNAseq the induction of five miRNAs in adipocytes of obese mice that are known to be p53 targets in other cell types such as cancer cells. On the other hand, Team 2 recently found a p53-dependent processing of the non-coding YRNAs (also called RNYs) into 24-34 nucleotides long small RNA species (referred to as s-RNYs) in lipid-laden macrophages (2 and unpublished data).The s-RNYs associate to the Ro60 protein to promote apoptosis and inflammation in macrophages. Importantly, through a collaborative study, the two teams found that s-RNY expression is deregulated in AT of obese mice.

Based on the above observations, we hypothesize a fundamental role of p53-regulated small non-coding RNAs in the pathogenesis of metabolic dysfunctions in AT, which ultimately leads to the onset of insulin resistance. To validate this hypothesis, we propose the following specific aims:

1) To investigate whether the identified miRNAs and s-RNYs are regulated by DNA damage and p53 activation in adipocytes and macrophages (Team 1)

2) To investigate the role of the identified miRNA/s-RNY in adipocyte metabolism (Team 1) and in lipid-laden macrophages (Team 2) and to decipher the mechanisms involved by identifying their targets (Team 2)

3) To determine the role of these miRNA/s-RNYs in animal models for insulin resistance (Team 1 and Team 2)

We foresee that the investigation of the molecular mechanism(s) by which small non-coding RNAs underpin AT metabolic dysfunction will significantly bring new insights into the pathogenesis of insulin resistance and Type 2 diabetes for the development of novel therapeutic strategies.

## RELATED PUBLICATIONS:

1. Vergoni B*, Cornejo P-J* et al. DNA damage and the activation of the p53 pathway mediate alterations in metabolic and secretory functions of adipocytes. Diabetes. Submitted for publication.
2. Repetto E, et al. RNY-derived small RNAs as a signature of coronary artery disease. BMC Med. 2015 Oct 8;13:259
3. Trabucchi M, et al.. The RNA-binding protein KSRP promotes the biogenesis of a subset of microRNAs. Nature. 2009, 18;459(7249):1010-1014

# Project id: 29-TARTARE-DECKERT/MARI

**"Myofibroblasts in cancer and fibrotic diseases: functional characterization of sub-populations heterogeneity"**

**KEYWORDS:** Mesenchymal cells, Melanoma, Fibrosis, Single cell, MicroRNA

**PI 1 (Labex SIGNALIFE team): TARTARE-DECKERT, Sophie**
Institute: *C3M*
Email: tartare@unice.fr , Phone: +33 (0)4 89 06 43 10
Website: http://www.unice.fr/c3m/index.php/research-teams/sophie-tartare-deckert/

**PI 2 (Labex SIGNALIFE team): MARI, Bernard (BARBRY, Pascal)**
Institute: *IPMC*
Email: mari@unice.fr , Phone: +33 (0)4 93 95 77 91
Website: https://www.ipmc.cnrs.fr/cgi-bin/ipmcx.cgi

**PHD PROJECT SUMMARY:**

Fibroblasts are the main cell type that produces and remodels the extracellular matrix in organs during embryonic and adult life. Their activation into myofibroblasts is a key process during physiological wound healing but also occurs in several pathological conditions associated with organ fibrosis and most cancers, in which fibroblasts recruitment to tumors has been implicated in primary tumor growth and progression to metastatic disease. This aggressive mesenchymal phenotype is associated with excessive and uncontrolled extracellular matrix synthesis and remodeling, increased migration, invasion and resistance to apoptosis as well as altered expression of autocrine and paracrine signaling molecules. These mesenchymal cell populations are highly heterogeneous and can originate from a variety of precursor cells. Moreover, their differentiation involves multiple developmental signaling factors including Transforming Growth Factor-β (TGF-β) and ligands of the Wnt, Notch and Sonic hedgehog pathways as well as matricellular proteins such as SPARC or Thrombospondin 2. Whether different cell origins represent the source of myofibroblasts in different tissues and pathological conditions remains to be determined as well as the relative contribution of these subpopulations in fibrogenesis and tumorigenesis.

