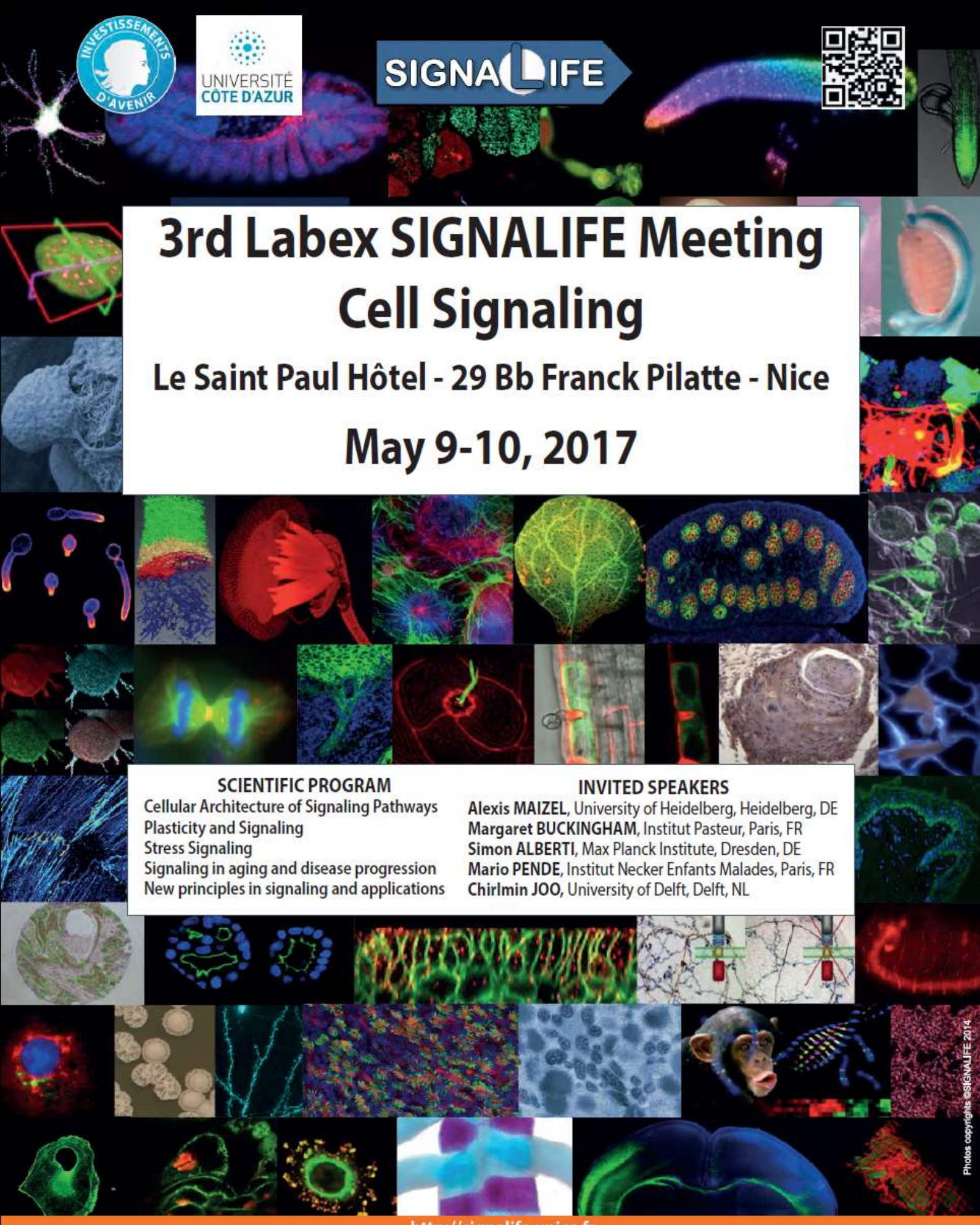

3rd Labex SIGNALIFE Meeting
Cell Signaling

Le Saint Paul Hôtel - 29 Bb Franck Pilatte - Nice

May 9-10, 2017

SCIENTIFIC PROGRAM

Cellular Architecture of Signaling Pathways
Plasticity and Signaling
Stress Signaling
Signaling in aging and disease progression
New principles in signaling and applications

INVITED SPEAKERS

Alexis MAIZEL, University of Heidelberg, Heidelberg, DE
Margaret BUCKINGHAM, Institut Pasteur, Paris, FR
Simon ALBERTI, Max Planck Institute, Dresden, DE
Mario PENDE, Institut Necker Enfants Malades, Paris, FR
Chirlmin JOO, University of Delft, Delft, NL

http://signalife.unice.fr

Front cover: Composite of images from 30 research groups

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Many thanks to all SIGNALIFE PhD Students

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PROGRAM OVERVIEW

3rd labex SIGNALIFE meeting May 9-10, 2017, Le Saint Paul Hôtel, Nice (DAY 1)

	Tuesday 9 May
13:00 - 14:00	**Registration**
14:00 - 14:15	*Welcome*
	Session I, Axis 1: Cellular Architecture of Signaling Pathways chair: G. Cristofari
14:15 - 15:00	*Invited Keynote Lecture:* **Alexis MAIZEL,** University of Heidelberg, DE "Morphogenesis of plant organs"
15:00 - 15:30	*SIGNALIFE Keynote* : **Robert ARKOWITZ**, iBV "Cell Polarity and Membrane Traffic in Fungal Growth"
15:30 - 15:50	**Najla EL-HACHEM,** C3M "Uncovering and deciphering the pro-invasive role of HACE1 in melanoma cells"
15:50 - 16:10	**Vishnu SARASWATHY ,** iBV "Analysing the role of Mindbomb in Neural tube morphogenesis"
16:10 - 16:40	**Coffee Break and Group Picture**
	Session II, Axis 2: Plasticity and Signaling chair: P. Thérond
16:40 - 17:25	*Invited Keynote Lecture:* **Margareth BUCKINGHAM**, Institut Pasteur, Paris, FR "Regulation of skeletal muscle stem cell fate"
17:25 - 17:55	*SIGNALIFE Keynote :* **Pascal BARBRY,** IPMC "Regulation of Cellular Differentiation by Non Coding RNAs"
17:55 - 18:15	**Ramona GALANTONU,** IRCAN "A link between steroid signaling pathways and L1 retrotransposition"
18:15 - 18:35	**Aitana PEREA-GOMEZ,** iBV "NR2F2 is required for steroidogenic cell development in the fetal mouse testis"
	Wine and Cheese Poster Session
19:00 - 21:30	**Wine and Cheese Buffet and Poster Session**

3rd Labex SIGNALIFE meeting May 9-10, 2017, Le Saint Paul Hôtel, Nice (DAY 2)

	Wednesday 10 May
	Session III, Axis 3: Stress Signaling chair: F. Besse
09:00 - 09:45	*Invited Keynote Lecture:* **Simon ALBERTI**, Max Planck Institute, Dresden, DE "RNP granules: how they form, age and cause disease"
09:45 - 10:15	*SIGNALIFE Keynote:* **Mireille CORMONT**, C3M "Senescent-like adipocytes in obesity-induced insulin resistance"
10:15 - 10:45	**Coffee Break**
10:45 - 11:05	**Serena TESTI,** ISA "Avh195, an oomycete plant pathogen effector that perturbs autophagy in distant eukaryotes"
11:05 - 11:25	**Derya DEVECI,** iBV "The neuroendocrine control of puberty"
	Session IV, Axis 4: Signaling in aging and disease progression chair: J.-F. Tanti
11:25 - 12:10	*Invited Keynote Lecture:* **Mario PENDE,** Institut Necker Enfants Malades, Paris, FR "mTOR pathophysiology in rare diseases of growth and senescences"
12:10 - 12:40	*SIGNALIFE Keynote :* **Hélène MARIE**, IPMC "APP fragments and synapse signaling: Aβ is not alone!"
12:40 - 14:00	**Lunch Buffet**
14:00 - 14:20	**Jozef BOSSOWSKI,** C3M "Low Protein diet reduces cancer progression through induction of anticancer immune response"
14:20 - 14:40	**Anida HASANOVIC,** IPMC "Inhibition of the drug efflux activity of Patched enhances chemotherapy efficiency *in vitro* and *in vivo* "
	Session V, Axis 5: New principles in signaling and applications chair: P. Brest
14:40 - 15:25	*Invited Keynote Lecture:* **Chirlmin JOO**, Delft University of Technology, NL "Single-Molecule View on CRISPR-Cas Adaptive Immunity"
15:25 - 15:55	*SIGNALIFE Keynote:* **Gérard LAMBEAU,** IPMC "From toxic venom phospholipases A2 to membranous nephropathy, a rare autoimmune kidney disease"
15:55 - 16:25	**Coffee Break**
16:25 - 16:45	**Sofia ALMEIDA,** Inria "Modeling and understanding the mammalian cellular clock"
16:45 - 17:05	**Sandra RUIZ GARCIA,** IPMC "Tracking cell trajectories by single-cell transcriptome analysis during normal and pathological regeneration of the airway epithelium"
17:05 - 17:30	*Poster awards*
17:30 - 17:45	*Concluding remarks*

ORAL COMMUNICATIONS

Session I, Axis 1
Cellular Architecture of Signaling Pathways

Chair : G. Cristofari

Invited Keynote Lecture : Alexis MAIZEL

Morphogenesis of plant organs

MAIZEL Alexis (1)

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Keywords : Plant, development, morphogenesis, root, auxin

Plants form new organs with patterned tissue organization throughout their lifespan. As plants cells are encaged in a rigid cell wall cell migration is impossible. In consequence, plants rely on oriented cell divisions and anisotropic growth to shape their organs and precisely organise their tissues. It is unknown if this robust post-embryonic organ formation results from stereotypic dynamic processes, in which the arrangement of cells follows rigid rules. We combined modelling with empirical observations of whole organ development to identify the principles governing lateral root formation in Arabidopsis. Lateral roots derive from a small pool of founder cells, in which some take a dominant role as seen by lineage tracing. The first division of the founders is asymmetric, tightly regulated, and determines the formation of a layered structure. While the pattern of subsequent cell divisions is not stereotypic between different samples, it is characterized by a regular switch in division plane orientation. This switch is also necessary for the appearance of patterned layers as a result of the apical growth of the primordium. Our data suggest that lateral root morphogenesis is based on a limited set of rules. They determine cells growth and division orientation. The organ-level coupling of the cell behaviour ensures the emergence of the lateral root's characteristic features. We propose that self-organizing, non-deterministic modes of development account for the robustness of plant organ morphogenesis.

Signalife Keynote : Robert ARKOWITZ

Cell polarity and membrane traffic in fungal growth

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Keywords : Cell Polarity, Membrane Traffic, Filamentous Growth , Cell Morphology, Dynamics

Site-specific regulation of small Rho GTPases is critical for cell morphology changes in diverse cell types and is thought to underlie symmetry breaking. How Rho GTPases trigger cell shape changes in an already asymmetric cell is less well understood. Candida albicans is a human fungal pathogen that can cause life-threatening infections in immunocompromised individuals, in part, due to its ability to switch between an oval budding form and a filamentous hyphal form. The highly conserved, small Rho GTPase Cdc42 plays a central role in cell polarity in virtually all eukaryotes. In filamentous cells, such as fungi, the active form of this GTPase localizes as a persistent tight cluster at the tips (1). We have been using a light-activated membrane recruitment system to control the recruitment of constitutively active Cdc42 to the plasma membrane in filamentous fungal cells and are investigating how such a photo-recruitment disrupts hyphal growth as well as where, when and how new growth is subsequently initiated. Our results demonstrate that, upon photo-recruitment of active Cdc42, filament extension is disrupted and new growth can subsequently occur throughout the cell. The location of new growth appears to correlate with filament length and in part reflects how well-established the initial growth site is. Prior to new growth, the initial filament stops extending, concomitant with disruption of the cluster of endogenous active Cdc42. We have begun to examine the dynamics of cellular organelles and structures, with a focus on the endocytic/exocytic pathway, following disruption of the endogenous growth site and subsequent site-specific initiation of a new filament.

(1) V. Corvest, S. Bogliolo, P. Follette, R. A. Arkowitz & M. Bassilana (2013). Mol Microbiol. 89: 626-48.

Supported by EU Marie Curie Initial Training Network FP7-PEOPLE-2013-ITN (#607963) FUNGIBRAIN and ANR LABEX SIGNALIFE (ANR-11-LABX-0028-01).

Presentation 1: Najla EL-HACHEM

Uncovering and deciphering the pro-invasive role of HACE1 in melanoma cells.

EL-HACHEM Najla (1), HABEL Nadia (1), NAIKEN Tanesha (1), CHELI Yann (1), BERANGER Guillaume (1), JAUNE Emilie (1), ROUAUD Florian (1), REINIER Frédéric (1), GAUDEL Céline (1,) COLOSETTI Pascal (2), BERTOLOTTO Corine (1) BALLOTTI Robert (1)

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Keywords : Ubiquitination, E3 ligase, Integrins, Adhesion, Metastasis

HACE1 is an E3 ubiquitin ligase described as a tumor suppressor because mice invalidated for HACE1 developed multi-organ late onset of cancers and because HACE1 expression is lost in several neoplasms such as Wilm's tumors. However, we found that HACE1 expression was maintained in melanomas. Further, we demonstrated that HACE1 favored migration and adhesion of melanoma cells. In vivo, we showed that HACE1 was required for short-term lung colonization and for long term melanoma tumor development, in mice. Transcriptomic analysis of HACE1-depleted melanoma cells revealed an inhibition of ITGAV and ITGB1, as well changes in other genes involved in cell migration. We revealed that HACE1 promoted K27 ubiquitination of fibronectin and regulated its secretion. Then, secreted fibronectin regulated ITGAV and ITGB1 expression as well adhesion and migration of melanoma cells. Our findings disclosed a novel molecular cascade involved in the regulation of fibronectin secretion, integrin expression and melanoma cell adhesion. By controlling this cascade, HACE1 displays pro-tumoral properties and is an important regulator of melanoma cell invasive properties.

