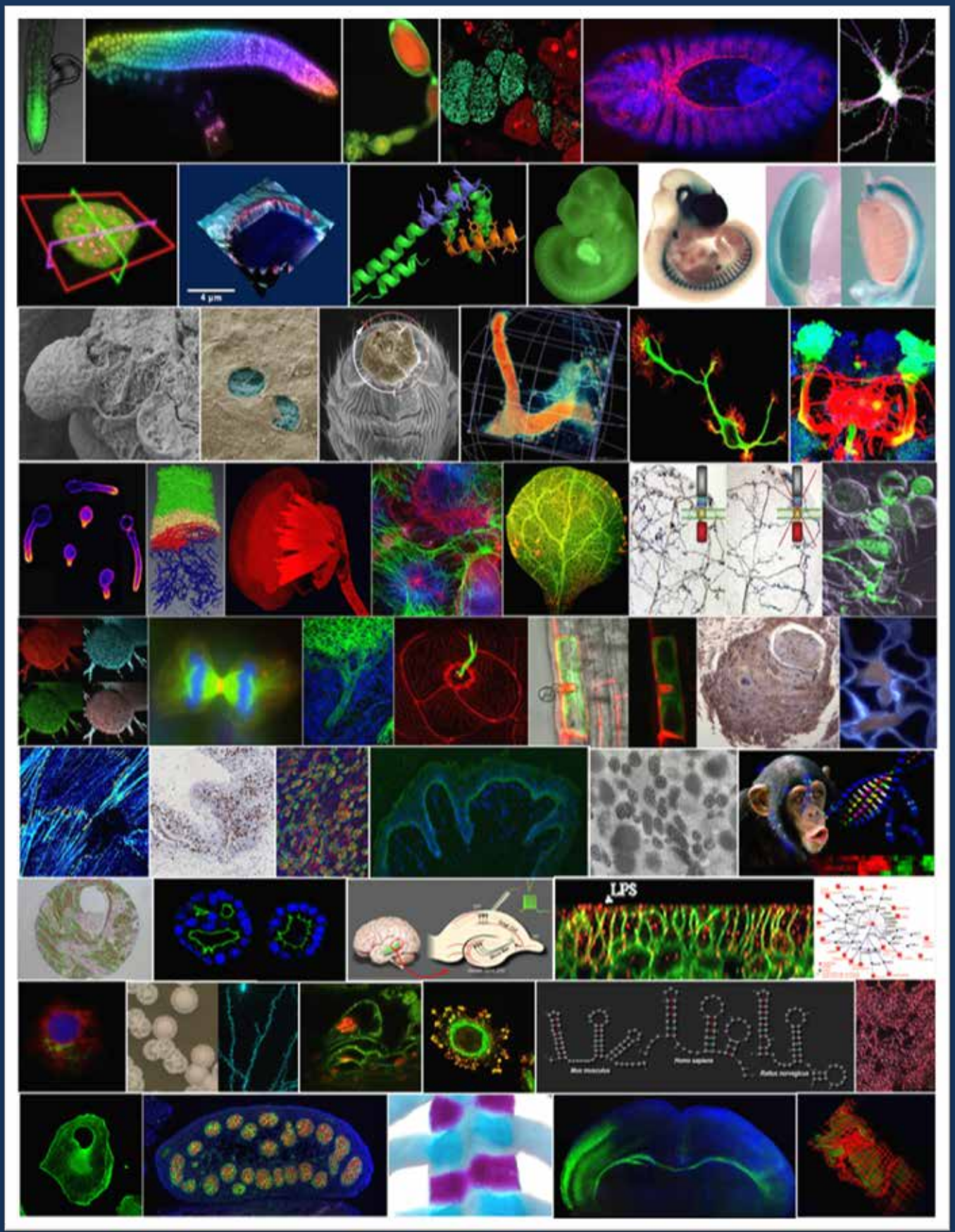
SIGNALIFE

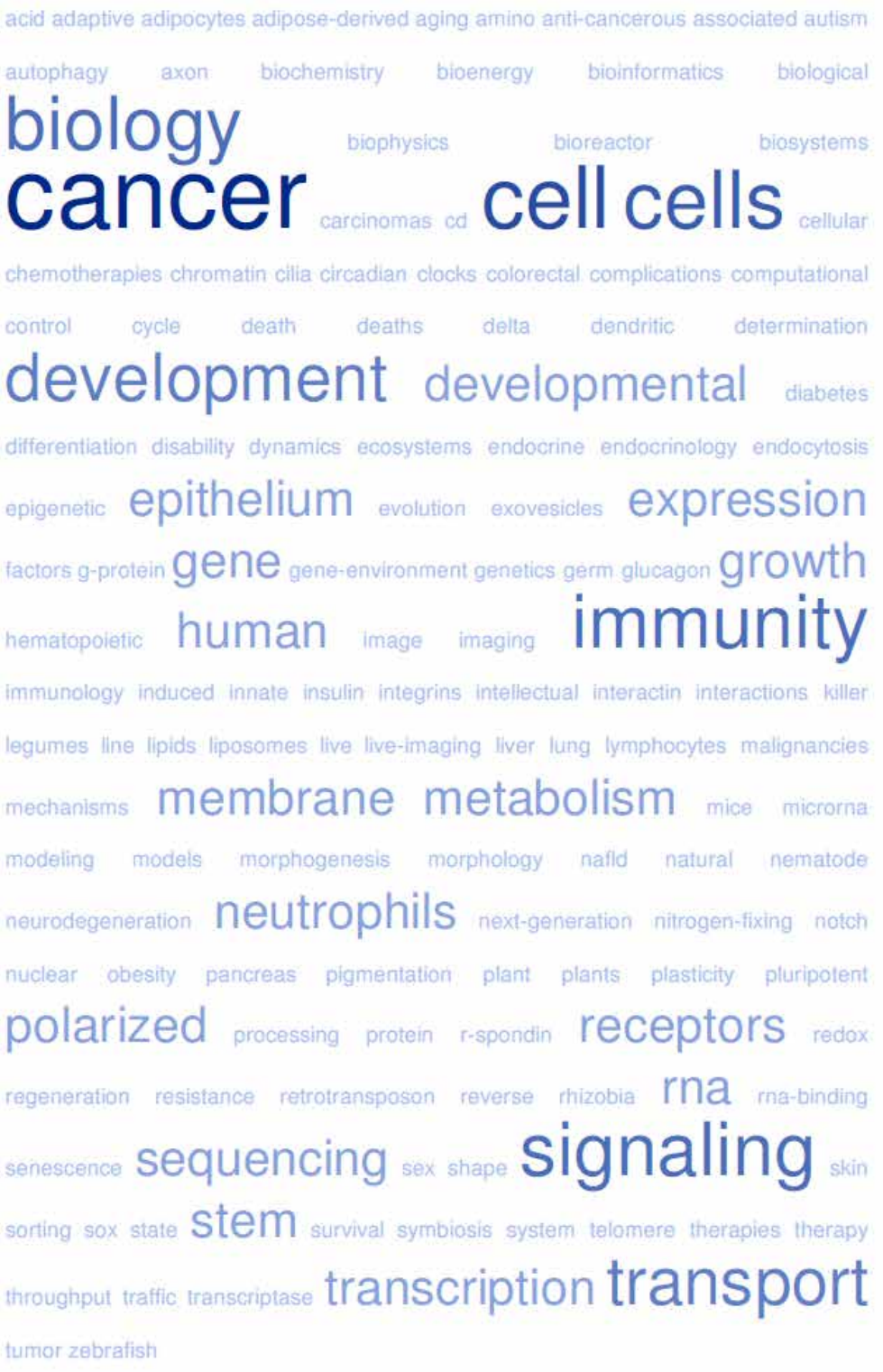
INTERNATIONAL PhD PROGRAM

Network for Innovation on Signal Transduction Pathways in Life Sciences



2016 PhD Projets

Nice Sophia Antipolis University, 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

IMPORTANT

INSTRUCTIONS TO FILL OUT ONLINE APPLICATION FORM

You'll be asked to give your top three choices of PhD projects among all 33 listed in this document

Please insert the Project identification (called "Project id") in the Application Form for all three PhD projects chosen. You'll find the Project id on the top of each 33 forms listed here *(exemple: 6-MARTIN/LAUMONNIER).*

Note : the 5 axes separation is only to give information about scientific fields concerned

PhD projects

Axis 1: Cellular architecture of signaling pathways

Axis 2: Plasticity and Signaling

Axis 3: Stress Signaling

Axis 4: Signaling in aging and disease progression

Axis 5: New principles in signaling and applications

Axis 1: Cellular architecture of signaling pathways

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: 2-ARKOWITZ

"Forces in fungal invasive filamentous growth"

KEYWORDS: Polarity, Force, Cell Shape, Fungi, Invasive filamentous growth

PI (Labex SIGNALIFE team): ARKOWITZ, Robert; BASSILANA, Martine
Institute: *iBV*
Email: arkowitz@unice.fr , Phone: +33 (0)4 92 07 64 25
Website: http://ibv.unice.fr/EN/equipe/arkowitz.php

PHD PROJECT SUMMARY:

Worldwide, fungal infections cause significant morbidity and mortality, with rates of >50% for invasive infections (~1.5 million deaths/year) and mucosal infections affecting 100's of millions of individuals. *Cryptococcus, Candida, Aspergillus* and *Pneumocystis* species account for >90% of fungal-related deaths. Candida species are the major etiological agent of such life-threatening infections and represent an emerging global microbial threat. Diseases caused by *Candida