The project will be devoted to better characterize the different mesenchymal subpopulations involved in two disease conditions both sharing the requirement for myofibroblasts and matrix remodeling: 1) a fibroproliferative disorder (idiopathic lung fibrosis), a chronic and rapidly fatal pulmonary disorder of unknown origin associated with activation of fibrogenic effector cells and the formation of fibroblasts foci; and 2) an aggressive and deadly form of skin cancer, melanoma, that drives multiple modification of constituent cell types within the tumor stroma including fibroblasts to promote a fibrotic network that facilitate chemoresistance and metastatic colonization.

We plan to analyze the expression of mesenchymal and cellular state markers including microRNAs previously associated with fibrosis using single-cell approaches, identify the most aggressive effector cells subpopulations, characterize the signaling pathways that drive their proliferation and differentiation in order to generate new knowledge on the diversity of different subsets of mesenchymal cells residing within the pulmonary fibrotic parenchyma and melanoma-associated reactive stroma and to propose new potential targeted therapeutics for fibrotic-associated diseases.

**RELATED PUBLICATIONS:**

1. Pottier N, Cauffiez C, Perrais M, Barbry P, Mari B: FibromiRs: translating molecular discoveries into new anti-fibrotic drugs. Trends Pharmacol Sci 2014, 35(3):119-126.

2. Lino Cardenas CL, Henaoui IS, Courcot E, Roderburg C, Cauffiez C, Aubert S, Copin MC, Wallaert B, Glowacki F, Dewaeles E et al: miR-199a-5p Is Upregulated during Fibrogenic Response to Tissue Injury and Mediates TGFbeta-Induced Lung Fibroblast Activation by Targeting Caveolin-1. PLoS Genet 2013, 9(2):e1003291.

3. Tichet, M., Prod'homme, V., Fenouille N., Ambrosetti, D., Cerezo, M., Ohanna, M., Mallavialle, A., Audebert, S. Rocchi S., Giacchero, D., Boukari, F., Allegra, M., Chambard JC., Lacour JP., Michiels, JF., Borg, JP., Deckert M., and Tartare-Deckert S. 2015. Tumour-derived SPARC drives vascular permeability and extravasation through endothelial VCAM-1 signaling to promote metastasis. Nat. Commun. Apr 30;6:699

# Project id: 30-DESCOMBES/VAN OBBERGHEN-SCHILLING

**"Characterization of the organization of the Extracellular Matrix (ECM) by Image Processing"**

**KEYWORDS:** ECM, fibronectin fibers, image analysis, fiber network detection and modeling

**PI 1 (Labex SIGNALIFE team):** **DESCOMBES, Xavier**
Email: Xavier.Descombes@inria.fr, Phone: +33 (0)4 92 94 27 28
Website: http://www-sop.inria.fr/morpheme/

**PI 2 (Labex SIGNALIFE team):** **VAN OBBERGHEN-SCHILLING, Ellen**
Institute: *iBV*
Email: Ellen.VAN-OBBERGHEN@unice.fr, Phone: +33 (0)4 92 07 64 30
Website: http://ibv.unice.fr/EN/equipe/van_obberghen_schilling.php

**PHD PROJECT SUMMARY:**

Cells of multicellular organisms interact continually with their local environment which is largely determined by the extracellular matrix (ECM). The biochemical, topological and physical properties (stiffness, elasticity) of the ECM regulate many physiological processes (embryonic development and tissue repair) and their dysregulation plays a key role in the evolution of inflammatory, fibrotic and tumoral diseases. Fibronectin (FN) is a major component of the ECM. The biology team of iBV has identified certain molecular mechanisms involved in the assembly of FN into fibrillar arrays (FN fibrillogenesis) on the cell surface [1]. The resulting fibrillar networks display variable densities and organizations that convey specific biological signals to the cells that encounter them (see figure).