Presentation 2: Vishnu SARASWATHY

Analysing the role of Mindbomb in Neural tube morphogenesis

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Keywords : Mindbomb, Delta/Notch Signalling, Planar cell polarity, C-divisions, neuro-epithelial morphogenesis

Delta-Notch signalling is one of the important pathways during the embryonic development. Mindbomb (Mib) which is an E3-ubiquitin ligase is known to be necessary for Delta ligands ubiquitination and endocytosis which further leads to Notch activation and signal transduction. In the pursuit of understanding the role of Mib in Zebrafish neural tube morphogenesis, we stumbled up on the fact that Mib plays an important role in maintaining apico-basal cell polarity of epithelial cells in neural tube via Delta-Notch Signalling. This apico-basal polarity regulation is achieved through the transcriptional regulation of polarity genes. Further analysis in Mib morphant condition revealed that midline crossing symmetric cell division of the neural tube known as C-divisions are perturbed. C-divisions in the neural tube help to maintain the bilateral symmetry and also lead to formation of future neural rod structure. C-divisions are known to be dependent on Planar Cell Polarity Pathway (PCP) as well as the polarity protein Par3. PCP act like a 'Compass' to a group of cells to define their anterior-posterior axis by asymmetric distribution of certain proteins perpendicular to the apico-basal axis. In order to understand the role of Mib in C-divisions, we characterised both Mib genetic mutant and Mib morpholino injected embryos. We could identify a clear reduction of C-divisions in both Mib morphant and mutant conditions. Strong reduction of c-divisions in Delta-D mutants injected with Delta-A morpholino and rescue of c-divisions in Mib mutants by NICD injection revealed that Mib regulates C-divisions via Delta-Notch signalling. To explore whether Mib plays any role in PCP, we analysed the PCP regulated process called Convergent Extension (CE). Zebrafish neural tube width and height is maintained through PCP pathway via CE. In our study, both Mib mutant and morphant showed an increase in the width to height ratio of neural tube which is typical to PCP mutants. In accordance with the literature, we confirmed that Pard3 protein is important for c-divisions in neural tube by using a validated Pard3 morpholino. Now we are studying the link between Mib in the regulation of Pard3 and PCP with or without the Delta-Notch signalling.

Session II, Axis 2
Plasticity and Signaling

Chair : P. Thérond

Invited Keynote Lecture : Margaret BUCKINGHAM

Regulation of skeletal muscle stem cell fate

BUCKINGHAM Margaret

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Keywords : Muscle stem cells, Myogenesis, Pax3, Myf5, ROS levels

All skeletal muscles in the trunk and limbs derive from multipotent progenitor cells present in somites of the developing embryo. Pax3 is a key upstream regulator of the onset of myogenesis, a role also played by Pax7 at later stages of development (1). From a genetic screen for Pax3 targets in the mouse embryo, we have identified a number of genes that intervene at different stages in the progression towards skeletal muscle formation. Reciprocal negative regulation between Pax3 and Foxc2 determines cell fates in the somite. The Foxc1/Pax3 balance is affected by Notch signalling which favours the Foxc-dependent non-myogenic cell fate, exemplified by endothelial versus myogenic derivatives that migrate from the somite to the limb (2, 3).
Head muscles and some neck muscles are not derived from somites and their formation does not depend on Pax3. The progenitor cells of these muscles depend on distinct gene regulatory networks (4), involving a number of transcription factors implicated in cardiogenesis. They derive from common progenitors that also contribute to the myocardium of the heart (5). This has interesting evolutionary implications, as well as biomedical relevance for congenital muscle disease.
Regeneration of adult skeletal muscle depends on satellite cells, quiescent cells that are closely associated with muscle fibres. These cells are marked by the expression of Pax7 and derive from the Pax3-positive cells of the somite (1). Unlike embryonic muscle progenitors, most satellite cells already transcribe the myogenic determination gene Myf5, with post-transcriptional regulation preventing immediate myogenesis (6).
Pitx2 is a Pax3 target in the embryo and Pitx2/3 double mutants have major foetal muscle defects (7). This is due to the central role of these factors in regulating the redox state. High levels of ROS lead to cell death. In adult satellite cells, moderate levels of ROS, acting through the p38α signaling pathway, determine the balance between proliferation and the onset of differentiation.

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Signalife Keynote : Pascal BARBRY

Regulation of motile ciliogenesis by microRNAs

BARBRY Pascal (1), ARGUEL Marie-Jeanne (1), CAVARD Amélie (1), DEPREZ Marie(1), LEBRIGAND Kévin (1), MAGNONE Virginie(1), MARCET Brice (1), PAQUET Agnès (1), PONZIO Gilles (1), RUIZ-GARCIA Sandra (1), WALDMANN Rainer (1), ZARAGOSI Laure-Emmanuelle (1)

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Keywords : multiciliogenesis, mucociliary epithelium, microRNA, single cell analyses, 3D culture

MiR-34/449 microRNAs are conserved regulators of multiciliated cell differentiation. They are highly and specifically expressed in multiciliated cells, where they trigger MCC differentiation by repressing cell cycle genes and the Notch pathway, and by controlling apical actin network formation through small GTPase pathways. Two isomiR variant sequences from the miR-34/449 family are expressed in human airway epithelial cells, where they represent additional mechanisms by which the miR-34/449 family finely controls several pathways to drive multiciliogenesis. MicroRNA34/449 function can also be integrated in a larger gene regulatory network, including key regulatory factors such as TP73, FOXJ1, RFXs, MYB, etc. Interestingly, miR-449 is expressed by a locus that contains three molecules that actively contribute to the mucociliary differentiation: MCIDAS, CCNO and CDC20B. Their study at a single cell level by RNA seq profiling reveals some unique properties of these molecules, and their contribution to centriologenesis, an important mechanism which allows the production of hundreds basal bodies at the begining of ciliogenesis.

This work is supported by the ANR, the FRM, the ARC, the Conseil Départmental 06, the Canceropôle PACA, Vaincre la Mucoviscidose

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Presentation 1: Ramona GALANTONU

A link between steroid signaling pathways and L1 retrotransposition

GALANTONU Ramona (1), PIZARRO Javier (1), MONOT Clément (1), LAGHA Nadira (1), MONTANDON Margo (1), KAZAKYAN Serdar (1), VALFORT Aurore-Cécile (1), VIDALAIN Pierre-Antoine (1), CRISTOFARI Gaël (1)

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Keywords : retrotransposons, steroids, interaction, tethering, regulation

Mobile genetic elements play important roles in the evolution and function of the human genome. Among them, the Long Interspersed Nuclear Element-1 (LINE-1 or L1) retrotransposon contributes to the genetic diversity of the human population, and occasionally leads to inherited genetic diseases. L1 elements are also reactivated in many tumors. L1 jumps through a 'copy and paste' mechanism. This process involves two L1-encoded proteins, ORF1p and ORF2p, which associate with the L1 mRNA to form a ribonucleoprotein particle, the core of the retrotransposition machinery. However, little is known about the cellular factors involved in L1 replication. Our laboratory has discovered by yeast 2-hybrid screens that ORF2p, an L1 protein with endonuclease and reverse transcriptase activities, interacts with the estrogen-related receptor α (ERRα), a member of the nuclear receptor family. This observation suggests a model by which ERRα could regulate retrotransposition, possibly by tethering the L1 machinery to chromatin or to specific genomic locations. The existence of several ERRα paralogs prompted us to test whether ORF2p could also interact with other members of this superfamily. To achieve this goal, we used a fluorescent two-hybrid assay (F2H) in mammalian cells. Our results indicate that ORF2p interacts with several other members of the steroid receptors group.
To further explore the potential role of this interaction in targeting L1 to chromatin, we artificially tethered ERRα to a unique LacO array and we measured de novo L1 insertions by a cellular retrotransposition assay.
Collectively, these data identify steroid signaling pathways as a potential regulatory mechanism for genome instability in human cells.

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Presentation 2: Aitana PEREA-GOMEZ

NR2F2 is required for steroidogenic cell development in the fetal mouse testis

PEREA-GOMEZ Aitana (1), McCLELLAND Kathryn (2), TANG Furong (1), ZHAO Fei (2), FRANCO Heather (2), VASSEUR-COGNET Mireille (3), YAO Humphrey H-C (2) and CHABOISSIER Marie-Christine (1)

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Keywords : NR2F2, mouse, embryo, testis, steroidogenesis

Adult Leydig cells (ALC) present in the adult testis are the primary source of testosterone, an essential regulator of masculinity and fertility. The orphan nuclear receptor NR2F2 (COUP-TFII) is required in rodents for the differentiation of ALC at puberty but also for the regeneration of ALC after chemical injury in the adult. NR2F2 is already expressed in the mouse male and female gonads during embryonic development. However, the origin, destiny and function of these fetal NR2F2 expressing cells are ill-defined.
Here we show that in the bipotential gonad, NR2F2 is expressed in the coelomic epithelium and in a few scattered mesenchymal cells. In the developing mouse testis, NR2F2 expression is excluded from the testis cords, and is detected in peritubular myoid cells and in interstitial cells. Importantly, NR2F2 appears to be downregulated in steroidogenic fetal Leydig cells (FLC). Conditional ablation of NR2F2 in the gonad using the Nr5a1-Cre line (Sf1-Cre) results in a reduction of FLC number from embryonic day 13.5 (E13.5) in the male gonad. Our results indicate that NR2F2 function is required in interstitial progenitors for the differentiation of FLC.

Session III, Axis 3
Stress Signaling

Chair : F. Besse

Invited Keynote Lecture : Simon ALBERTI

Organizing living matter: the role of phase transitions in cell biology and disease

ALBERTI Simon

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Keywords : Environmental stress, Phase separation, Compartment formation, Age-related diseases, Protein quality control

Stressed cells undergo changes on multiple levels to alter their physiology, metabolism and architecture. Our recent work shows that many of these changes occur in a controlled manner and involve a reorganization of the cytoplasm and the formation of membrane-free compartments via a process known as phase separation. This challenges an established paradigm in cell biology, which posits that compartmentalization requires containment by membranes. Our very recent findings show that the material properties of the cytoplasm are widely adjustable and can be modified locally and globally along a continuum of physical states from liquid to gel to solid. Such changes in the cytoplasmic state, which on the molecular level are reflected by the formation of nanometer- to micrometer-sized assemblies, endow cells with spatiotemporal control over diffusion-limited biochemical processes. Most importantly, we recently discovered that the initially beneficial ability to change the material properties of the cytoplasm and form membrane-less compartments becomes detrimental with increasing age. This is because many compartment-forming proteins are hypersensitive to changing conditions and have a tendency to form aberrant structures that cause aging-associated diseases. Thus, we propose a new model for many age-related neurodegenerative diseases, where we link the physiological function of compartment-forming proteins with their role in disease.

Signalife Keynote : Mireille CORMONT

Senescent-like adipocyte in obesity-induced insulin resistance

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Keywords : adipocyte stresses, p53, insulin resistance, obesity, DNA damage

Activation of the p53 pathway in adipose tissue contributes to insulin resistance associated with obesity. However, the mechanisms of p53 activation and the impact on adipocyte functions are still elusive. Here we found a higher level of DNA oxidation and a reduction in telomere length in adipose tissue of high-fat diet mice and an increase in DNA damages and activation of the p53 pathway in adipocytes. Interestingly, hallmarks of chronic DNA damages associated to senescent cells (gammaH2AX nuclear foci, the expression of the CDKN2a locus, activation of p53, and induction of p21) are visible in adipocyte at the onset of obesity. Furthermore, treatment of lean mice with doxorubicin, a drug inducing DNA damage, increased the expression of several chemokines in adipose tissue and promoted its infiltration by pro-inflammatory macrophages and neutrophils together with adipocyte insulin resistance. In vitro, DNA damages in adipocytes increased the expression of chemokines and triggered the production of chemotactic factors for macrophages and neutrophils. They also triggered the secretion of inhibitors of adipocyte differentiation and pro-apoptotic factors for preadipocytes. Also, insulin signaling and effect on glucose uptake and Glut4 translocation were decreased by DNA damages while lipolysis was increased. These events were prevented by p53 inhibition whereas its activation by nutlin-3 reproduced the DNA damage-induced adverse effects. This study reveals that senescent-like adipocytes in obesity could trigger p53-dependent signals involved in alteration of adipocyte metabolism and secretory function leading to an altered adipose tissue homeostasis characterized by adipose tissue inflammation, adipocyte dysfunction and insulin resistance.