albicans* are particularly difficult to treat due to the small number of effective antifungal drugs and the development of pathogen resistance. Advances in medical treatment as well as the proliferation of invasive medical devices, broad-spectrum antimicrobial agents and assisted ventilation have all increased life expectancy. However, such treatments have also dramatically increased the population of severely ill, immuno-compromised patients, highly susceptible to nosocomial infections, in particular those caused by fungi such as *C. albicans*.

C. albicans is normally a harmless commensal, which exists on mucosal surfaces of the gastrointestinal and urogenital tract in most healthy individuals. This fungal pathogen can cause superficial as well as life-threatening systemic infections in response to alterations of its environment, and is particularly aggressive in immuno-compromised individuals, *e.g.* AIDS patients, chemotherapy and organ transplant recipients. As an opportunistic pathogen, it can colonize and infect different body sites. The ability of this organism to switch from an ovoid to a filamentous form is critical for its pathogenicity, in particularly its ability to invade host tissues and evade host immune cells; this transition is concomitant with changes in cell surface antigens, tissue affinities and enzyme production. Little is known about the forces generated by hyphal filaments and the importance of such physical forces in cell and tissue penetration or escape. Turgor pressure, which is controlled by osmolyte synthesis and ion uptake from the external media, is thought to be the major driving force for filament tip extension in a range of fungi. However there is only limited knowledge about the relationships between turgor pressure, tip growth, and intracellular organization. Specifically, how external (resistive) forces are perceived and responded to by this human fungal pathogen are largely unknown.