The overall objective of this study is to understand how certain factors regulate the organization of the ECM. The goal of the PhD project is to develop and test numerical criteria for the analysis of FN images allowing characterization of the networks, in terms of density and organization, and quantification of fiber arrangement. The analysis of individual fibers and their structure is possible using morphological tools of currently available software. However, to study dense meshes (e.g. actin, FN) alternative approaches are necessary since binarized images are not suitable.

There are two fundamental steps in the analysis of such fibrillar networks: i) detection of the fibers from acquired images, taking into account variations of acquisition conditions (contrast or noise), and ii) definition of a numerical index (or indexes) which will allow automatic discrimination of the networks according to their density and organization.

First we will investigate standard tools of image processing for texture characterization such as SIFT detectors, wavelet/curvelets transforms or structure tensor from which numerical criteria for quantifying the type of organization will be developed. Thereafter we will undertake a more refined approach by modeling and analyzing the networks extracted from FN images, in order to link fiber organization to biological features. Using a fiber network model will help both detection and characterization. Two different approaches will be undertaken to develop original models. The first involves the use of measures and projections on measure sets [2] and the second entails modeling the network using graph models [3].

The successful candidate must have a solid background in applied mathematics and image processing in addition to a strong interest in the biology component of the project.

**RELATED PUBLICATIONS:**

1. Cseh, B., S. Fernandez-Sauze, D. Grall, S. Schaub, E. Doma and E. Van Obberghen-Schilling (2010). "Autocrine fibronectin directs matrix assembly and crosstalk between cell-matrix and cell-cell adhesion in vascular endothelial cells." J Cell Sci 123: 3989-3999.

2. *A projection algorithm on measures sets.* N. Chauffert, P. Ciuciu, J. Kahn, P. Weiss (2015) sumitted. http://www.math.univ-toulouse.fr/~weiss/Publis/Journals/2015/Measure_Projection_Chauffert_Ciuciu_Kahn_Weiss_2015.pdf

3. E. Martín-Badosa, A. Elmoutaouakkil, S. Nuzzo, D. Amblard, L. Vico, F. Peyrin, *A method for the automatic characterization of bone architecture in 3D mice microtomographic images*, Comput Med Imaging Graph. 27, 447-458, 2003.

# Project id: 31-GOUZÉ

**"Control of models of genetic regulatory networks
Applications: growth control in E. coli, toxicogenomics"**

**KEYWORDS:** Gene networks, mathematical models, control, dynamical systems, bacteria growth control

**PI (Labex SIGNALIFE team):** **GOUZÉ, Jean-Luc**
Institute: *Inria BIOCORE*
Email: jean-luc.gouze@inria.fr , Phone: +33 (0)4 92 38 78 75
Website: http://www-sop.inria.fr/members/Jean-Luc.Gouze/

**PHD PROJECT SUMMARY:**

Biological networks play a major the role in the regulation of living organisms and raise many regulation and control questions, such as stabilization towards a desired state. However, classical control problems have to be revisited in a new light [2,4], as the control laws should satisfy biological constraints as well as be liable to experimental implementation. Synthetic biology experiments [1] have shown that it is possible to design and implement systems that exhibit a particular dynamical behavior, by assembling molecular components with the corresponding properties.

In addition, different mathematical formalisms may be used to model biological networks, for which different possible methods of analysis are available, each contributing with some new information. This project will focus on combining Boolean with piecewise affine models, to improve the characterization of the systems. These are useful modeling frameworks, based on a qualitative description of the systems that can be easily compared with the experimental data obtained from gene and protein expression [3]. One of the goals of the project is to develop methodologies for constructing piecewise affine and Boolean models from a given continuous model, to take advantage of the analytical tools available for the more abstract models [5].

This project will also address the problem of controlling the class of piecewise affine systems, under biologically appropriate restrictions. In general, the parameters of PWA systems represent synthesis and degradation rates of the molecular components of the biological network, and can be used as experimentally controlled "inputs" to the system. Possible control functions will be in the form of piecewise constant inputs to the system (constant in time intervals or in regions of space), and ranging in a qualitative scale. In a more advanced stage, control laws that depend on the variables of the system or dynamic feedback laws will also be explored. The control will be compared to a classical continous one, and strategies will be studied to implement it with biological components.