Presentation 1: Serena TESTI

Avh195, an oomycete plant pathogen effector that perturbs autophagy in distant eukaryotes

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Keywords : Autophagy, Cell death, Phytophthora parasitica, Plant, Immunity

Oomycetes from the genus Phytophthora are plant pathogens, which have devastating impacts on agriculture and natural ecosystems. Phytophthora parasitica is a root pathogen with a hemibiotrophic lifecycle: during the initial stages of infection (biotrophy) the oomycete establishes an intimate contact with the living cells of the host, before inducing plant cell death to complete its life cycle (necrotrophy). cDNA libraries that were obtained from P. parasitica-infected tomato plants and onion epidermis cells display several sequences that encode secreted proteins with a canonical RxLR translocation signal, such as Avh195. Avh195 possesses three potential binding sites for ATG8, a key protein in the process of autophagy. Heterologous expression of Avh195 in tobacco plants slows down cell death responses such as those induced by proapoptotic BAX, and the HR inducers cryptogein and AvrPtoB. On this basis, we investigate the antagonism between death-inducing agents and Avh195 aiming at identifying the manipulated host signaling pathways, with a particular focus on the link between Avh195 and the autophagy machinery. To identify the molecular targets of Avh195, we initiated a trans-phylum analysis on plants, human cells, and green microalgae. Genetic expression of Avh195 dramatically alters the cellular phenotype in all these organisms, indicating that this protein targets an evolutionary-conserved mechanism.

Presentation 2: Derya DEVECI

The neuroendocrine control of puberty

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Keywords : Puberty, Hormones, Metabolism, Allatostatin A, PTTH

How does an organism know when to undergo puberty? This is a fundamental question in biology that remains unanswered. Puberty marks the metamorphosis of a child into an adult, which is referred to as juvenile maturation transition (JMT). In addition, in organisms that undergo determinate growth this transition is associated with cessation of growth, fixing its final body size. Both events occur due to a peak of steroid hormones that induce maturation at the same time as growth inhibition. In vertebrates, the onset of JMT is marked by a peak of steroid hormones. In Drosophila melanogaster a similar mechanism takes place. A peak in the prothoracicotropic hormone (PTTH) by the PTTH producing hormones induces the production of the insect steroid hormone ecdysone. Modulating PTTH levels affects the timing of JMT and subsequently final body size. In order to understand which incoming signals are regulating PTTH we have conducted a RNAi screen in the PTTH producing neurons. Here we obtained one candidate gene in particular, Allatostatin A receptor 1 (AstA-R1), that was giving a robust delay of JMT and larger animals. AstA-R1 is a GPCR that is known to bind its ligand allatostatin-A (AstA) which is produced by AstA neurons in the brain. We found that knocking down AstA-R1 decreases PTTH mRNA levels and reduces the secretion of PTTH from the PTTH neurons. Additionally, we found that the AstA-R1 receptor is also expressed on the Drosophila insulin producing cells (IPCs) which is important in the coupling of nutrition with final body size. Surprisingly, knocking down AstA-R1 in these neurons results in smaller animals without affecting the timing of JMT, suggesting that AstA-R1 is also involved in the regulation of growth. These results propose two functions for AstA: regulating the timing of JMT via PTTH and the regulation of growth through the IPCs. Up next it is important to study the regulation of AstA in order to understand how an organism knows when to undergo puberty.

Session IV, Axis 4
Signaling in aging and disease Progression

Chair : J.-F. Tanti

Invited Keynote Lecture : Mario PENDE

mTOR pathophysiology in rare diseases of growth and senescence

PENDE Mario

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Keywords : growth, signal transduction, nutrition, ageing, cancer

The mammalian Target Of Rapamycin is a master regulator of growth. mTOR is a serine/threonine protein kinase that exists in two distinct complexes in the cell (mTORC1 and mTORC2) and transduces virtually all anabolic signals from the environment: nutrients, such as glucose and amino acids, growth factor peptides, such as insulin and insulin like growth factors, oxygen, mitochondrial metabolites, energy status. mTOR is required to sustain cell responses to nutrient availability including cell growth, proliferation, macromolecule biosynthesis, and suppress autophagy. During the past ten years we have generated and characterized a wide panel of mouse mutants in the mTOR pathway. We were involved in revealing specific and interesting phenotypes that increased our knowledge of mTOR roles in pathophysiology: mutants with small cells, mutants resistant to tumorigenesis in specific tissues and after specific oncogenic, mutants with muscle dystrophy, mutants mimicking caloric restriction and promoting longevity, mutants with altered insulin action.
I will present our progress on the molecular mechanisms of cell size control and organismal longevity. I will show how nutrient sensing pathways impact on cell senescence through the activation of mTORC1-S6 kinases and the phosphorylation of ZRF1. I will also detail our efforts to understand rare human genetic diseases that arise from pathological changes in the activity of the mTOR pathway, including Tuberous Sclerosis Complex and lipin1 deficiency.

Signalife Keynote : Hélène MARIE

APP fragments and synapse signaling: Aβ is not alone!

MARIE Hélène

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Keywords : Synapse, Alzheimer's disease, neuron plasticity, signal transduction, neuromodulation

Identifying the pathological mechanisms causing Alzheimer's disease is a crucial challenge of the 21st century as by 2050 we expect 1/85 persons living with the disease worldwide and no cure or effective palliative therapies are currently available. Genetic and pre-clinical evidence led to a major hypothesis regarding the etiology of the disease, which centers on the toxic effects of amyloid-beta (Aβ) peptide assemblies at synapses within the hippocampus. This Aβ peptide originates from amyloid precursor protein (APP) cleavage and accumulates into oligomers, peptide assemblies that perturb synapse plasticity processes such as long term potentiation and long term depression. Yet, several human clinical trials show that removing Aβ aggregates from brain areas controlling memory processes, such as the hippocampus, did not provide the expected protection against cognitive decline. What if Aβ was not the only APP fragment perturbing synapse function in the context of Alzheimer's disease? I will present results demonstrating that other fragments originating from APP cleavage also modulate the function of hippocampal synapses, arguing for a role of these fragments as neuromodulators. These findings shed new light on the biological relevance of APP processing at synapses in physiological and pathological conditions.

Presentation 1: Jozef BOSSOWSKI

Low Protein diet reduces cancer progression through induction of anticancer immune response.

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Keywords : cancer, ER stress, Diet, immune response, macronutrient modulation

Although cancer cells are very different in origin, they share some characteristics like the ability to escape cell death and the use of different methods of energy production that are common to most of them. That's why in recent years there is huge interest in targeting their metabolism in order to make them more susceptible toward chemotherapy treatment and to reduce their growth. Caloric restriction is known to play a central role in preventing cancer development, however the underlying mechanism remains to be identified. As research continues to reveal the link between metabolism and cancer, non-pharmacologic interventions as CR become clinically interesting. Our work revealed, as opposed to general belief, that the antitumor effect of nutritional restricted diets are not due to an alteration of cancer cell proliferation but rather to an efficient induction of an anti-cancer immune response, through endoplasmic reticulum stress induction within tumor cells. We established that up-regulation of ER stress is a consequence of lower protein intake leading to increase cytokine production, which amplify immune cells infiltration into cancer tissue and enhance their cytotoxic capabilities. We identified main pathway triggering ER stress under low protein condition. My work will describe molecular mechanisms that should bring news insights on the induction of an effective anticancer immune response.

Presentation 2: Anida HASANOVIC

Inhibition of the drug efflux activity of Patched enhances chemotherapy efficiency in vitro and in vivo

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Keywords : adrenocortical cancer, Patched, chemotherapy, doxorubicin, xenograft

Adrenocortical cancer is a rare, heterogenous and malignant endocrine tumor which affects about one person in a million and whose 5-year survival rate is only 35% on average. The best treatment available at the present time is composed of a mixture of chemotherapeutic agents combined with the adrenolytic substance mitotane. However, the response to this treatment remains modest, which means that more effective therapy is urgently required. We recently demonstrated that Hedgehog receptor Patched is involved in the efflux of drugs such as doxorubicin, a chemotherapeutic agent used for clinical management of recurrent cancers. This suggests that Patched could also contribute to chemotherapy resistance of cancer cells.
In order to identify small molecules that are able to inhibit multidrug resistance activity of Patched and to increase chemotherapeutic treatment efficiency, we developed a screening based on the ability of small molecules to inhibit growth of yeast that express human Patched in medium containing doxorubicin. One of the identified compounds had the ability to increase cytotoxic, antiproliferative and apoptotic effect of doxorubicin in a dose- and time – dependent manner on adrenocortical cancer cell line H295R and increase the effect of doxorubicin on tumor formation in H295R xenograft mice model.
We have shown that these effects of the compound are due to the inhibition of the doxorubicin efflux activity of Patched and could represent a new approach in adrenocortical cancer treatment.

Session V, Axis 5
New principles in signaling and applications

Chair : P. Brest

Invited Keynote Lecture : Chirlmin JOO

Single-Molecule View on CRISPR-Cas Adaptive Immunity

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Keywords : CRISPR, Cas9, Cascade, Single-molecule FRET, helicase

Prokaryotes mediate defense against invading genetic elements using RNA-guided adaptive immune systems encoded by CRISPR (clustered regularly interspaced short palindromic repeats)-Cas (CRISPR-associated) loci. Since its discovery, CRISPR/Cas system has been at the focus of fundamental researchers, genome engineers and the general public alike. Despite being in the spotlight for several years now, aspects of the precise molecular mechanism of CRISPR/Cas activity remains ambiguous. We use single-molecule FRET (Forster resonance energy transfer) to reveal CRISPR/Cas mechanisms with nanometer sensitivity.
We demonstrate that Cas9 (type II CRISPR/Cas system) facilitates one-dimensional diffusion along the DNA strand to find its target. We investigate the weak interaction between Cas9 and PAM sequences and show that Cas9 scrutinizes DNA for PAM by using lateral diffusion. We further demonstrate lateral diffusion between target sites by using a tandem target DNA target assay. We reveal the underlying mechanism of the lateral diffusion, by altering the distance between two targets and the strength of the electrostatic interaction between Cas9 and DNA. Based on our findings, we suggest a new model for the molecular basis of Cas9 target search.
In the type I system, the most ubiquitous CRISPR-Cas system, immunity relies on the RNA-guided surveillance complex Cascade (CRISPR-associated complex for antiviral defense) and the transacting Cas3 protein with helicase and nuclease activities. Cascade targets foreign DNA by hybridizing its crRNA with DNA strands and recruiting the Cas3 protein for DNA degradation. It was recently shown that immunity is strengthened when DNA degradation products of the Cas3 helicase-nuclease protein are repurposed to update CRISPR memory. However, it remains unclear how the nuclease and helicase activity of Cas3 is coupled to generate precursors that are proficient for the spacer integration. We show that the Cascade-Cas3 complex repeatedly reels in single-stranded DNA with distinctive steps of 3 base pairs. This non-processive unwinding presents a defined length of single-stranded DNA to the nuclease domain of Cas3 for cleavage. Our study demonstrates that the inherently discontinuous and burst-like helicase properties of Cas3 drive the generation of precursors proficient for primed spacer integration.

Signalife Keynote : Gérard LAMBEAU

From venom phospholipases A2 to membranous nephropathy, a rare autoimmune kidney disease

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Keywords : Phospholipase A2, lipids, human diseases, venom, structure

Secreted phospholipases A2 (sPLA2s) are disulfide-rich low molecular mass (14-19 kDa) enzymes that hydrolyze multiple phospholipids to release free fatty acids and lysophospholipids. sPLA2s are diverse in nature. They were discovered in snake and insect venoms. Venom sPLA2s exert digestive and toxic functions towards preys but are also endowed with pharmacological and therapeutical properties. More than two decades ago, we started to work on toxic venom sPLA2s and discovered specific sPLA2 receptors (M and N) including the so-called M-type receptor or PLA2R1, a 180 kDa C-type lectin membrane receptor.
Because of the large diversity of venom sPLA2s, we hypothesized that a similar diversity of sPLA2s might exist in mammals. These mammalian sPLA2s would exert their functions as enzymes but also endogenous ligands of the above receptors identified with venom sPLA2s, bringing the concept that sPLA2s act as both enzymes and ligands. We and others cloned several mammalian sPLA2s, bringing the total number of mammalian sPLA2s to 12 members. Interestingly, recent evidence indicates that snakes also contain, like humans, a diversity of sPLA2s in their various tissues, beyond the venom gland. Since more than a decade, our challenge is to identify the biological roles of the different sPLA2s and their receptors in physiological and pathophysiological conditions. Like venom sPLA2s, mammalian sPLA2s are not functional isoforms. They are diverse in structure, tissue distributions and enzymatic properties, suggesting distinct functions. Several of them also bind to specific proteins including PLA2R1, which may serve to inhibit or promote sPLA2 action. It is now clear that individual sPLA2s are involved in diverse physiological settings through enzymatically-dependent and -independent mechanisms, act redundantly or non-redundantly in physiopathological situations, and represent potential drug targets or bioactive drugs. Moreover, PLA2R1 is likely a polymodal receptor with multiple ligands and functions, beyond its interaction with sPLA2s. In this talk, I will present some novel biological roles of both venom and mammalian sPLA2s and of PLA2R1 in host defence, atherosclerosis, s perm fertility, cancer and membranous nephropathy, a rare but severe human auto-immune kidney disease in which PLA2R1 is the major autoantigen. Together, mammalian sPLA2s and PLA2R1 constitute attractive drug targets and active biomolecules in multiple human diseases.