Objectives

1) **Quantitate forces during invasive growth using a combination of micro-fabrication and live-cell microscopy.**
2) **Determine cellular responses to resistive forces in wild-type and mutant C. albicans strains**

We postulate that the cell wall and its remodeling will play a crucial role in response to resistive forces and that there is a dramatic cellular reorganization upon contact and penetration into the substrate.

RELATED PUBLICATIONS:

1. V. Ghugtyal, R. Garcia-Rodas, A. Seminara, S. Schaub, M. Bassilana & R. A. Arkowitz Phosphatidylinositol-4-phosphate-dependent membrane traffic is critical for fungal filamentous growth. *PNAS U.S.A.,* 2015, **112**: 8644-8649.
2. V. Corvest, S. Bogliolo, P. Follette, R. A. Arkowitz & M. Bassilana. Spatiotemporal regulation of Rho1 and Cdc42 activity during *Candida albicans* filamentous growth. *Mol. Microbiol*., 2013, **89**: 626-648.
3. A. Vernay, S. Schaub, I. Guillas, M. Bassilana & R. A. Arkowitz A steep phosphoinositide-bis-phosphate gradient forms during fungal filamentous growth. *J. Cell. Biol.,* 2012 **198**: 711-730.

Project id: 3-ARKOWITZ/BESSE

"Role of asymmetric RNA distribution during filamentous growth"

KEYWORDS: Polarity, Filamentous Growth, RNA binding, Asymmetric mRNA

PI 1 (Labex SIGNALIFE team): ARKOWITZ, Robert; BASSILANA, Martine
Institute: *iBV*
Email: arkowitz@unice.fr , Phone: +33 (0)4 92 07 64 25
Website: http://ibv.unice.fr/EN/equipe/arkowitz.php

PI 2 (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:

Imp is the sole member of a conserved family of proteins in flies that bind target mRNAs to promote their subcellular targeting. Imp is required for the regrowth and ramification of axonal branches that have undergone pruning and is actively transported to axons undergoing developmental remodeling. Localized mRNAs are also important for development of elongated fungal hyphae. This project will investigate the role of asymmetric RNA distribution and in particular the RNA binding protein Khd1, which shares similarity to Drosophila Imp, in hyphal development of the fungal opportunistic pathogen *Candida albicans*. The function of this RNA binding protein and its role in cell wall integrity/Rho1 activation will be examined. Candidates found to interact with Khd1 in fungal hyphal filaments will be further examined in fly axon development and mRNA targeting.

RELATED PUBLICATIONS:

1. C. Medioni, M. Ramialison, A. Ephrussi, F. Besse. Imp promotes axonal remodeling by regulating profilin mRNA during brain development. Curr Biol. 2014 **24**:793-800.
2. V. Corvest, S. Bogliolo, P. Follette, R. A. Arkowitz & M. Bassilana. Spatiotemporal regulation of Rho1 and Cdc42 activity during Candida albicans filamentous growth. Mol. Microbiol. 2013 **89**: 626-48.
3. A. Vernay, S. Schaub, I. Guillas, M. Bassilana & R. A. Arkowitz A steep phosphoinositide-bis-phosphate gradient forms during fungal filamentous growth. J. Cell. Biol. 2012 **198**: 711-30.
4. C. Medioni, K. Mowry, F. Besse. Principles and roles of mRNA localization in animal development. Development. 2012 **139**: 3263-76

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: 6-MARTIN/LAUMONNIER

"Investigating the dynamic trafficking properties of the PTCHD1 receptor in neurons"

KEYWORDS: PTCHD1, Synapse, receptor trafficking, signaling pathways, endocytosis

PI 1 (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

PI 2: LAUMONNIER, Frédéric
Institute: INSERM U930 ; 10, Boulevard Tonnellé, 37000 TOURS
Email: frederic.laumonnier@univ-tours.fr, Phone: +33 (0)2 47 36 60 62
Website: http://www.u930.tours.inserm.fr/teams/team-2-welcome-400359.kjsp?RH=1365084757242

PHD PROJECT SUMMARY:

Autism spectrum disorders (ASD) and intellectual disability (ID) are neurodevelopmental disorders affecting >1% of the general population and consequently represent a major social and economical problem worldwide. Although many genes have been identified and point to several neurological pathways, the biological causes of such disorders are still undetermined. Among these mutated genes is the X-chromosomal PTCHD1 (Patched domain-containing 1) gene, which encodes for the PTCHD1 protein (1,2). While PTCHD1 is still seen as a putative receptor of uncharacterized function in brain development, mutations within its encoding gene is leading to ASD and ID, indicating that PTCHD1 fulfils important functions in the establishment and/or the maintenance of neuronal communication and in learning and memory processes.