The methods developed in this project will be applied to the genetic network that regulates growth in E. coli, with the goal of limiting growth rate under high nutrient availability (in collaboration with the biologists of the IBIS group, Grenoble). The aim is to implement the theoretical control in a biologically feasible form.

The other main application will be toxicogenomics, and is done with Bayer Crop Science Sophia-Antipolis. Chemicals may have a toxic effect, due to the response of some genes of the cell to the toxic exposure, via signalling pathways. Our aim is to build a model of the response, and to study the possible controls to mitigate the toxic effects.

**RELATED PUBLICATIONS:**

1. E. Andrianantoandro, S. Basu, D.K. Karig and R. Weiss. Synthetic biology: New engineering rules for an emerging discipline. Molecular Systems Biology, 2:2006.0028, 2006
2. E.D. Sontag. Some new directions in control theory inspired by systems biology. IET Systems Biology, 1:9-18, 2004
3. H. de Jong, J.L. Gouzé, C. Hernandez, M. Page, T. Sari and J. Geiselmann. Qualitative simulation of genetic regulatory networks using piecewise linear models. Bull. Math. Biol. 66:301-340, 2004
4. M. Chaves and J.-L. Gouzé. Exact control of genetic networks in a qualitative framework: the bistable switch example. Automatica, 47:1105–1112, 2011.
5. Wassim Abou-Jaoudé, Madalena Chaves, Jean-Luc Gouzé. Links between topology of the transition graph and limit cycles in a two-dimensional piecewise affine biological model. Journal of Mathematical Biology, Springer Verlag, 2014, 69 (6-7), pp.1461-1495.

# Project id: 33-LITI/GILSON

"The impact of telomere variation on global organismal fitness"

**KEYWORDS:** natural variation, population genomics, genome editing, chromatin, experimental evolution

**PI (Labex SIGNALIFE team): LITI, Gianni**
Institute: *IRCAN*
Email: gianni.liti@unice.fr , Phone: +33 (0)4 93 37 76 72
Website: http://www.ircan.org/

**PI 2 (Labex SIGNALIFE team): GILSON, Eric**
Institute: *IRCAN*
Email: Eric.Gilson@unice.fr
Website: http://www.ircan.org/

**PHD PROJECT SUMMARY:**

Telomeres are active nucleo-protein sites that constitute the ends of chromosomes in most eukaryotic species. Telomere length is a complex trait is controlled by multiple loci and by the environment. Its regulation is critical to the process of aging, and altered length control can result in either senescence or immortalization. Previous reports in a wide range of organisms, including human, have shown that natural variation in multiple pathways results in telomere length variation among individuals and populations. So far, only a handful of genetic variants have been associated with telomere length. Furthermore, these studies have remained descriptive and it is unknown what is the impact of telomere phenotypic variation on the organismal fitness.

Here, we propose take advantage of a classic model system, the budding yeast S. cerevisiae, to dissect the impact of telomere variation. Initially, we will investigate the extent of telomere variation in natural population by analysing a large population genomics dataset that our lab has been leading (http://1002genomes.u-strasbg.fr/). The candidate will attempt to infer telomere sequence by analysing the NGS data and run genome wide association to identify causative variants. Other relevant phenotypes such as ageing and drug resistance for the same strain resource are already available and will be used to search for correlations. Similarly, we have extensive resources of sequenced strains that are originated from genetic crosses and will be used to identify causative genetic variants by linkage analysis.

We will then experimentally validate the effect of natural variants and their impact on other telomere phenotypes (e.g. telomere silencing and chromatin by Rap1 Chip). We will also screen 100's of environmental factors to reveal how these genetic variants interact with the environment.