Presentation 1: Sofia ALMEIDA

Modeling and understanding the mammalian cellular clock

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Keywords : circadian clock, mammalian cell, mathematical modeling, synthetic biology, coupled biological oscillators

The circadian clock is a highly conserved process found in most living beings that controls 24 h rhythms, providing an adaptation to the day/night cycle. Most organisms have a central circadian clock controlled by the brain that coordinates the sleep/wake cycle, metabolism, body temperature, behavior, cortisol secretion and more. However, the circadian clock is also present at a single cell level and is responsible to ensure energy homeostasis and to allow the adaptation of cell physiology in anticipation to recurring changes. Aiming to study and analyze the dynamics of the mammalian cellular clock, we develop a mathematical model to describe it. From this model, it is possible to focus on the essential mechanisms of the mammalian cell clock, which allows us to design a transcriptional regulatory synthetic system capable of mimicking the circadian rhythm in mammalian cells. This system can be further used to study the coupling between the clock and another important biological oscillator: the cell cycle.

This work is supported by Labex SIGNALIFE Network for Innovation on signal Transduction Pathways in Life Sciences (Grant ANR-11-LABX-0028-01).

Presentation 2: Sandra RUIZ GARCIA

Tracking cell trajectories by single-cell transcriptome analysis during normal and pathological regeneration of the airway epithelium.

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Keywords : airway epithelium, multiciliogenesis, differentiation, progenitor/stem cells, gene expression

The upper airway epithelium is mainly composed of 3 cell types: multiciliated (MCCs), goblet, and basal cells. After respiratory injuries, the tissue must repair to reproduce a functional mucociliary epithelium through processes of proliferation and differentiation of a subpopulation of progenitor cells1. In chronic airway diseases, such as chronic obstructive pulmonary disease or asthma, the injured epithelium frequently displays defective repair and remodeling characterized by a loss of MCCs with goblet cell hyperplasia leading to mucus hyper-secretion2. No therapy has proven to be efficient to reduce the remodeling of the tissue mostly because the accurate molecular events governing the differentiation of the epithelium have not yet been characterized.
We are aiming at characterizing the sequence of cellular and molecular events taking place during airway mucociliary epithelium regeneration in healthy or pathological conditions such as asthma, mimicked by IL13 treatment which induces tissue remodeling with mucus hypersecretion of mucus and MCC differentiation defects3. Single cell transcriptomics makes possible the accurate characterization of subpopulations with high resolution.
After having reported, for the first time, single cell transcriptomes of in vitro differentiated airway epithelium4, we have established signatures of cell populations in the time course of in vitro regeneration of the human airway epithelium. Our results should allow to track cell trajectories from progenitor cells to differentiated cells. Moreover, we have applied this technique to the analysis of tissue remodeling upon IL13 treatment and report a drastic modification of cell population with redistribution within the basal cell compartment, decrease of MCCs and increase in the goblet cell populations.

This work is supported by the Labex-Signalife PhD program, Vaincre a la mucovisidose (VLM), Université Côte d'Azur (UCA) and Centre National de Recherche (CNRS).

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POSTERS

Wine and Cheese Poster Session

LIST OF 44 POSTERS PRESENTATIONS				
Number	**Last Name**	**First Name**	**Scintific Axis**	**Abstract title**
1	AIRA DIAZ	Lazaro Emilio	Axis 1 – Cellular architecture of signaling pathways	Caspase 1/11 deficiency in mice leads to a decrease in the induced psoriasis-like phenotype
2	AWINA	Hala	Axis 1 – Cellular architecture of signaling pathways	A survival mechanism controlled by cadherins and Dlg1 polarity complex inhibits Fas cell death receptor signaling.
3	BEN JOUIRA	Rania	Axis 4 – Signaling in aging and disease progression	Extracellular matrix produced by BRAF inhibitor-resistant melanoma cells promotes therapeutic resistance to drug-sensitive cells
4	BERGER	Antoine	Axis 2 – Plasticity and Signaling	Contribution of nitrate reductases and hemoglobins to nitric oxide (NO) balance in the Medicago truncatula – Sinorhizobium meliloti symbiosis
5	BILLARD	Benedicte	Axis 2 – Plasticity and Signaling	Characterizing the molecular genetic basis of natural variation in C. elegans developmental plasticity
6	BOUGET	Gwenaelle	Axis 4 – Signaling in aging and disease progression	Rab4b-dependent endocytic processes in macrophages are involved in glucose homeostasis
7	CABRAL DO NASCIMENTO	Danila	Axis 1 – Cellular architecture of signaling pathways	WEE1: a key cell cycle regulator involved in plant-root knot nematode interaction
8	CASTAGNOLA	Sara	Axis 2 – Plasticity and Signaling	Fragile X Mental Retardation Protein regulates calcium signaling via Cacna1a
9	CAVARD	Amélie	Axis 1 – Cellular architecture of signaling pathways	Characterizing isomiRs of the miR-34/449 superfamily of microRNAs : role in multiciliogenesis
10	CHAMBON	Lucie	Axis 5 – New principles in signaling and applications	Control of a negative feedback loop in a gene network
11	CHARAZAC	Aurélie	Axis 1 – Cellular architecture of signaling pathways	Quantitative image based analysis of endocrine disruptor effects on mitochondria morphology-function in prostate cancer cells.
12	DA SILVA	Fabio	Axis 1 – Cellular architecture of signaling pathways	Retinoic acid signaling promotes cardiomyocyte survival in cardiac development and repair
13	DE ALMEIDA ENGLER	Janice	Axis 1 – Cellular architecture of signaling pathways	A cell biology view on the susceptible interaction between plants and obligate sedentary parasitic root-knot nematodes: the plant cytoskeleton and cell cycle
14	DE GARAY	Tomás	Axis 1 – Cellular architecture of signaling pathways	CD98hc (SLC3A2) presents a novel longer variant with an alternative promoter
15	DIDIER	Robin	Axis 4 – Signaling in aging and disease progression	Targeting the proteasome-associated deubiquitinating enzyme USP14 induces melanoma cell death and overcomes resistance to MAPK-targeting therapies.
16	EFTHYMIOU	Georgios	Axis 4 – Signaling in aging and disease progression	Oncofetal fibronectin splice variants: functional analysis and generation of tunable fibroblast-derived extracellular matrices
17	FABRIS	Gaia	Axis 4 – Signaling in aging and disease progression	Reduces liver development in progeny of rat dams having suffered from protein restriction: possible role of altered microrna biogenesis
18	FAYAD	Racha	Axis 1 – Cellular architecture of signaling pathways	Loss of EFA6-B, an EMT regulator, facilitates breast cancer development in vivo
19	FELSKE	Torsten	Axis 2 – Plasticity and Signaling	Direct reprogramming of cortical neurons
20	FORMICOLA	Nadia	Axis 1 – Cellular architecture of signaling pathways	CaMKII: a novel regulatory component of Imp neuronal RNA granules ?
21	GARCIA	Elsa	Axis 3 – Stress Signaling	Characterization of the anti-virulence immune response against bacterial toxins
22	GRAPA	Anca-Ioana	Axis 5 – New principles in signaling and applications	Classification of the 2D FN variants using curvelets
23	GREGOIRE	Elodie	Axis 2 – Plasticity and Signaling	NRG1 signalling is involved in testis development in mice.
24	HALLIN	Johan	Axis 5 – New principles in signaling and applications	Understanding the genetic basis for hybrid sterility
25	HUBSTENBERGER	Arnaud	Axis 5 – New principles in signaling and applications	P-bodies are integration centers for the coordination of mRNA expression
26	JAMECNA	Denisa	Axis 1 – Cellular architecture of signaling pathways	Investigation into the function of the N-terminal region of OSBP
27	KAMINSKI	Lisa	Axis 3 – Stress Signaling	PGC-1a controls an onco-metabolic program to limit prostate cancer aggressiveness
28	KIM	Chami	Axis 3 – Stress Signaling	Deciphering Drosophila immune resistance to endoparasitoid wasps: mechanisms, specificity and evolution.
29	LE ROLLE	Morgane	Axis 2 – Plasticity and Signaling	WNT/Ctnnb1 signaling pathway controls germ cell development in mamals
30	LEBEAUPIN	Cynthia	Axis 4 – Signaling in aging and disease progression	Pharmacological inhibition of IRE1alpha RNase activity rescues BI-1-deficient mice fed a high fat diet from steatohepatitis development
31	LOTOTSKA	Liudmyla	Axis 3 – Stress Signaling	RNA-mediated role of TRF2 in pericentromere function
32	MATEGOT	Raphaël	Axis 2 – Plasticity and Signaling	Investigating the functions of nuclear RNA interference
33	NAPOLITANO	Tiziana	Axis 2 – Plasticity and Signaling	Deciphering the role of ft1 during pancreas morphogenesis and throughout adulthood
34	NOVELLI	Caterina	Axis 2 – Plasticity and Signaling	Hedgehog secretion mechanisms in Drosophila epithelial tissues
35	PICCO	Vincent	Axis 4 – Signaling in aging and disease progression	AKT1 activity restricts migration capacities of an oral carcinoma cell line harboring a constitutive active PI3 Kinase activity.
36	PUSHPALATHA	Kavya Vinayan	Axis 3 – Stress Signaling	Identification and characterisation of potential interacting partners in IMP granule assembly and function
37	ROGER	Estelle	Axis 4 – Signaling in aging and disease progression	Microrna involvement in the control of brown adipose tissue activity in a model of predisposition to type 2 diabetes
38	ROVERA	Christopher	Axis 4 – Signaling in aging and disease progression	Melanoma educates fibroblasts of the distant lymph node pre-metastatic niche
39	RUBERTO	Anthony	Axis 4 – Signaling in aging and disease progression	KLF10 establishes the landscape of diurnal expression in the liver
40	SABOURAULT	Cecile	Axis 2 – Plasticity and Signaling	Plasticity and regulation of a cnidarian-Symbiodinium endosymbiosis
41	SCHOROVA	Lenka	Axis 5 – New principles in signaling and applications	Regulation of the SUMOylation balance at the neuronal synapse
42	TANG	Furong	Axis 2 – Plasticity and Signaling	Rspo1 in female sex determination
43	VIJAYAKUMAR	Jeshlee	Axis 3 – Stress Signaling	Role of the Prion-like domain of dImp in RNP granule regulation
44	WAKADE	Rohan Sanjay	Axis 1 – Cellular architecture of signaling pathways	The Rab GTPase Ypt6 is critical for Candida albicans invasive growth and virulence

1 - AIRA DIAZ Lazaro Emilio – Axis 1

Caspase 1/11 deficiency in mice leads to a decrease in the induced psoriasis-like phenotype

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Keywords : Inflammatory caspases, pro-inflammatory cytokines, keratinocytes, human skin biopsies, psoriasis

Psoriasis is a chronic inflammatory skin disorder characterized by epidermal thickening, immune cell infiltration and the release of several pro-inflammatory cytokines such as TNF-α, IL17 and IL-1β/IL-18. Inflammatory caspases, which are activated through multiprotein complexes called inflammasomes, are reponsible for the maturation and secretion of IL-1β/IL-18. While the expression of these cytokines in psoriasis was demonstrated several years ago, little is known about the role of the inflammatory caspases in this context. Here, we showed that inflammatory caspases are expressed in lesional biopsies as compared to non-lesionnal skin area of psoriatic patients, however none caspases expression is observed in another inflammatory skin disease, like atopic dermatitis. In different mice models of psoriasis-like disease, we established that IL-1β and inflammasome components are expressed in injured skin as compared to normal skin. Accordingly, when we induced a psoriasis-like disease in caspase-1/11 deficient mice, a decrease in ear thickness, inflammatory cytokines expression and immune cells infiltration was found. Moreover, as we observed that keratinocytes were primed to secrete IL-1β when cultured in condition mimicking psoriasis (TNF-α + IL17-A), we decided to generate chimeric mice deficient for caspase-1/11 either in the immune system or in keratinocytes/fibroblasts (by adoptive transfer) in order to decipher the respective contribution of each tissue compartment in the activation of inflammatory caspases during psoriasis-like inflammatory response. Our data showed that the presence of caspase-1/11 in the immune system is necessary for a full inflammatory response whereas the absence of caspase-1/11 in keratinocytes/fibroblasts had no or little effect. Our study indicates that inflammatory caspases are implicated in the pathogenesis of psoriasis.

2 - AWINA Hala– Axis 1

A survival mechanism controlled by cadherins and Dlg1 polarity complex inhibits Fas cell death receptor signaling.

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Keywords : Fas receptor, cell death, Signaling, Stability, PDZ domain

A fine regulation of epithelia cell death is required to maintain tissue integrity and homeostasis. At a cellular level, this life and death decision is controlled by environmental stimuli including death receptors activation. Here, we show that establishment of cell polarity and AJ formation control the pro-apoptotic signaling emanating from the death receptor Fas. We demonstrate that in colon epithelia or in invasive melanoma cells, Fas concentrates at cell-cell junctions with the E- or pro-invasive N- cadherin, respectively. The Fas-cadherin association protects cells from FasL-induced cell death. We also show that this protection is reinforced by the interaction of Fas with the polarity molecule Dlg1, which stabilizes Fas into cell-cell junctions. Therefore inhibition of FasL-induced cell death by Fas-cadherin-Dlg1 complex is a double-edged sword mechanism that: (i) helps to maintain epithelial homeostasis by protecting normal epithelia from apoptosis and promoting elimination of compromised non-polarized cells; (ii) favors tumor cells invasion by guarding invading N-cadherin expressing cells from immune surveillance.