Previous findings reported that PTCDH1 could modulate the sonic hedgehog (SHH) signalling pathway1. The similarity of PTCHD1 and PTCH1 (SHH receptor) protein sequences suggests that PTCHD1 could be a receptor for SHH. Our preliminary data indicates that PTCHD1 is expressed at the plasma membrane and at post-synaptic sites where it can interact with key synaptic signalling elements. We thus hypothesized that PTCHD1 is a synaptic receptor performing important post-synaptic signalling functions, and that its deficiency leads to ID and ASD.

The current PhD project is part of an integrative multidisciplinary research program that uses genetic, molecular neurobiology, electrophysiology and behavioural approaches in both cellular and animal models to unravel the physiological and pathophysiological implication of PTCHD1 in brain development.

We are looking for a highly motivated candidate holding a Master degree in Neurosciences, Cell Biology or Cell imaging to investigate the trafficking properties of PTCHD1 in neuronal cells using state-of-the-art approaches (3-5). Importantly, all of the necessary tools and protocols are already in place and experiments can be run from the start. The selected PhD student will use biochemical and live-cell imaging techniques to:

1- Assess how the plasma membrane expression of PTCHD1 receptors is regulated in neurons.
2- Characterize the endocytic properties of synaptic PTCHD1 receptors.
3- Decipher the activity-dependent regulation of PTCHD1 transport in neurons.

These experiments will address the fundamental mechanisms underlying the transport, synaptic recruitment and retention of PTCHD1 and explain how pathogenic mutations may affect these trafficking properties.

RELATED PUBLICATIONS:

1. Noor A et al. (2010) Sci Transl Med 2:49ra68
2. Chaudhry et al. (2015) Clin. Genet. 88:224-33
3. Martin & Henley (2004) Embo Journal 23:4749-59
4. Martin et al (2008) J. Biol Chem 283:36435-40
5. Loriol et al. (2014) Nature Communications 5:5113

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

Axis 2: Plasticity and Signaling

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: 11-NAHON

""Primate-specific" gene expression and functional characterization in the brain using macaque and humanized mouse models "

KEYWORDS: Melanin-concentrating hormone (MCH), PMCHL1 gene, lncRNA, "humanized" mouse, behavioural regulation

PI (Labex SIGNALIFE team): **NAHON, Jean-Louis**
Institute: *IPMC*
Email: nahonjl@ipmc.cnrs.fr , Phone: +33 (0)4 93 95 77 53
Website: http://www.ipmc.cnrs.fr

PHD PROJECT SUMMARY:

Our knowledge regarding structural and functional characterization of "species-specific" brain organization and mediator signaling has dramatically increased during the last decade. Neurons producing melanin-concentrating hormone (MCH), a neuropeptide acting as a major controller of energy homeostasis, are typical in this context. MCH neural anatomy diverges from fishes to mammals, following evolutionary trends reflecting singular functional features. Indeed, MCH mediates color change in teleost fishes and regulate energy balance in mammals. Furthermore, in a pioneer work we provided evidence for the emergence in higher Primates of two chimeric genes, namely the *PMCHL1* and *PMCHL2* genes. These genes have been submitted to strong regulatory constraints during Hominoid evolution, *PMCHL1* gene being predominantly expressed as long non-coding RNAs (lncRNAs) in the brain. Intriguingly, one of these, the PMCHL1$^{exons1-2}$ lncRNA, co-localizes with MCH mRNA in the macaque cortex, adjacent to neurons expressing the "human-specific" MCH receptor, namely MCHR2. This suggests a functional relationship between the expression of a "primate-specific" lncRNA and its gene template in order to provide a new ligand source for MCH receptor family. Collectively, Primates-specific functional innovations are very puzzling and required throughout investigations we would like to explore in a PhD project. Two specific objectives (SO) have been defined in the PhD research program as follows.

SO1: Cellular expression of the PMCHL1$^{exon1-2}$ gene transcripts, pro-MCH derived peptides and MCHR2 in the primate brain.

Precise mapping of cellular expression of the PMCHL1$^{exon1-2}$ gene will be attempted in primate brain (M. fascicularis and C. jacchus) by using ISH. Immunohistochemistry of pro-MCH derived peptides and co-localisation studies will be also performed. The expression mapping of the PMCHL1$^{exon1-2}$ gene and pro-MCH neuropeptides will be finally compared with this of MCHR2.

S02: Construction of the AAV9-PMCHL1$^{exon1-2}$-IRES-eGFP vector, *in vivo* delivery procedure, MCH gene expression analysis and behavioural characterization in "humanized" mice.

AAV9 vectors carrying human PMCHL1$^{exon1-2}$ sequences under the genuine gene promoter (AAV9-PMCHL1$^{exon1-2}$-IRES-eGFP) will be administered at two key stages of development of mice, i.e. at post-natal day 1 (P1) and at post-natal day 5 (P5). We posit that PMCHL1$^{exon1-2}$ genetically engineered mice will exhibit changes in MCH gene expression within the cortex similar to what was found in the macaque brain. We plan therefore to characterize coding transcripts (and cognate proteins) from *MCH* gene and PMCHL1$^{exon1-2}$ lncRNAs using RT-PCR, qPCR (Roche apparatus), ISH (for mRNAs) and Western-blot, ELISA and RIA assays and immunohistochemistry (for proteins/peptides). Finally, behavioural studies will allow establishing the functions of the non-hypothalamic MCH neurons in "humanized" mice.