FInally, we will engineer allelic variation in a single background and use an experimental evolution approach to investigate the long term consequence telomere variation. In addition to the natural variants discovered, we will use constructs that reconfigure the yeast repeats (TG1-3) to a vertebrate-like repeat (TTAGGG). We previously show that these repeats lead to partially dysfunctional telomeres that activate a mild chronic DNA damage response. We will evolve cell lines harbouring artificial and natural variation both under selection (e.g. continuous competitive growth) as well as propagate them without selection (mutation accumulation lines by single cell bottle neck). Overall, these experiments will reveal how an organism adapts to telomere variation and the impact on organismal phenotype. This project will take advantage of the complementary expertise's of the two teams that are leader in the fields of population genomics and telomere biology. The selected candidate will be benefit from an exciting mix of technologies and topics and will perform both the computational and experimental analysis.

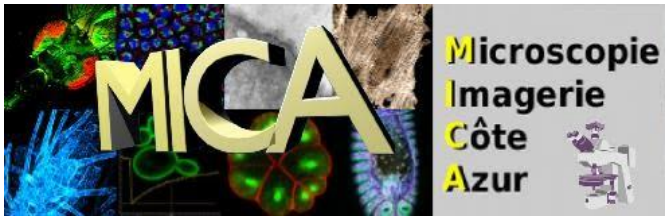
**RELATED PUBLICATIONS:**

1. Liti, G. et al. Segregating YKU80 and TLC1 alleles underlying natural variation in telomere properties in wild yeast. PLoS Genet. 5, e1000659 (2009).
2. Long, A., Liti, G., Luptak, A. & Tenaillon, O. Elucidating the molecular architecture of adaptation via evolve and resequence experiments. Nat. Rev. Genet. 16, 567–582 (2015).
3. Ye, J., Renault, V. M., Jamet, K. & Gilson, E. Transcriptional outcome of telomere signalling. Nat. Rev. Genet. (2014). doi:10.1038/nrg3743

# 4. LABEX FACILITIES AND EQUIPMENT

The SIGNALIFE Institutes have state-of-the-art technology platforms with open access for all local scientists (see http://signalife.unice.fr/?page_id=1288):

- 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*.

# 5. RESOURCES

## 5.1 Fellowship

The SIGNALIFE PhD thesis funding is for three years. A possible 6 month extension may be added at the end of the 3rd year.

All students participating in the Program will receive a monthly salary of 2,020 € gross and provides social benefits. University tuition fees will be included. An installation allowance upon of 1,700 € upon arrival will be given to each student. Free French classes will be provided for foreigners.

## 5.2 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 advices with respect to the institutions and local authorities (*i.e.* lodging, visa, social security, bank account, *etc.*).