3 - BEN JOUIRA Rania– Axis 4

Extracellular matrix produced by BRAF inhibitor-resistant melanoma cells promotes therapeutic resistance to drug-sensitive cells

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Keywords : Melanoma, ECM, resistance, microenvironment, BRAF

Cutaneous melanoma remains one of the most challenging and difficult cancer to treat because of its high plasticity, metastatic potential and resistance to treatment. New therapies targeting oncogenic BRAFV600E mutation have shown remarkable clinical efficacy. However, drug resistance invariably develops. Thus, the need for improving existing therapies remains critical. Recent studies have indicated that tumor resistance arises from (epi)genetic cancer cell alterations and from the tumor microenvironment in which the extracellular matrix (ECM) is a determinant factor. Both stromal and tumor cells contribute to ECM deposition and remodeling during disease progression. Here, we found that BRAF inhibitor (BRAFi)-resistant melanoma cells, but not BRAFi-sensitive cells, abundantly produced matrix proteins and remodeled a 3D ECM displaying fibronectin (FN) and collagen fibers. The ability of BRAFi-resistant cells to produce a fibrous ECM is associated with an exacerbated invasive mesenchymal phenotype characterized by increased expression of epithelial-to-mesenchymal transition (EMT) markers, focal adhesion markers and RHO GTPases . These cellular and biochemical characteristics are enhanced in a rigidity-dependent manner highlighting the increased mechanosensitivity of the BRAFi-resistant melanoma cells compared to the drug-sensitive cells.
Interestingly, our results show that the 3D ECM produced by resistant melanoma cells is able to induce an elongated morphology of the therapy-sensitive cells and more importantly protect them from the anti-proliferative effect of the BRAFi Vemurafenib. In conclusion, our results suggest that resistance to targeted therapy is associated with the production by melanoma cells of a pathological matrisome that may affect cell behavior and therapeutic response.

4 - BERGER Antoine– Axis 2

Contribution of nitrate reductases and hemoglobins to nitric oxide (NO) balance in the Medicago truncatula – Sinorhizobium meliloti symbiosis

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Keywords : Medicago truncatula, symbiosis, nitric oxide, hemoglobins, nitrate reductases

The symbiosis between legumes and bacteria of rhizobium type leads to the formation of nitrogen-fixing nodules. In the symbiotic model Medicago truncatula/Sinorhizobium meliloti, nitric oxide (NO) is produced throughout the whole symbiotic process, from early interaction between the plant and the bacteria to senescence of nitrogen fixing nodules. Toxic, signalling or metabolic effects of NO depend on its concentration at the site of action. Therefore, NO steady-state concentration inside the cells should be tightly controlled to limit toxic effects and allow the signalling and metabolic functions to occur. In plants, several sources of NO have been described including nitrate reductase (NR), mitochondrial electron transfer chain (ETC) and NOS-like activity. Hemoglobins (Hbs) are known to act as NO storage or scavenger. Based on their sequence homology and affinity for oxygen, three classes of Hbs have been essentially described in plants: non-symbiotic hemoglobins (ns-Hbs, Class 1), leghemoglobins (Lbs, Class 2) and truncated hemoglobins (tr-Hbs, Class 3). The three types of Hbs were reported to be expressed in legumes.

To precisely assess the occurrence of NO during the whole symbiotic process, and the respective role of the different NRs and Hbs in its balance, we analysed the production of NO, the expression of 3 NR and 5 Hb genes, and the global NR activity during short term (0 to 9 days post-inoculation and long term (0 to 9 weeks post-inoculation) symbiosis experiments.

Four peaks of NO production, which levels depend on nitrate concentration in culture medium, were observed 10 hours, 4 days, 3-4 weeks and 6 weeks post-inoculation. NO production was correlated with NR1, NR2, ns-HBs and tr-Hbs genes expression at the different stages of nodule formation. The use of various NO source inhibitors showed that NO production mainly depends on NR activity during early interaction steps as well as in mature and senescent nodules.

The different roles of NO, as a signalling and/or metabolic molecule, and its regulation by NRs and Hbs, in young, mature and senescent nodules are discussed.

5 - BILLARD Bénédicte– Axis 2

Characterizing the molecular genetic basis of natural variation in *C. elegans* developmental plasticity

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Keywords : C. elegans, developmental plasticity, evolution, QTL mapping , dauer

Virtually all organisms possess the capacity to flexibly adjust their development in response to environmental changes, a phenomenon called developmental plasticity. A prime example of adaptive developmental plasticity is the process of dauer formation in the nematode C. elegans, during which larvae can adopt an alternative, stress-resistant larval stage (termed dauer) in response harsh environmental conditions (high population density, starvation, or high temperature). The molecular genetic mechanisms regulating dauer induction have been well-characterized and involve Insulin, TGF-Beta and steroid hormone signalling pathways. In contrast, few studies have focused on characterizing the molecular variants explaining differences in dauer induction among natural C. elegans isolates. Here we identified a C. elegans isolate (JU751, France), which shows an unusually strong tendency to form dauers, even at low population densities (where other natural isolates do not form dauers). To identify the genetic basis underlying this difference in dauer formation we quantified dauer formation in 144 F2 recombinant inbred lines (RILs) generated from an intercross between JU751 and another isolate displaying dauer induction only under harsh environmental conditions (JU1200, UK). RILs were SNP-genotyped at 150 loci across the whole genome to allow for QTL (Quantitative Trait Locus) analysis, which identified a single, highly significant QTL on chromosome III, spanning approximately 700kb. We are currently aiming to confirm the effect of this QTL region on dauer formation through establishment of near-isogenic lines (NILs) and we will perform fine-mapping of the target region to isolate the causal molecular variants underlying natural variation in C. elegans dauer formation.

6 - BOUGET Gwenaelle– Axis 4

Rab4b-dependent endocytic processes in macrophages are involved in glucose homeostasis

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Keywords : insulin resistance, cardiometabolic diseases, endocytosis, macrophages, Rab4b

Introduction: During obesity, insulin resistance is a key event for type 2 diabetes development and is associated with an increase in pro-inflammatory macrophages in adipose tissues (AT). We previously observed that the expression of the small GTPase Rab4b, a Rab protein involved in endocytic recycling, was decreased in F4/80-positive macrophages purified from AT of mice fed a high fat diet. Our objective was to study the consequences of the inhibition of Rab4b expression in macrophages in vivo on metabolic and inflammation homeostasis.
Material and Methods: We have generated mice invalidated for Rab4b specifically in macrophages (Rab4bMacKO) by crossing Rab4bflox/flox mice and mice expressing the Cre-recombinase under the control of a macrophage-specific promotor (LysM-Cre). We then characterized the metabolic and inflammatory phenotype of the mice.
Results: Under normal diet, the Rab4bMacKO mice are hyperglycemic and hyperinsulinemic in fasting condition. Their glucose tolerance tests are however identical, as circulating NEFA and hepatic and muscle triglycerides. Under high fat diet, the Rab4bMacKO mice have a higher weight, higher fat mass, and are hyperphagic. They are glucose tolerant as their control but secrete more insulin during the IP-GTT. On the immunity side, the Rab4bMacKO mice presented no differences in the numbers of circulating immune cells (monocytes, neutrophils, CD4+ and CD8+ T cells, and B cells quantified by flow cytometry). Under normal diet, the AT macrophages from Rab4bMacKO mice expressed a higher amount of CD11c, a pro-inflammatory marker, at the cell surface while they expressed less of the anti-inflammatory molecules CD206. However, the macrophage content in AT is identical. Under high fat diet, the number of pro-inflammatory macrophages and of CD8+ lymphocytes increased in the AT of Rab4bMacKO mice. In vitro, the differentiation of bone marrow derived monocytes into anti-inflammatory macrophages, using IL-4, was decreased in absence of Rab4b whereas the differentiation into pro-inflammatory macrophages by LPS was favored.
Conclusion: The decrease in Rab4b expression in macrophages that we observed during obesity could permit their pro-inflammatory polarization and contribute to insulin resistance without marked dyslipidemia.

7 - CABRAL DO NASCIMENTO Danila– Axis 1

WEE1: a key cell cycle regulator involved in plant-root knot nematode interaction

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Keywords : Arabidopsis thaliana, DNA-repair, mitosis, endoreduplication, galls

Plant-parasitic nematodes are among the most devastating plant pathogens. Root-knot nematodes (RKN; Meloidogyne spp.) infect plant roots and trigger the formation of specialized feeding sites named “galls” by substantial reprogramming of root cell development. They usurp and modulate the plant cell cycle machinery for their benefit. RKN induced giant-feeding cells undergo acytokinetic mitosis and DNA endoreduplication and are surrounded by actively dividing neighboring cells. The cell cycle machinery is important to allow the induction and maintenance of the nematode feeding site development and certain core cell cycle genes have been shown to be crucial for nematode feeding site development. Among them WEE1-1,a nuclear kinase involved in terminal phosphorylation and inactivation of cyclin-dependent kinase 1-bound cyclin B, induces G2 cell cycle arrest in response to DNA damage in Arabidopsis.WEE1 is a component of the cell cycle checkpoint control with major role in preventing cells from dividing until DNA is repaired and replication normalized. Our functional analysis using tailored microscopy approaches permitted us to gain insight into the possible role of this key cell cycle regulator during RKN feeding site development. In addition, we have shown that stress inducing drug treatments on nematode infected roots, slows down mitosis in all gall cells most likely by inducing check point control.

8 - CASTAGNOLA Sara– Axis 2

Fragile X Mental Retardation Protein regulates calcium signaling via Cacna1a

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Keywords : Fragile X, Intellectual Disability, Autism, Calcium signaling, Calcium channel

Fragile X Syndrome (FXS) is the most common form of intellectual disability and primary cause of autism. It originates from the lack of Fragile X Mental Retardation Protein (FMRP), which is an RNA-binding protein encoded by the FMR1 gene. FMRP is involved in different steps of RNA metabolism, ranging from RNA transport (from the nucleus to the cytoplasm, but also along neuronal prolongments) to translational control of mRNAs at soma and at synapses. In the last 20 years researchers have found a large number of FMRP targets, but it is still not clear which are those playing a critical role in the syndrome. We performed Cross-Linking ImmunoPrecipitation (CLIP) experiments and found many putative targets of FMRP (around 4000), and one of the most enriched was Cacna1a. There are many studies in the recent literature correlating FXS with defects in ion channels (also called channelopathies), ranging from K channels, to h-channels, and of course Ca2+ channels, but Cacna1a was never studied in relation to FXS. The Cacna1a gene encodes for the pore-forming subunit of a Voltage-Gated Calcium Channel (VGCC) particularly expressed in neurons, both in the axon terminals and in the somatodendritic compartments. It allows the entry of calcium in the cytosol of neurons upon arrival of an action potential, and this promotes many intracellular changes, like neurotransmitter release and calcium-dependent gene transcription. Our goal is to analyze the correlation between the lack of FMRP and the expression of Cacna1a in primary neuronal cultures, in order to define the exact role of Cacna1a in the pathophisiology of FXS. For this purpose, we carried out calcium-imaging experiments on cultured Fmr1-null cortical/hippocampal neurons and we observed that these neurons display a weaker and slower Ca2+ response to KCl (which mimicks the arrival of a depolarizing action potential) than wild type neurons. This abnormality is due to a reduced activity/expression of Cacna1a. Our findings concerning the regulation of the expression level of Cacna1a by FMRP will also be presented.

9 - CAVARD Amélie– Axis 1

Characterizing isomiRs of the miR-34/449 superfamily of microRNAs: role in multiciliogenesis

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Keywords : MicroRNA, Airway epithelia, Multiciliogenesis, Differentiation, Ciliopathies

Cilia are sensory organelles ranging from non-motile primary cilium to motile cilium involved in signaling and mechanical flow generation of biological fluids. In vertebrates, some cells can project hundreds of motile cilia (multiciliated cells, MCCs) which beat in a coordinate manner to propel biological fluids. MCCs lining the luminal surface of some tissues play key physiological roles such as in respiratory tract where they act to airway cleansing. Defects in motile cilia can cause ciliopathies (e.g primary ciliary dyskinesia, PCD) or worsen the symptoms of chronic respiratory diseases. The MCC biogenesis is a complex process called multiciliogenesis that occurs during embryonic development or regeneration of some specialized epithelia. Multiciliogenesis involves hundreds of players which the identity of many of them remains to be elucidated.
We previously showed that miR-34/449 microRNAs are conserved regulators of MCC differentiation. Here, we evidence and characterize expression of two novel isomiR variant sequences from the miR-34/449 family in human airway epithelial cells. These isomiRs differ from their canonical counterparts miR-34b and miR- 449c by one supplemental uridine at their 5'-end, leading to a one-base shift in their seed region. Overexpression of canonical miR-34/449 or 5'-isomiR-34/449 induces distinct gene expression profiles and biological effects. However, some target transcripts and functional activities are shared by both canonical microRNAs and isomiRs. Indeed, both repress important targets that result in cell cycle blockage and Notch pathway inhibition. Our findings suggest that 5'-isomiR-34/449 may represent additional mechanisms by which they cooperate with miR-34/449 family to finely control several pathways to drive multiciliogenesis.