RELATED PUBLICATIONS:

1. Courseaux A. and **Nahon J.L** Birth of two chimeric genes in the Hominidae lineage. **Science** (2001) 291, 1293-1297 (Human Genome Issue).
2. Courseaux A., Richard F., Grosgeorge J., Ortola C., Viale A., Turc-Carel C., Dutrillaux B., Gaudray P. and **Nahon J.L**. Segmental duplications in euchromatic regions of human chromosome 5 : a source of evolutionary instability and transcriptional innovation. **Genome Res.** (2003) 13, 369-381.
3. Conductier G*, Brau F*, Viola A*, Langlet F, Ramkuma N, Dehouck B, Lemaire T, Chapot R, Lucas L, Rovère C, Maitre P, Hosseiny S, Petit-Paitel A, Adamantidis A, Lakaye B, Risold PY, Prévot V**, Meste O**, **Nahon JL**§, Guyon A**§ Melanin-concentrating hormone regulates beat frequency of ependymal cilia and ventricular volume. **Nature Neurosci** (2013) doi: 10.1038/nn.3401

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

Axis 3: Stress Signaling

Project id: 13-ABAD

"Identification of plant cellular functions directly targeted and manipulated by plant pathogens"

KEYWORDS: Plant, pathogens, nematodes, targets, hubs

PI (Labex SIGNALIFE team): **ABAD, Pierre**
Institute: *ISA*
Email: pierre.abad@sophia.inra.fr , Phone: +33 (0)4 92 38 66 02
Website: http://www6.paca.inra.fr/institut-sophia-agrobiotech/Equipes-ISA/IPN

PHD PROJECT SUMMARY:

This project aims at identifying plant cellular functions directly targeted and manipulated by different phytopathogens, and that are essential for disease development. Plant pathogens have developed specialized strategies, which allow them to overcome host defenses, to invade and then multiply within the plants. It is well established that plant pathogens, bacteria, fungi, oomycetes or nematodes secrete an array of proteins, collectively called effectors, which target plant components to corrupt the host cell machinery to their benefit. Different plant pathogens were shown to deploy effectors that interact with a limited set of highly connected cellular hubs to induce diseases1,2. Giving evidence that some plant components are targeted by a variety of pathogens differing in physiology, lifestyle and colonization strategies should open perspectives for generating broad-spectrum resistance.

We will focus our study on one soil borne pathogen of worldwide economic importance: the root-knot nematode *Meloidogyne incognita* (Mi). This root pathogen is extremely polyphagous and is among the most important pests of Solanaceae such as tomato worldwide. Mi is able to infect the roots of almost all cultivated plants and establish and maintain in roots permanent feeding cells supplying the nematode with nutrients. Mi secretes effector proteins directly into the host cell cytoplasm using its syringe-like stylet, corrupting several key cellular functions to allow disease3. Using previously characterized Mi effectors as baits, we will perform a large-scale analysis of tomato targets by screening a tomato cDNA yeast-two-hybrid library. We will seek for candidate interactors known to be targeted by other phytopathogens, and such targets for which an interaction will be validated in yeast and *in planta* will be characterized further. Using a VIGS approach or mutants (when available), we will study the physiological role of these plant targets and analyze how their effector-mediated subversion plays a role to favor disease. Loss of function or allelic variations of target host genes that will be identified in tomato and other Solanaceae is predicted to result in resistance traits that are difficult to be overcome by pathogens, because host "susceptibility" factors are required for the establishment and maintenance of the infection process.

RELATED PUBLICATIONS:

1. Mukhtar et al. (2011). Independently evolved virulence effectors converge onto hubs in a plant immune system network. Science, 333, 596-601
2. Weßling R et al (2014). Convergent targeting of a common host protein-network by pathogen effectors from three kingdoms of life. Cell Host and Microbe, 16, 364 -375
3. Quentin M, Abad P and Favery B (2013). Plant parasitic nematode effectors target host defense and nuclear functions to establish feeding cells. Front. Plant Sci. 4:53. doi: 10.3389/fpls.2013.00053

Project id: 14-ABAD/PANABIÈRES

"Characterization of small RNAs involved in the plant response to root pathogens: the root knot nematode *Meloidogyne incognita* and the oomycete *P. parasitica* "

KEYWORDS: nematodes, miRNAs, oomycetes, Plant-pathogen interactions, silencing

PI1 (Labex SIGNALIFE team): ABAD, Pierre
Institute: *ISA*
Email: pierre.abad@sophia.inra.fr , Phone: +33 (0)4 92 38 66 02
Website: http://www6.paca.inra.fr/institut-sophia-agrobiotech/Equipes-ISA/IPN

PI2 (Labex SIGNALIFE team): PANABIÈRES, Franck
Institute: *ISA*
Email: franck.panabieres@sophia.inra.fr , Phone: +33 (0)4 92 38 65 18
Website: http://www6.paca.inra.fr/institut-sophia-agrobiotech/Equipes-ISA/IPO

PHD PROJECT SUMMARY:

Plant response to bioagressors involves wide modifications of gene expression. Recently, small non coding RNAs came out as crucial regulators of gene expression during plant response to several pathogens: bacteria (Boccara *et al*. 2014), fungi (Weiberg *et al*. 2013). Moreover, a recent study in *Arabidopsis* supports a model whereby the miR472- and RDR6-mediated silencing pathway represents a key regulatory checkpoint modulating both PTI and ETI responses through the post-transcriptional control of disease resistance genes.