## 5.3 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.

## 5.4 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.

## 5.5 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.

## 5.6 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

## 6. 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.


## 7. 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.

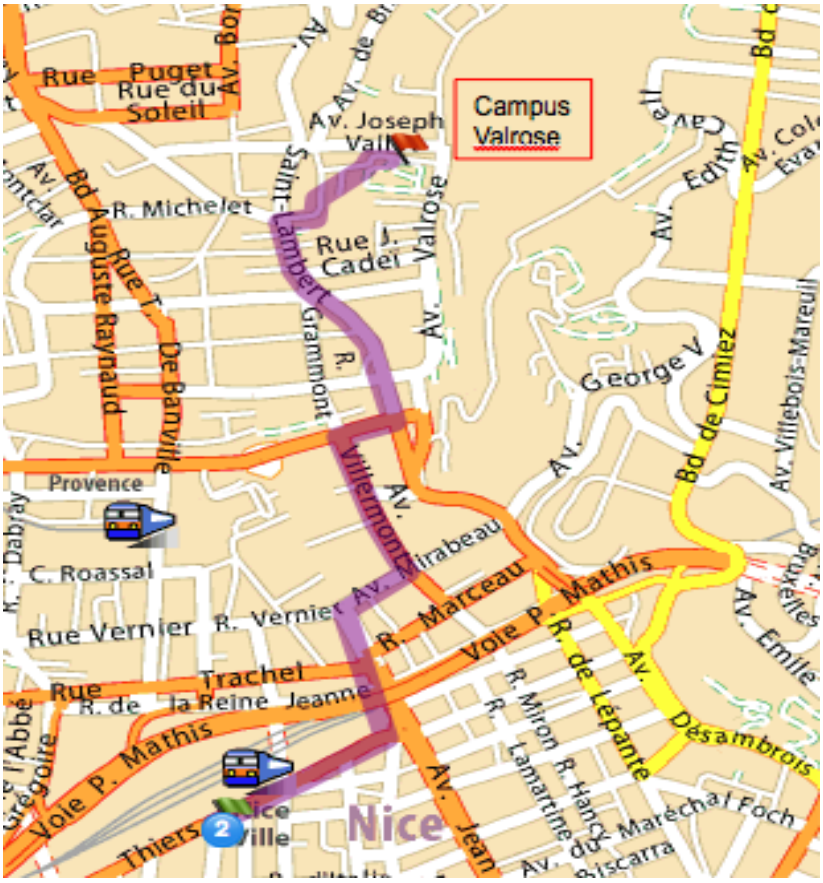
For further information on Nice and its surroundings: http://www.nicetourism.com/