10 - CHAMBON Lucie– Axis 5

Control of a negative feedback loop in a gene network

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Keywords : Gene Network, Mathematical modelling, Oscillations, Control, Negative loop

Genetic regulatory networks play an essential role in living organisms by controlling specific cell functions. A better understanding of such networks might be helpful to explain some diseases and identify methods to treat them by controlling some elements in the network. However, in most cases, the high number of genes involved in the regulatory network and the nature of their interactions lead to an intractable complex system. This high complexity requires the use of simplified mathematical models.
Our present work consists on building, simplifying, studying and controlling negative feedback loop in genetic models. This kind of loop is one of the most simple, but also one of the most common motifs (also called building blocks) in complex regulatory networks, often leading to oscillatory behaviour. In a network of two genes, in which a first gene activates a second gene and the second gene inhibits the first gene, the concentration of each protein expressed by both genes oscillates before eventually converging towards a constant value. Our goal is to conceive a simple control law able to remove the oscillations and make the system converge faster towards the steady state. One efficient and easy way is to introduce an appropriate piece-wise constant control for the production rate of the first transcription factor. Naturally, this control has to be relevant for a possible biological implementation. Our results are extended to higher dimensional systems with more than two genes.

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11 - CHARAZAC Aurélie– Axis 1

Quantitative image based analysis of endocrine disruptor effects on mitochondria morphology-function in prostate cancer cells.

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Keywords : Endocrine disruptor, Prostate Cancer, Metabolism, Mitochondria, Screening

Persistent organic pollutants (POPs) are environmental contaminants that interfere with normal hormonal homeostasis and act as endocrine disrupting compounds (EDC). These molecules can mimic hormone effects on metabolism. The links between metabolism and cancer are now well established. Metabolism generates reactive oxygen species (ROS), which contribute to mutations and induces oncogenic transformation. In turn, cancer cells display high metabolic flexibility allowing them to grow in various cellular environments and favoring their proliferative and invasive capacities. Mitochondria are key players in this complex interplay since they produce ROS, generate energy and participate in nucleotide synthesis and in glutamine metabolism of cancer cells. Regarding the importance of hormones on prostate cancer risk and outcomes, we are developing a multiple parameters in vitro assay conducted in a high-throughput screening format relevant for prostate cancer metabolism and aggressiveness. This screening method includes a microscopy based analysis of mitochondria structure and functions as well as flow cytometry analysis. We analyzed the effects of five EDCs (Aldrin, BDE28, TCDD, PCB153, PFOA) identified in the plasma of patients on two prostate cancer cell lines, 22RV1 (androgen-responsive) and DU145 (androgen-unresponsive). Each compound was tested in a dose dependent manner to determine its effects on ROS production, mitochondrial membrane potential, mitochondrial biogenesis and mitophagy. In addition, we performed an image based computational analysis of the mitochondrial network morphology and dynamics. This strategy allows us to extract some quantitative parameters on the mitochondrial network as fragmentation index, compactness, average volume, etc. When combined, morphological and functional parameters allow us to discriminate subtle perturbations of the mitochondrial structure-function induced by EDCs in prostate cancer cells. We are confident that this multiparameter analysis strategy could represent a new perspective in identification and characterization of EDCs based on their effects on cell metabolism (phenoscore) in order to estimate their potential risk on human health.

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12 - DA SILVA Fabio– Axis 1

Retinoic acid signaling promotes cardiomyocyte survival in cardiac development and repair

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Keywords : Regeneration, Apoptosis, Retinoic acid, Cardio-protection, Cardiomyocytes

Ischaemic heart disease is one of the leading causes of death worldwide. Patient recovery after myocardial infarction is difficult since cardiomyocytes, the principle cardiac cell-type, have limited potential to proliferate and repair the damaged heart. Hence, preventative treatments aimed at minimizing ischaemic damage are of great importance in treating cardiovascular disease. Retinoic acid (RA) metabolites, the active derivatives of vitamin A, are essential for heart looping and ventricular compaction during embryonic development. Recent data has shown that RA signaling is reactivated in adult hearts after myocardial infarction. However, the precise cell types that respond to RA signaling in both development and after myocardial infarction have not been clearly defined. In order to define and follow these cells we have developed a novel Retinoic acid response element (RARE) reporter line utilizing CreER technology. With this line we have observed a striking and hitherto undescribed cardiomyocyte response during mid-late embryonic development. More importantly, we have detected a significant RA-response in hearts subjected to myocardial infarctions. In order to further understand the role of RA signaling in cardiac development and repair we have employed an inducible CAGCreER line to ubiquitously and temporally delete floxed alleles of the RA-producing enzymes Raldh1, 2 and 3. We have also employed the same technique in adult mice before subjecting them to myocardial infarction. Strikingly, deletion of the Raldh enzymes during mid-late gestation lead to an increase in cardiomyocyte apoptosis. Even more impressive, Raldh-null animals that underwent myocardial infarctions had significantly larger infarct areas and a drastic increase in cell death. RNA sequencing analysis of primary cardiomyocytes treated with RA revealed an upregulation in several anti-apoptotic genes. This data suggests that RA signaling promotes cardiomyocyte survival during embryonic development and after myocardial infarction.

13 - DE ALMEIDA ENGLER Janice– Axis 1

A cell biology view on the susceptible interaction between plants and obligate sedentary parasitic root-knot nematodes: the plant cytoskeleton and cell cycle

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Keywords : cytoskeleton, cell cycle, nematodes, galls, Arabidopsis

Sedentary endoparasitic root-knot nematodes (Meloidogyne spp.) are competent to modify plant root cells into specialized feeding structures causing vast damage to crop plants. Giant multinucleate feeding cells (GCs) undergo repetitive endocycling and acytokinetic nuclear divisions becoming oversized and filled with a dense cytoplasm essential to supply nutrients for the nematodes to develop into fertile females. The complex changes that occur during feeding cell morphogenesis involve the plant cytoskeleton and cell cycle. Studies of in vivo as well as fixed GCs have shown that the microtubule (MT) cytoskeleton and the actin-filaments (AF) are partially depolymerised in the cytoplasm. On the other hand, cortical MT and AF arrays are bundled along the thick GCs wall. Genes involved in these cytoskeleton rearrangements include major genes like α-, β- and γ-tubulins, γ-tubulin complex protein 3 actin-depolymerizing factors (ADF2) and fimbrins. Functional analysis and drug treatments have shown that stabilization of the cytoplasmic cytoskeleton blocks nematode development most likely perturbing nematode feeding. We have shown that activation of the cell cycle followed by a drastic rise in ploidy levels (>DNA synthesis) plays a key role in NFS development. The systematic temporal and spatial examination by in situ hybridization revealed the expression pattern of core cell cycle genes in galls of the model host Arabidopsis thaliana. Functional analyses of a selection of cell cycle genes are on course and resulted in the identification of a subset of genes strongly implicated in gall development (*e.g.* CDKs, Cyclins, CCS52s, DEL1, E2Fs, APCs and KRPs). A detailed analysis of the KRP gene family revealed that all the KRP gene members control gall development. Strikingly, KRP1-5 and KRP7 inhibited mitosis while KRP6 induced mitosis suggesting its possible role in giant-feeding cell multinucleation.
Our investigations illustrate that the plant cell cycle and cytoskeleton play major roles in gall and nematode-feeding cell development.

14 - DE GARAY Tomas– Axis 1

CD98hc (SLC3A2) presents a novel longer variant with an alternative promoter

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Keywords : CD98hc (SLC3A2), Alternative ATG, Protein interaction, Integrins, Transcriptional regulation

CD98hc, encoded by SLC3A2 gene, is a type II transmembrane protein implicated in cell proliferation and migration as well as extracellular matrix assembly. It is overexpressed in tumor cells. It regulates the expression at the membrane of the catalytic chain of a heteromeric amino acid transporter and simultaneously modulates integrin outside-in signaling, by direct interaction via its extra and intracellular domains respectively. The rise of high throughput sequencing studies allowed the identification of a longer CD98hc mRNA variant, including an extra exon at the 5' end, in the mouse genome, extending the protein at the C terminus intracellular part with 39 amino acids. This unexpected variant is not characterized yet and its function is unknown. Our work aims at exploring (1) the existence of CD98hc long variant at a protein level, (2) its possible differential functionality compared to the short variant and (3) its transcriptional regulation by an alternative promoter upstream of the short variant. We were able to detect this long variant at both mRNA and protein level in several mouse and human cell lines. Current work is focusing on identifying possible new protein interactions for this longer version. In parallel, we test the functionality of each variant separately using reconstituted knock out dermal fibroblasts, a model well established in the lab. We also evaluate the mRNA expression levels of both variants in multiple cell types and conditions; this information will be used to choose candidate transcription factors from a list obtained in an *in silico* analysis of both variant promoters to assess their differential transcriptional regulation. Altogether, this work will shed the light on CD98hc function and expression regulation in view of those two variants.

15 - DIDIER Robin– Axis 4

Targeting the proteasome-associated deubiquitinating enzyme USP14 induces melanoma cell death and overcomes resistance to MAPK-targeting therapies.

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Keywords : Melanoma, Ubiquitin Proteasome System, USP14, Deubiquitinases, Signaling

Advanced cutaneous melanoma is one of the most challenging cancers to treat because of its high plasticity, metastatic potential and resistance to treatment. New targeted therapies and immunotherapies have shown remarkable clinical efficacy. However, such treatments are limited to a subset of patients and relapses often occur, warranting validation of novel targeted therapies.
Post-translational modification of proteins by ubiquitin is a complex signaling system that coordinates essential cellular functions, including ubiquitin-proteasome system (UPS) function and protein homeostasis. Deubiquitinating enzymes (DUBs) have been associated to multiple diseases, including cancer. However, their exact involvement in melanoma development and therapeutic resistance remains poorly understood.
Using a DUB trap assay to label cellular active DUBs, we have observed an increased activity of USP14 (Ubiquitin-specific peptidase 14) in melanoma cells compared to melanocytes. USP14 is an essential regulator of the proteasome and one of the three proteasome-associated DUBs involved in the trimming of poly-ubiquitin chains from proteins addressed to the proteasome. Our survey of public gene expression databases indicates that high expression of USP14 correlates with melanoma progression and with a poorer survival rate in metastatic melanoma patients. Downregulation or pharmacological inhibition of USP14 dramatically impairs the viability of melanoma cells irrespective of the mutational status of BRAF, NRAS or TP53 and their transcriptional cell state, and overcomes resistance to MAPK-targeting therapies both in vitro and in human melanoma xenografted mice. At the molecular levels, we found that inhibition of USP14 rapidly triggers accumulation of poly-ubiquitinated proteins and chaperones, mitochondrial dysfunction, ER stress and a ROS production leading to a caspase-independent cell death. Our results provide a pre-clinical rationale for targeting the proteasome-associated DUB USP14 to treat and combat melanomas.

16 - EFTHYMIOU Georgios– Axis 4

Oncofetal fibronectin splice variants: functional analysis and generation of tunable fibroblast-derived extracellular matrices

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Keywords : extra-cellular, matrix, fibronectin, extra-domain, oncofetal

Cellular fibronectin (FN) isoforms differ from circulating plasma FN by the presence of highly conserved FN Type III Domains termed Extra Domain B (EDB) and Extra Domain A (EDA). Isoforms containing these domains, generated by alternative splicing of a single gene, display an extremely restricted distribution in normal adult tissues and high expression in fetal and tumor tissues. The presence of these “onco-fetal” domains, flanking the cell-binding RGD and synergy site in the molecule, have been suggested to confer specific properties to the protein that affect protein solubility, integrin binding and cell signaling. EDB and EDA-deficient mice are viable and fertile but the combined knockout of both leads to multiple cardiovascular defects and embryonic lethality. Whereas single Extra Domain-targeted deletion studies in the mouse have revealed roles for EDA in the morphogenesis of lymphatic valves, atherosclerosis and wound healing, no obvious in vivo phenotype was observed in EDB-null mice. To investigate how the presence of the alternative domains impact FN assembly and functions in the tumor stroma, we constructed lentiviral vectors harboring the full length coding sequence of human FN containing one, both or none of the alternatively-spliced Extra Domains. The alternatively-spliced variants were expressed in assembly-incompetent cells and purified from conditioned medium for use in functional assays. Variant-specific fibrillar matrices, for use as substrates for different cells of the tumor microenvironment, were produced by providing the recombinant variants to FN-deficient fibroblasts. Moreover, we generated FN knockout mouse embryo fibroblasts (MEFs) in which the human cFN variants have been re-expressed.
Our studies revealed variant-specific differences in fiber architecture, reflecting changes in TGF-b signaling and cytoskeletal remodeling. These results and findings from our studies on the impact of Extra Domains on FN-induced cell proliferation, motility, contractile behavior and underlying signaling events will be shown.