Root-knot nematodes *Meloidogyne incognita* (RKN) are biotrophic plant parasitic worms those parasite more than 3000 plant species. *Phytophthora parasitica* (syn *P. nicotianae*) is an hemibiotrophic devastating pathogen with one of the widest host ranges of any described *Phytophthora* species, infecting more than 255 genera of plants (Panabières et al., 2016). Together, these two pathogens dramatically threaten agriculture worldwide, and share several hosts, like solanaceous plants, including tomato, or the model plant *Arabidopsis thaliana*. Because their ability to infest a wide diversity of plants, they are thought to manipulate essential and conserved plant molecular pathways.

Our study aims to characterise the role of smallRNAs during the plant response to these two wide host pathogens. Plant smallRNA populations expressed in roots infected with *M. incognita* or *P. parasitica* will be identified by high throughput technology. In order to identify mechanisms shared by the plant response to these two pathogens, small RNA populations expressed in each condition will be compared. The evolutionary conservation of this plant response will be investigated with two natural hosts of these pathogens: the tomato *Lycopersicon esculentum* and the model plant *Arabidopsis thaliana*.

RELATED PUBLICATIONS:

1. Boccara M, Sarazin A, Thiébeauld O, Jay F, Voinnet O, Navarro L, Colot V. (2015). *The Arabidopsis* miR472-RDR6 silencing pathway modulates PAMP- and effector-triggered immunity through the post-transcriptional control of disease resistance genes. **PLoS Pathog**. 2015 Apr 10;11(4):e1004814.

2. Cabrera J, Barcala M, Garcia A, Rio-Machin A, Medina C, Jaubert-Possamai S, Favery B, Maizel A, Ruiz-Ferrer V, Fenoll C, Escobar C (2015). Differentially expressed small RNAs in Arabidopsis galls fromed by Meloidogyne javanica: a functionak role for miR390 and its TAS3-derived tasiRNAs. **New Phytol** 2015 Nov 6. doi: 10.1111/nph.13735.

3. Panabières F., Ali GS, Allagui MB, Dialo RJD, Gudmestad NC, Kuhn ML, Guha Roy S, Schena L., Zampounis A (2016). *Phytophthora nicotianae* diseases worldwide: old wine in new bottles. **Phytopathol. Meditter**. *in press.*

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.

Axis 4: Signaling in aging and disease progression

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: 21-DECKERT/RICCI

"Role of the lymphatic fibroblast-derived stroma in lymphoma development and drug resistance"

KEYWORDS: lymph node, fibroblast, lymphoma, metabolism, survival

PI 1 (Labex SIGNALIFE team): DECKERT, Marcel (TARTARE-DECKERT, Sophie)
Institute: *C3M*
Email: deckert@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): RICCI, Jean-Ehrland
Institute*: INSERM U1065, C3M*
Email: ricci@unice.fr , Phone: +33 (0)4 89 06 43 04
Website: http://www.unice.fr/c3m/index.php/research-teams/jean-ehrland-ricci/

PHD PROJECT SUMMARY:

B cell neoplasms develop in specialized microenvironments, such as those found in secondary lymphoid organs. The lymphoid tissue is an immunologically specialized environment inhabited by immune cells, blood and lymphatic vessels providing irrigation and routes of tumor dissemination, and mesenchymal stromal cells known as fibroblastic reticular cells (FRC), whose extracellular matrix (ECM) scaffolding function controls adaptive immunity and lymph node (LN) viscoelastic properties upon immunological or tumoral challenge. The LN tumor microenvironment must be actively shaped by lymphoma cells to create hospitable niches in which cancer cells receive in return extracellular signals that promote tumor cell proliferation and survival, metabolic reprogramming, therapeutic resistance and immune escape. Thus, LN constitute a crucial checkpoint in the initiation and progression of B cell malignancies, yet the ways by which cancer cells remodel the LN microarchitecture and adapt to this environment is poorly understood. In line with our previous and current work on molecular pathways controlling cancer metabolism, growth, survival and migration, and studies on how microenvironment influences tumor progression and dissemination, we will address the following key questions: i) which signals do tumor cells transmit to the lymphatic stroma and how FRC contribute to lymphoma development and drug resistance? ; ii) what are the composition and biophysical structure of the lymphoma-associated LN ECM network?; iii) do biochemical and biomechanical cues from tumor-associated LN ECM govern lymphoma phenotypic heterogeneity?; iv) how targeting the studied pathways (metabolism, BCR-associated PTKs signaling…) can improve clinical management of lymphoid cancers?
We will address these questions using a combination of experimental approaches based on 2D and 3D co-cultures models and investigations conducted in mouse models of B-cell lymphomagenesis. We will analyze how FRC microenvironnement modulates lymphoma cell survival/proliferation, metabolic reprogramming, motility and response to chemo- and targeted therapies. To better understand how malignant B cells may educate LN fibroblasts, a phenotypic and functional characterization of the populations of lymphoma-associated FRC will be conducted. Alterations of the LN architecture and ECM remodeling induced by the expansion of malignant B-cells and the impact of therapeutic treatments will be also investigated.
Our findings will bring a more comprehensive view of the interactions between lymphoma and stromal cells within the LN microenvironment and on the regulatory mechanisms that may control lymphoma expansion and drug resistance. This project is fundamental in nature, but has important implications for clinical oncology as it may unveil new therapeutic targets.