# 8. DIRECTIONS to Valrose Campus

## 8.1. From the train station

### By foot :

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

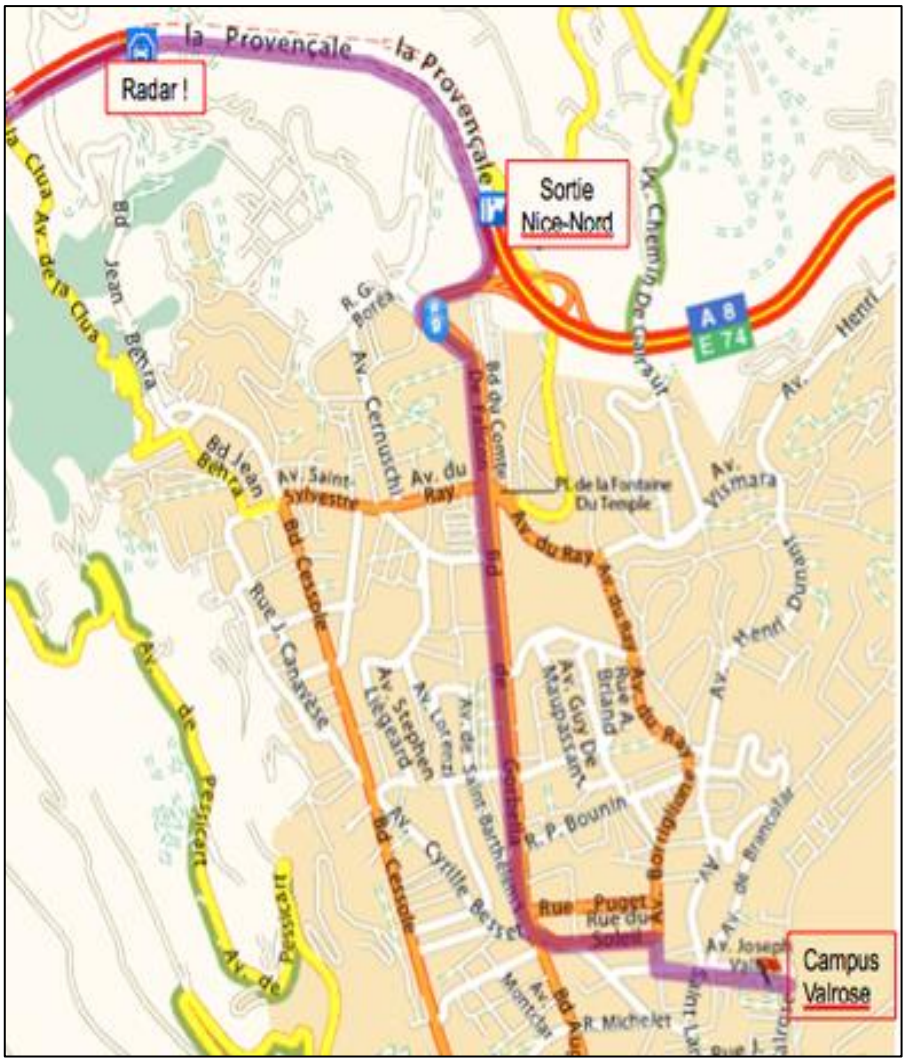



### By tram :

- Tram Direction Las Planas
- Stop at Valrose University

## 8.2 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

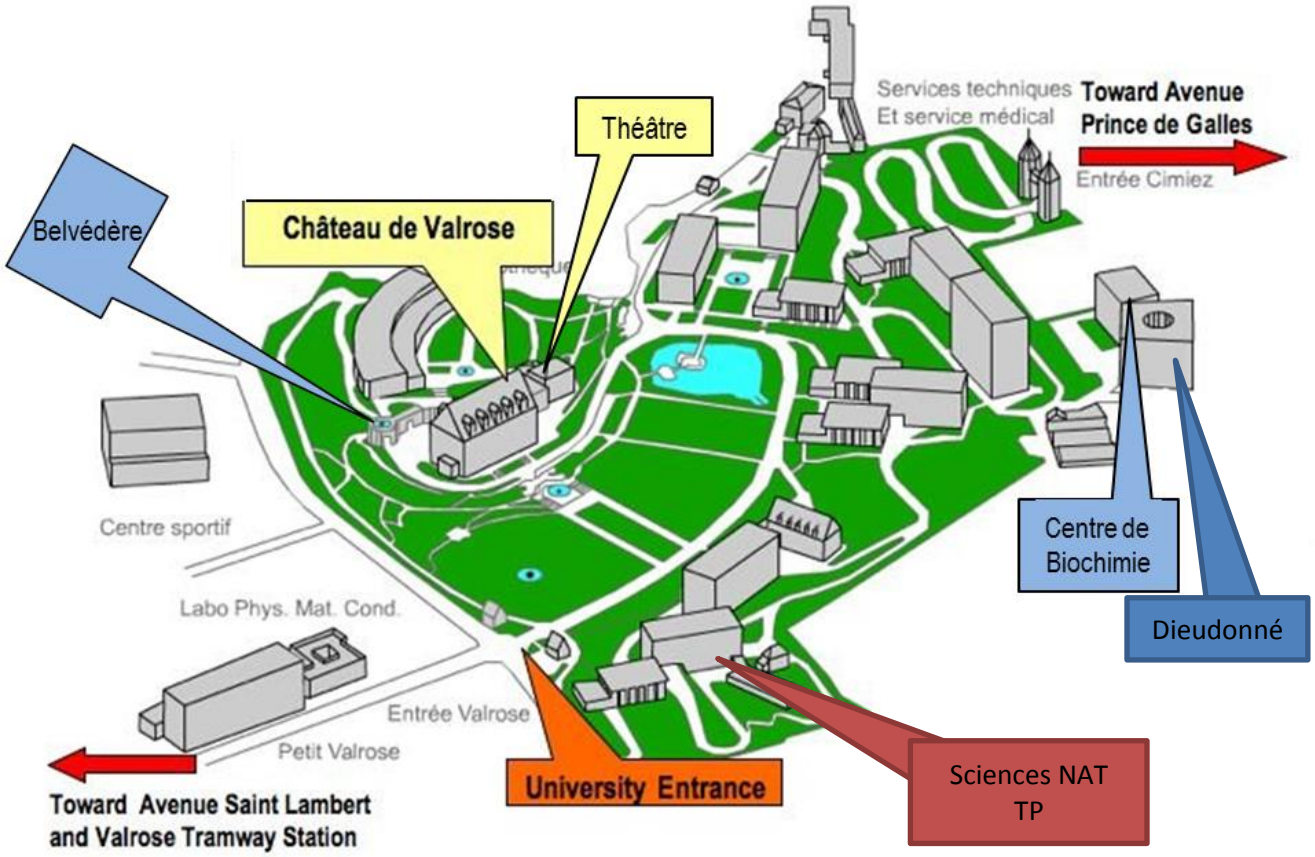



## 8.3 From Airport (by bus)

- Direct bus line 23- towards Vallon des Fleurs; Stop Vallot/Valrose: duration about 1h
- Express bus 98 - to historic city centre, plus Tram T1 towards Henri Sappia; stop Valrose Université
- Express bus 99 - to central train station, plus Tram T1 towards Henri Sappia; stop Valrose Université

## 8.4 Valrose Campus

Valrose Campus and room location for the on-site visits: open days of May 31st-June 1st and June 21st – 22nd, 2016.



## 9. LABEX SIGNALIFE CONTACTS

**Stéphane Noselli**
*iBV Director*
*Labex SIGNALIFE Scientific Coordinator*
*President of SIGNALIFE Labex Council*

noselli@unice.fr

Labex SIGNALIFE
Institut de Biologie Valrose (iBV)
Centre de Biochimie
Université Nice Sophia Antipolis (UNS)
Parc Valrose
06108 Nice Cedex 2

**Martine Avella**
*Labex SIGNALIFE and iBV Project Manager*
*SIGNALIFE Website Manager*

Tel 04 92 07 68 57
avella@unice.fr

Labex SIGNALIFE
Institut de Biologie Valrose (iBV)
Bâtiment Sciences Naturelles
Université Nice Sophia Antipolis (UNS)
Parc Valrose
06108 Nice Cedex 2

SIGNALIFE PhD

### International PhD Program

PhD.signalife@unice.fr

**Hélène Marie**
*President of the Labex Education Committee*