17 - FABRIS Gaia– Axis 4

Reduces liver development in progeny of rat dams having suffered from protein restriction: possible role of altered microrna biogenesis

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Keywords : cell signaling, miRNAs, amino acid restriction, liver, metabolic disorders

A general consensus exists in human and animal physiology that maternal nutrition impacts on the metabolic disease risk of the progeny. For the last years our laboratory has been focusing on the increased risk for diabetes in the progeny of rat dams having been exposed to amino acid restriction (aaR) and on the role that microRNAs (miRNAs) have in this particular context. It is known that such maternal deprivation during pregnancy leads to fetal metabolic reprogramming and favors the development of type 2 diabetes (T2D) in adulthood. MiRNAs are small molecules containing 20-22 nucleotides which act as post-transcriptional repressors by interfering with mRNA translation. Their biogenesis is governed by a complex machinery which includes Dicer, Drosha and Ago2. Although their mode of action is well described, the regulation of their expression is still elusive. Interestingly, we showed increased miRNA expression in the fetal pancreas of aaR rat progeny and we provided evidence that this altered expression could be involved in decreased β-cell proliferation and metabolic failure of the offspring. Recently, we observed a similar miRNA upregulation in the fetal liver of these descendants together with a reduction in hepatocyte proliferation. Remarkably, we found a similar increased miRNA expression in the fetal liver of other maternal malnutrition models. Our working hypothesis is that cells exposed to nutritional restriction increase miRNA expression to reduce their proliferation. Indeed, we discovered that amino acid (aa) absence directly upregulates miRNA expression in primary rat hepatocytes. Further, we observed an increase in Drosha and a decrease in mTOR phosphorylation. Remarkably, the restoration of the essential aa in the depleted culture medium normalizes mTOR phosphorylation, Drosha protein level and miRNA expression. We are currently investigating the relationship between miRNA biogenesis and hepatocyte proliferation. To sum up, our results suggest that a regulate miRNA biogenesis by controlling the Drosha protein level. Given the major role of the liver in organismal health, our observations could have important implications for the prevention of metabolic disease in the offspring having been exposed to maternal malnutrition.

18 - FAYAD Racha– Axis 1

Loss of EFA6-B, an EMT regulator, facilitates breast cancer development in vivo

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Keywords : EFA6B, Junctions, Breast cancer, Claudin-low, EMT

In breast cancer, 90% of death cases are due to aggressive metastatic tumors. The epithelial-mesenchymal transition (EMT) is believed to be a key process to mediate metastasis. One of the earliest events of EMT is the dissolution of the tight junction and the loss of cell polarity, two features essential to maintain epithelial functions. We observed that EFA6B, a guanine nucleotide exchange factor for the small G protein Arf6, helps assemble and stabilize tight junctions and is required to maintain epithelial apico-basal polarity and phenotypic characteristics in mammary cells (Zangari et al, Cancer Res, 2014). Next, using human breast cancer cell lines, we investigated the role of EFA6B (PSD4) in breast cancer initiation and progression. Organotypic 3D cell cultures, flow cytometry and in vitro functional assays highlighted the engagement into EMT and the acquisition of tumorigenic properties of cells downregulated for EFA6B. Orthotopic xenografts showed that MCF7 shEFA6B tumors grew twice as fast as their wild-type counterparts indicating that downregulation of EFA6B is causal to the increase of MCF7 cells tumorigenicity. In agreement, the analysis of EFA6B expression and histoclinical features of tumors from a cohort of 5252 breast cancer patients associated low levels of EFA6B with the aggressive triple-negative and claudin-low breast cancer subtypes. And in order to further develop our research, we recently established, using CRISPR/Cas9, knockouts of EFA6B in MCF10A, a normal human mammary epithelial cell line and in HMLE, a cell line representing the three epithelial cell population of a normal human mammary gland. This will allow elucidating the importance of the absence of EFA6B in driving breast cancer development.
Finally, transcriptomic analysis of the MCF7 shEFA6B cells revealed some differentially regulated proteins and enzymes of the extra-cellular matrix as well as cell-cell adhesion molecules that will help us to decipher the mechanism by which EFA6B acts.
Our results identified EFA6B as a novel antagonist in breast cancer and they point to its regulatory and signaling pathways as rational therapeutic targets in aggressive forms of this disease.

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19 - FELSKE Torsten– Axis 2

Direct reprogramming of cortical neurons

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Keywords : Reprogramming, Neocortex, Development, Lmo4, Fezf2

Terminally differentiated cells rarely change their identity and functional properties. In particular neurons of the mammalian central nervous system reveal a stable cell type. In the adult brain only a few niches produce neuronal cells while the majority of neuronal cells are generated during the embryonic and early postnatal stages and remain post-mitotic. Interestingly, the discovery of induced pluripotent stem cells (iPS) revealed the potential of finally differentiated cells to change their molecular identity and even bring them to become pluripotent stem cells by overexpressing a cocktail of distinct transcription factors. Yet, direct reprogramming follows a similar approach but in the difference that terminally differentiated cells can change their molecular identity, connection and function without passing a pluripotent state. Here, we demonstrate that post-mitotic upper layer neurons of the neocortex can change their identity and connectional behaviour by overexpressing Fezf2, an important regulator of lower layer neurons in the developing brain, together with Lmo4, a nuclear co-transcriptional regulator, at embryonic and postnatal stages. Our results reveal a remaining potential plasticity of neuronal cells of the neocortex after being terminally differentiated.

20 - FORMICOLA Nadia– Axis 1

CaMKII: a novel regulatory component of Imp neuronal RNA granules ?

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Keywords : Imp, RNP, CaMKII, Drosophila, CNS development

Ribonucleoprotein (RNP) granules are supramolecular structures composed of RNA and proteins, found in many cellular contexts, and known to be tightly regulated in space and time. In the cytoplasm, different kinds of RNP granules are known, including Processing Bodies, Stress Granules and diverse other ones found in germ cells and in the nervous system.
Neuronal granules were shown to contain translational repressors as well as components of the translational machinery, and to switch from packed to translationally active conformations in response to stimulation. During development, RNP granules have been demonstrated to transport peculiar mRNAs to growing axons, thus participating to nervous system maturation. To date, the identity of the factors controlling RNP dynamics remains largely unknown.
We study the regulation and function of cytoplasmic ribonucleoprotein particles (RNPs) characterized by the presence of the Imp protein during Drosophila CNS development. Drosophila Imp is a RNA binding protein homolog to the human IGF-II mRNA-binding protein (IMP) and its function is required for axonal remodeling during development. Furthermore, Imp accumulates together with target mRNAs in RNA granules that are dynamically transported to axons.
In order to find components of Imp RNP granules, we purified Imp complexes and identified 69 Imp interacting proteins by Mass Spectrometry. One potential interactor was particularly intriguing: the Calcium (Ca2+) and Calmodulin (CaM)-dependent serine/threonine kinase II (CaMKII). This conserved kinase has been involved in synaptic plasticity, learning and memory in Drosophila, and is known to respond to neuronal activity. To validate the CaMKII-Imp interaction, we have performed Co-IP experiments and showed that CaMKII and Imp associate in an RNA-independent manner. To study the impact of CaMKII activation/inactivation on the regulation of Imp RNPs, we have used a combination of transgenic lines encoding constitutively activated or inactivated forms. Our first results suggest that CaMKII may regulate both the dynamics and the assembly of Imp granules. As CaMKII is regulated by neuronal activity, we are currently testing if Imp granules are sensitive to changes in synaptic activity.
With this work, we hope to better understand the mechanisms underlying the spatio-temporal regulation of neuronal granules in response to physiological signals.

21 - GARCIA Elsa– Axis 3

Characterization of the anti-virulence immune response against bacterial toxins

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Keywords : bacterial toxins, CNF1, signaling, inflammation, IL-1b

How does the immune system distinguish between pathogenic and non pathogenic bacteria? The detection of the activities of pathogen-encoded virulence factors by the innate immune system has emerged as a new paradigm of pathogen recognition. Using Drosophila we previously demonstrated that the E. coli CNF1 toxin-induced activation of Rac2 is sufficient to initiate an evolutionarily defense signal conserved from flies to mammals that we called Anti-Virulence Immunity. We further addressed the importance of this innate immune mechanism during infection. We demonstrated the central role of the IL-1β signaling axis in controlling the Escherichia coli burden in the blood of mice in response to the sensing of the CNF1 toxin. Consistently, this innate immune response is abrogated in caspase-1/11-impaired mice. In vitro experiments further revealed the synergistic effects of CNF1 and LPS in promoting the maturation/secretion of IL-1β and establishing the roles of Rac2, ASC and caspase-1 in this pathway. Now, we want to find new partners of Anti-Virulence Immunity and determine their role in the maturation and/or secretion of IL-1β. Our recent data allowed us to identify the inflammasome activated by CNF1.

22 - GRAPA Anca-Ioana– Axis 5

Classification of the 2D FN variants using curvelets

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Keywords : extracellular matrix, fibronectin, feature extraction, curvelets, classification

We are interested in the numerical characterization of the extracellular matrix (ECM), and its role in the evolution of certain diseases. Fibronectin (FN) is a major component of the ECM, which is assembled in fibrilar networks that can display various conformations. Our goal is to develop numerical quantitative criteria for the analysis and modeling of the 2D FN textured images. These criteria could indicate a link between the fiber organization and the biological features. In order to explore the geometrical properties of the ECM, we investigated mathematical methods that can detect the FN filament features, and then we verified the validity of our methods by performing a classification among the different variants of FN upregulated in disease states. For a multiscale and multidirectional object representation, we used the curvelet transform, a technique that is well-adapted to detect curves and contours in an image. It performs a decomposition of the image into a series of curvelet coefficients at different scales, orientations and locations. Subsequently, we designed a method to ensure the invariance to rotation of the curvelets, by assuming the FN images have a certain dominant orientation. The results that we have obtained with a standard classifier indicate that the curvelets offer an appropriate discriminative model for the FN networks. This model can help us explore fiber characteristics and distinguish the different types of tissues. In a future work, we will derive a generative model for the simulation of the ECM and prediction of different behaviors.

This work was supported by the French Government (National Research Agency, ANR) through the « Investments for the Future » LABEX SIGNALIFE: program reference # ANR-11-LABX-0028-01

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23 - GREGOIRE Elodie– Axis 2

NRG1 signalling is involved in testis development in mice

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Keywords : Testis development, Nrg1, Sertoli cells, vascularization, hypoplasia

NRG1 is a signaling protein that plays a critical role in the neural system and heart development (Meyer and Birchmeier 1995; Newbern and Birchmeier 2010). Moreover conditional deletion of Nrg1 in post natal Sertoli cells leads to spermatogonial proliferation and meiotic initiation defects and consequently to testicular hypoplasia (Zhang et al. 2011). However, Nrg1 is expressed as early as 10 dpc in the genital ridges and in the interstitial cells of the embryonic testis from 12.5 dpc. This suggests that Nrg1 is also required for testicular development. To assess the contribution of Nrg1 in this process, we analyzed the consequences of Nrg1 conditional ablation in XY embryonic gonads in mice. Our results show that Nrg1 is involved in the establishment of the Sertoli cell stock and the partitioning of the embryonic testis cords. Altogether these data demonstrate that Nrg1 is involved in the formation of the testis and then in the maintenance of the fertility in adulthood.

24 - HALLIN Johan– Axis 5

Understanding the genetic basis for hybrid sterility

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Keywords : Hybrid sterility, genomic variation, meiosis, genetic incompatibilities, chromosome segregation

When a species' lineage divides into two, hybrid sterility is often the mechanism by which it does so. The sterility of a hybrid stems from it being unable to produce viable and fully functional gametes. This lack of functional gametes likely arises from incompatibilities between the parents and is enforced in the hybrid by faulting chromosome segregation or genetic incompatibilities between the parental genomes, but which mechanisms are at play and in what frequencies? How does divergence between parents influence hybrid sterility? Constructing hybrids using diverged *Saccharomyces cerevisiae* lineages allows us to investigate the contributions of parental genetic makeup to hybrid sterility, and sequencing a large number of their gametes allows us to elucidate the mechanisms behind their inviability. We used four parents representative of diverged lineages isolated from four continents and distinct ecological niches, and constructed all possible hybrid combinations. We constructed near perfect end-to-end genome assemblies for the four parents, i.e. we have full knowledge of the variation between them, both single nucleotide polymorphisms (SNPs) and structural variation. Not limited to look at SNP variation we are in a position to give an accurate description of how gamete viability in a hybrid is dependent on the genetic makeup of the parents. We are sequencing 2500 gametes from each of the six hybrids, resulting in a dataset of 15000 whole genome sequenced gametes. With the whole genome sequences, we can investigate the recombination landscape of the different hybrids, and we can see how recombination can influence hybrid sterility and how recombination is influenced by the genomic differences of the parents. By sequencing gametes from meiotic events where not all gametes are viable we will be able to infer the genetic composition of the inviable gametes and consequently be able to understand why it is inviable. Proper formation of gametes is important in any aspect of mating, whether it be in yeast or in humans. For example, chromosome segregation errors are the leading genetic cause of birth defects in humans. Our study can shed light on underlying reasons for these types of errors and answer fundamental questions in biology and genetics.

25 - HUBSTENBERGER Arnaud– Axis 5

P-bodies are integration centers for the coordination of mRNA expression

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Keywords : mRNA processing pathways, pathway compartmentalization and integration, supramolecular network, RNP granules and RNA regulons, RNP phase transitions

Within cells, compartmentalization into membrane-less organelles organizes the processing and signaling pathways that control the fate of mRNAs. Instead of free diffusing throughout the cytosol, soluble mRNPs can switch states to coassemble and condense into liquid or solid bodies. We previously showed how these phase transitions are tightly controlled during development and identified regulatory pathways (1,2). Although phase transitions have been reconstituted, for endogenous bodies the diversity of the components, the specificity of the interaction network, and the function of the co-assembly remain to be identified. Here, by developing a Fluorescent Activated Particle Sorting method to purify cytosolic P-bodies from human cells, we identified hundreds of proteins and thousands of mRNAs that structure a uniquely dense network of specific interactions, separating P-bodies from other RNPs. mRNAs segregating to P-bodies are translationally repressed but not decayed, which explains part of poor genome-wide correlation between mRNA and protein abundance. Condensation itself strengthens the repression of thousands of mRNAs, adding a layer of coordination. Last, P-body mRNAs strikingly encode regulatory processes. Thus, we uncovered how P-body condensation, by compartmentalizing and segregating repressed mRNAs, provides a physical substrate for the coordinated expression of mRNA regulons.