RELATED PUBLICATIONS:

1. Fletcher AL, Acton SE, Knoblich K. Lymph node fibroblastic reticular cells in health and disease. Nat Rev Immunol. 2015 Jun;15(6):350-61.
2. Chiche J, Pommier S, Beneteau M, Mondragón L, Meynet O, Zunino B, Mouchotte A, Verhoeyen E, Guyot M, Pagès G, Mounier N, Imbert V, Colosetti P, Goncalvès D, Marchetti S, Brière J, Carles M, Thieblemont C, Ricci JE. GAPDH enhances the aggressiveness and the vascularization of non-Hodgkin's B lymphoma via NF-kB-dependent induction of HIF-1alpha. Leukemia. 2015 May; 29(5):1163-76.
3. Baudot, A.D., Jeandel, P.Y., Mouska, X., Maurer, U., Tartare-Deckert, S., Raynaud, S.D., Cassuto, J.P., Ticchioni, M., and Deckert, M. The tyrosine kinase Syk regulates the survival of chronic lymphocytic leukemia B cells through PKCdelta and proteasome-dependent regulation of Mcl-1 expression. Oncogene 2009 Sep 17;28(37):3261-73.

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: 25-GUAL/RICCI

"MicroRNA in the liver complications of obesity"

KEYWORDS: Obesity, Liver, Cancer, Metabolism

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): RICCI, Jean-Ehrland
Institute*: INSERM U1065, C3M*
Email: ricci@unice.fr , Phone: +33 (0)4 89 06 43 04
Website: http://www.unice.fr/c3m/index.php/research-teams/jean-ehrland-ricci/

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. Although some individual proteins, genes and genetic modifiers (SNP) related to NAFLD have been identified, the role the miRNA in the progression and the severity could play an important role. miRNA regulated metabolism, inflammation and cell apoptosis which are involved in the pathogenesis of NAFLD and carcinogenesis. The two partners located in the Mediterranean Center for Molecular Medicine (C3M, Nice) will share their expertise in the clinical and basic aspects of fatty liver disease (Philippe Gual), and metabolism and immune response associated with cancer (Jean-Ehrland Ricci) to identify novel therapeutic targets on the progression of fatty liver disease. The project will benefit from the access to sample from a large cohort of patients, availability of a variety of techniques and approaches, animal models and primary cultures of liver cells that will be shared by the two groups.
We will 1) in humans, identify novel actors (miRNAs and their targets) from our cohort of obese patients with NAFLD (1008 patients) and HCC; 2) in cells evaluate the relevance and the role of the identified actors (miRNA) and 3) to study and evaluate in pre-clinical models the impact of targeting this pathway in the progression or correction of NAFLD (focusing on HCC), 4) to evaluate the role of the identified miRNA which regulated cellular metabolism in other cancers
This project should allow a better understanding of NAFLD and metabolism associated with cancer and leading to propose new therapeutic approaches.

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. Chiche, J., et al. (2015) GAPDH enhances the aggressiveness and the vascularization of non-Hodgkin's B lymphomas via NF-kappaB-dependent induction of HIF-1alpha. *Leukemia* 29, 1163-1176 (I.F. 10.43).

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

Axis 5: New principles in signaling and applications

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: 32-LITI

"A natural genomics framework for global dissection of organismal fitness"

KEYWORDS: natural variation, population genomics, genome editing, life cycle, 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/

PHD PROJECT SUMMARY:

Most traits, including many human diseases, are regulated by multiple interacting quantitative trait loci (QTLs). Dissecting the genetic mechanisms underlying this phenotypic variation is a central issue in modern biology. Perhaps, even more challenging is to understand what evolutionary forces maintain the variability in natural populations.

In my lab, we use the budding yeast in population genomics, QTL mapping and experimental evolution studies in order to understand how complex traits are regulated. We are co-leading a major resequencing effort that aims to release high quality genomes for 1002 natural S. cerevisiae strains (http://1002genomes.u-strasbg.fr/). This large sample size of full genome sequences coupled to high-throughput phenotyping will provide powerful opportunities for genome wide association studies. Furthermore, we previously generated extensive resources of genotyped and phenotyped recombinant strains obtained by genetic crosses. The selected PhD candidate will use these resources to identify genetic variants and environmental factors that contribute to important aspects of the yeast life cycle in the wild and investigate how they impact the species fitness. Yeast fitness has been largely approximated to mitotic growth, which disregards mortality during periods that do not support reproduction. However, it is likely that yeasts in nature spend most of their chronological life in a non-dividing state. The ability to survive in that state is therefore probably exposed to strong selection. Thus, measuring the impact of natural genetic variation on longevity related traits might be crucial for understanding the selective pressures that yeasts are exposed to during their life cycle. Consideration will also be given to other aspects of the natural life cycle, such as sporulation, spore viability and germination time, each of which are also complex traits and strongly affected by the environment.

The candidate will be involved in both experimental and computational analysis. The computational part consists in analysing existing populations genomics datasets and identifying genetic variants relevant to phenotypes, which are also available to the hosting lab. Subsequently, these variants will be engineered by applying the latest genome editing technologies in order to experimentally measure their effect on the global organismal fitness. Exploiting the natural variation of S. cerevisiae and its close relatives using genomics methodologies is enabling a new era of functional and evolutionary genetics studies of this classic model organism.