*IPMC SIGNALIFE Team Group Leader*

IPMC
Tel : 04 93 95 34 40
marie@ipmc.cnrs.fr

**Marcel Deckert**
*Vice-President of the Labex Education Committee*
*C3M Group Leader*

C3M
Tel : 04 92 15 77 06
Marcel.DECKERT@unice.fr

**Konstanze Beck**
*Labex SIGNALIFE PhD Program Officer*
beck@unice.fr

Petit Valrose, UNS
Tel : 04 92 07 69 98
Fax : 04 92 07 69 18
PhD.signalife@unice.fr

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

Photo copyrights © 2013 by Antonny, Auberger, Ballotti, Barbry, Bardoni, Besse, Braendle, Chaboissier, Collombat, Cormont, Cristofari, Dani, Delaunay, Descombes, Féral, Franco, Frendo, Fürthauer, Gilson, Glaichenhaus, Gouzé, Gual, Hofman, Lalli, Lemichez, Léopold, Liti, Luton, Magnaldo, Meneguzzi, Marie, Martin, Noselli, Panabières, Poirié, Rassoulzadegan, Robichon, Schedl, Tanti, Tartare-Deckert, Thérond, Trabucchi, Tran, Van Obberghen, V.O.-Schilling

All rights reserved for all pictures included in the document

Pamphlet produced in Nice, June 2016, MA

# SIGNALIFE PARTICIPATI NG GROUP LEADERS 2016


Antonny


Auberger


Ballotti


Barbry


Bardoni


Besse


Braendle


Chaboissier


Collombat


Cormont


Cristofari


Dani


Delaunay


Descombes


Féral


Franco


Frendo


Fürthauer


Gilson


Glaichenhaus


Gouzé


Gual


Hofman


Lalli


Lemichez


Leopold


Liti


Luton


Magnaldo


Meneguzzi


Marie


Martin


Noselli


Panabières


Poirié


Rassoulzadegan


Robichon


Schedl


Tanti


Tartare-Deckert


Thérond


Trabucchi


Tran


Van Obberghen


VO-Schilling