RELATED PUBLICATIONS:

1. Liti, G. et al. Population genomics of domestic and wild yeasts. Nature 458, 337–341 (2009).
2. Bergström, A. et al. A high-definition view of functional genetic variation from natural yeast genomes. Mol. Biol. Evol. 31, 872–888 (2014).
3. Liti, G. The fascinating and secret wild life of the budding yeast S. cerevisiae. Elife 4, (2015).

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.

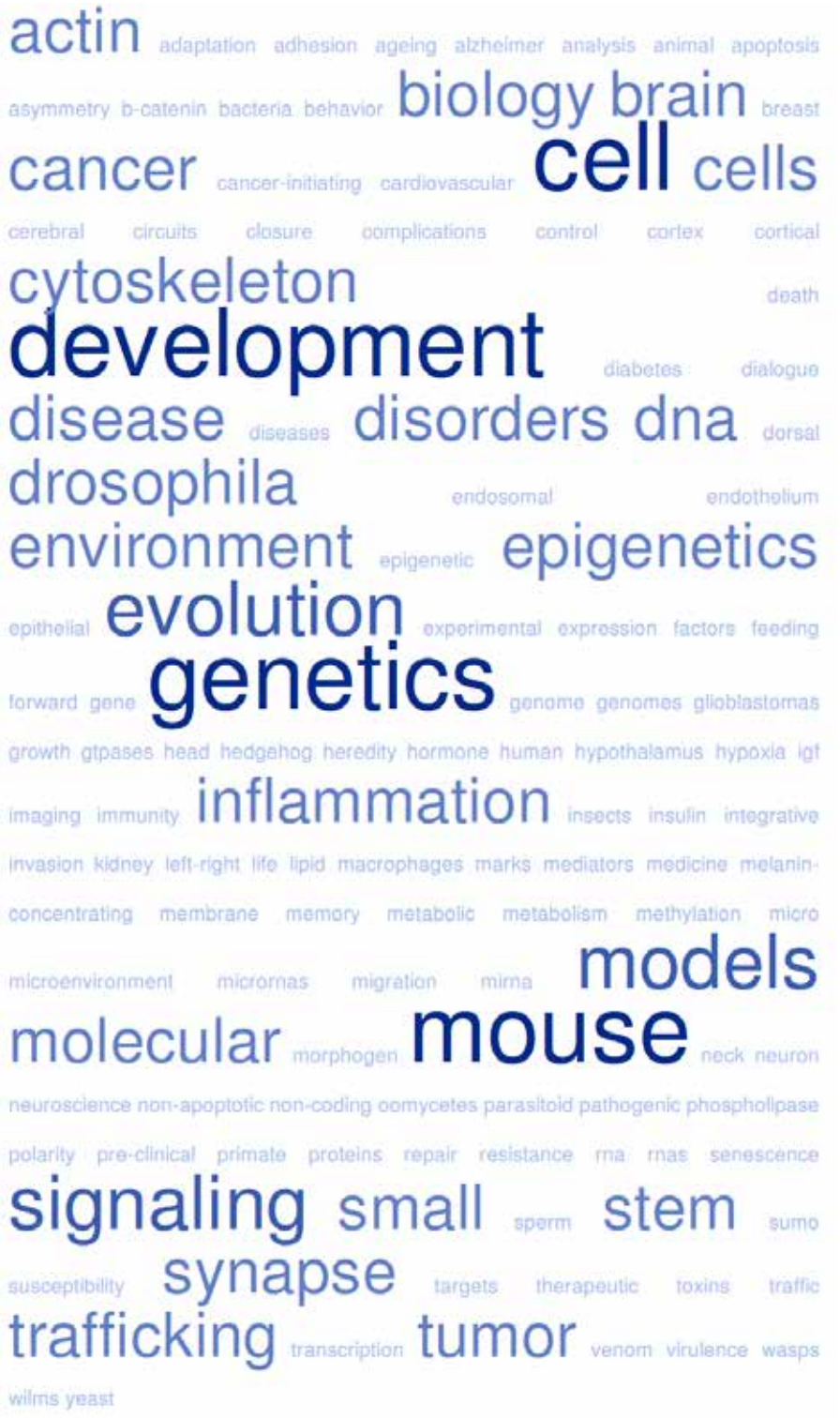
Here, we propose take advantage of a classic model system, the budding yeast S. cerevisiae, to dissect the impact of telomere variation. Initially, we will investigate the extent of telomere variation in natural population by analysing a large population genomics dataset that our lab has been leading (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



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

SIGNALIFE GROUP LEADERS


Abad


Antonny


Arkowitz


Auberger


Ballotti


Barbry


Bardoni


Besse


Braendle


Braud


Anjuère


Chaboissier


Collombat


Cristofari


Dani


Delaunay


Descombes


Feral


Frendo


Fürthauer


Gilson


Glaichenhaus


Gouzé


Gual


Tran


Hofman


Hueber


Lalli


Lambeau


Lemichez


Leopold


Liti


Luton


Franco


Magnaldo


Meneguzzi


Marie


Martin


Nahon


Noselli

Panabières

Poirié

Rassoulzadegan

Ricci

Robichon

Schedl

Studer

Tanti

Cormont

Tartare-Deckert

Thérond

Trabucchi

Van Obberghen

VO-Schilling