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26 - JAMECNA Denisa– Axis 1

Investigation into the function of the N-terminal region of OSBP

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Keywords : membrane, tethering, cholesterol, liposomes, Golgi

Oxysterol binding protein (OSBP) is a lipid transfer protein that regulates cholesterol distribution in cell membranes. OSBP consists of a pleckstrin homology (PH) domain, two central coiled-coils, a “two phenylalanines in acidic tract” (FFAT) motif and a C-terminal lipid binding OSBP-Related Domain (ORD). The PH domain recognizes PI4P and the small G protein Arf1-GTP at the Golgi membranes, whereas the FFAT motif interacts with the ER-resident protein Vap-A. By binding all these determinants simultaneously, OSBP creates membrane contact sites between ER and Golgi, allowing the counter-transport of cholesterol and PI4P by the ORD.
OSBP also contains an interesting N-terminal sequence, composed mostly of glycine, proline and alanine (GPA-rich region). The sequence is predicted to be unstructured, with zero net charge. The function of N-terminus in membrane tethering and lipid transfer activity of OSBP is unknown. To elucidate this issue, we compare the in vitro liposome tethering activity of two truncated OSBP constructs called “N-PH-FFAT” (N-terminus present) and “PH-FFAT” (N-terminus absent). We show that N-PH-FFAT is not capable to aggregate PI4P-containing liposomes, whereas PH-FFAT promotes aggregation. This is confirmed using confocal microscopy with fluorescent Golgi-like liposomes. In experiments with fluorescent giant unilamellar vesicles (GUVs), we observe an enrichment of PH-FFAT at membrane contact sites formed between PI4P-containing GUVs.
Our observations suggest that the N-terminus creates a steric hindrance around the PH domains that prevents tethering of two PI4P-containing membranes. In cells, the N-terminus could play a role in proper spacing OSBP on Golgi membranes, thus preventing abnormal membrane stacking.

27 - KAMINSKI Lisa– Axis 3

PGC-1a controls an onco-metabolic program to limit prostate cancer aggressiveness

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Keywords : Metabolism, Prostate cancer, Metastasis, Metabolic stress, c-myc

Prostate cancer (PCa) is the third cause of cancer death in men and deaths are due to advanced metastatic PCa. Metabolic reprograming has been shown to play a major role in cancer aggressiveness; however, the metabolic pathways implicated in the formation of metastasis are poorly understood. In this context, we chose to study peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a) which plays a major role in cell metabolism and more specifically the regulation of Oxidative Phosphorylation. PGC-1a is a master regulator of mitochondrial biogenesis and a recent paper suggests that low levels of PGC-1a may be associated with a poor prognosis in PCa. Then, we decided to study the role of PGC-1a on PCa aggressiveness and metabolism. We performed a knockdown (KD) of PGC-1a in prostate cancer cell lines using different shRNA or siRNA. PGC-1a KD enhanced PCa cell proliferation, migration and invasion of LNCaP and DU145 cells. Conversely, overexpression of PGC1-a decreased cell migration. To determine the molecular mechanism implicated in this phenotype, we analyzed the expression of several genes controlling oncogenesis and metabolism. We found that c-myc and some other genes implicated in glutaminolysis were up regulated in PGC-1a KD cells. We then performed proliferation and transwell migration assay using c-myc inhibitors. These inhibitors reversed the pro-proliferative and the pro-migratory effects induced by the downregulation of PGC-1a. To characterize the metabolic modifications modulated by PGC1-a, we performed a steady-state metabolomic analysis. We demonstrated that the polyamine pathway (arginine, putrescine, spermine) is significantly up-regulated in cells where PGC1-a is downregulated. In accordance, the ornithine decarboxylase (ODC), a rate limiting enzyme of this pathway controlled by c-myc, is up-regulated in PGC-1a KD cells. We then decided to inhibit ODC with DFMO (α-difluorométhylornithine) and performed migration assay. We showed that the pro-migratory effects of PGC-1a KD cells are blocked by DFMO. Finally, in accordance with the results presented here, we demonstrated that the expression of PGC-1a is significantly downregulated in PCa patients and logically, c-myc and ODC are up regulated. Altogether, our results demonstrate that the downregulation of PGC1a increased c-myc expression and up-regulated polyamine synthesis. These onco-metabolic modifications are directly implicated in PCa aggressiveness.

28 - KIM Chami– Axis 3

Deciphering Drosophila immune resistance to endoparasitoid wasps: mechanisms, specificity and evolution

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Keywords : Drosophila melanogaster, parasitoids, immunology, RNAi, hemocytes

Drosophila melanogaster is a model organism for many fields in biology including immunology.
Drosophila innate immunity is well described in case of bacterial and fungal infections but other parasites, such as parasitoids, can be harmful and even lethal to Drosophila.
We are working on the immune interaction between Drosophila larvae and the endoparasitic wasp, Leptopilina boulardi, a species that lay eggs inside Drosophila larvae. The parasitoid larval stages then develop at the expense of the host leading to its death. The adult parasitoid emerges from the Drosophila pupa.
Drosophila larvae recognizes the parasitoid egg as a foreign body and, depending on the fly strain, they can mount a successful immune response: the egg is surrounded by layers of hemocytes forming a melanized capsule, and it is a fly that will emerge. To counteract the immune response, female wasps rely on venom components injected together with the egg which prevent the encapsulation.
A major biallelic gene (alleles R and S) responsible for the resistance / susceptibility of Drosophila to L. boulardi has been identified. I am involved in deciphering the role of this gene in the resistance mechanism using different approaches including: Flow cytometry to track the variation in quantity / proportion of the different types of hemocytes following parasitism; Bioinformatics to identify potential interactants of this gene; Mutants and strains UAS-RNAi to understand the potential role of these genes in the anti-parasitic immune defence of Drosophila.

29 - LE ROLLE Morgane– Axis 2

WNT/Ctnnb1 signaling pathway controls germ cell development in mamals

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Keywords : Ctnnb1, Germ cells, signaling , sex determination, R-spondin1

Sex determination is an essential developmental process leading to the differentiation of the bipotential gonad into a testis (XY individuals) or into an ovary (individuals XX). Differentiation of germ cells into male gonocytes or female oocytes is a central event for sexual reproduction. Proliferation and differentiation of fetal germ cells depend on the differentiation of their somatic environment. In the female embryo, ovarian differentiation requires activation of the WNT/b-catenin signalling pathway in the somatic cells by the secreted protein RSPO1. Using mouse models, we now show that Rspo1 also activates the WNT/bcatenin signalling pathway within germ cells. In XX germ cells in which Ctnnb1 gene (encoding b-catenin) has been conditionally deleted, proliferation, differentiation and adhesion are all impaired. Moreover, using XX gonads in which Ctnnb1 has been deleted in somatic cells, we also show that the somatic cells are required for germ cells to differentiate and enter into meiosis. Our results demonstrate that b-catenin signalling is involved in germ cells to promote oogonial proliferation and differentiation.

This work is supported by the Ligue Contre le Cancer.

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30 - LEBEAUPIN Cynthia– Axis 4

Pharmacological inhibition of IRE1alpha RNase activity rescues BI-1-deficient mice fed a high fat diet from steatohepatitis development

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Keywords : Endoplasmic reticulum stress, Lipid accumulation, Inflammation, Cell death, Liver

The obesity epidemic is accompanied by a worldwide burden of nonalcoholic fatty liver disease. Endoplasmic reticulum (ER) stress responses are linked to metabolic dysfunctions and the activation of inflammatory and cell death mechanisms associated with the development of this chronic liver disease. Elucidating how ER stress escalates from an adaptive to a terminal cellular response is therefore necessary to propose therapeutic options for obesity-associated pathologies.
We hypothesized that the genetic ablation of Bax Inhibitor (BI)-1, an evolutionarily conserved and cytoprotective ER-membrane protein, would render the liver vulnerable to unresolved ER stress. Upon challenge with high-fat diet, BI-1-/- mice developed type-2 diabetes and steatohepatitis due to IRE1alpha-dependent NLRP3 inflammasome activation, hepatocyte death and fibrosis, on top of dysregulated lipid homeostasis. Specifically targeting IRE1alpha endoribonuclease (RNase) activity rescued BI-1-/- mice from developing the hallmarks of these diseases. Therefore, inhibiting IRE1alpha signaling directly with pharmacological agents or via BI-1 may represent a tangible option for the treatment of metabolic diseases, such as NAFLD or type-2 diabetes.

31 - LOTOTSKA Liudmyla– Axis 3

RNA-mediated role of TRF2 in pericentromere function

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Keywords : TRF2, pericentromeres, Sat3 RNA, telomeres, genome stability

Genome stability is dependent on the maintenance of telomere and (peri)centromere functions.
Telomeres are repetitive DNA structures that together with a shelterin complex protect ends of linear chromosomes from DNA damage response (DDR) activation. Mammalian shelterin complex is comprised of 6 proteins. Among them TRF2 (telomeric repeat-binding factor 2) is a key subunit known to protect telomeres against ATM-dependent DDR checkpoint and recombinational repair, as well as replicative DNA damage (van Steensel 1998, Celli 2006, Benarroch-Popivker 2016, Ye 2010, Saint-Leger 2014). Centromeres are required for a proper segregation of chromosomes during cell division.
Pericentromere are made of megabases of Satellite 2 and 3 repeats (Sat2 and Sat3) and form the largest part of constitutive heterochromatin.
We have recently shown that TRF2 is not solely associated with telomeric DNA, but can also be found outside telomeres: both at interstitial telomeric sequences (ITS) and at Sat3 repeats, which constitute the major part of the pericentromeric heterochromatin (Simonet 2011, Mendez-Bermudez submitted). However, nothing was known about how TRF2 is recruited to Sat3, what role it has there and whether there is a link between TRF2 and Sat3 RNA.
Here we demonstrate that recruitment of TRF2 to Sat3 repeats is increased upon different cellular stress conditions such as replicative and topological stress. We also show that TRF2 binding to pericentromeres is RNA-mediated and counteracted upon RNAseH1 down-regulation. In addition, the expression of the pericentromeric Sat3 RNA is positively controlled by TRF2.
Altogether, we suggest that the binding of Sat3 RNA to TRF2 increases its stability and decreases the formation of R-loops, providing a TRF2-dependent mechanism for pericentromeric Sat3 repeat stability. A non-exclusive hypothesis is that TRF2 increases the transcription rate of Sat3 DNA.
Therefore, the precise function of TRF2 in Sat3 RNA expression level and R-loop formation should shed light on how TRF2 couples telomere and pericentromere integrity.

32 - MATEGOT Raphaël– Axis 2

Investigating the functions of nuclear RNA interference

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Keywords : Nuclear miRNAs, Mammals, RNA interference, Gene silencing, Inflammation

The discovery of RNA interference (RNAi) has unravelled a fundamental principle for regulation of gene expression, as well as producing new tools for medicine. MicroRNAs (miRNAs) are 19-22 nt small RNAs that post-transcriptionnally suppress gene expression by a sequence-specific mechanism known as RNAi. Mature miRNAs are loaded into an Argonaute-2 protein (Ago2) in the cytoplasm to target messenger RNAs 3'UTR through as few as 7 nucleotides Watson-Crick base pairing, leading to translational repression and/or degradation of the target mRNA.
In mammals, miRNAs roles have been dogmatically confined to the cytoplasm because of initial observations that excluded RNAi components from the nucleus, leading to widespread scepticism on the existence of a nuclear RNAi pathway. However, emerging data sheds light on the occurrence of a nuclear RNA induced silencing complex.
Herein we show that endogenous RNAi components such as Ago2 and miRNAs also localize to the nucleoplasm of mammalian cells, and potentially contact chromatin. In the nucleoplasm, miRNAs act to destabilize mRNAs through a post-transcriptional mechanism potentiated by paraspeckles proteins such as SFPQ, an RNA-binding protein.
Through a combination of cellular fractionation and biochemical experiments, we found that nuclear miRNAs elicit direct degradation of imperfectly base-paired target RNAs, highlighting the activity of a nuclear RNA induced silencing complex.
Moreover, miRNAs nuclear localization is not restricted to cell lines but also occurs in primary cells. In fact, LPS-stimulated bone-marrow derived macrophages show nuclear localization of miR-155, a miRNA whose expression and function is related to activated immune cells, raising the question of the nuclear targetome of miRNAs in-vivo and in physiopathological context.
Taken as a whole, our work extend the scope of RNA interference to the nucleus, and anticipates novel mechanisms by which cells control nuclear gene expression.

33 - NAPOLITANO Tiziana– Axis 2

Deciphering the role of ft1 during pancreas morphogenesis and throughout adulthood

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Keywords : Exocrine pancreas, Type I Diabetes, Type II Diabetes, Cell plasticity, Ghrelin

Aiming to identify genes of importance for pancreatic beta-cell (neo-)genesis, we initiated several screens by combining in vitro and in vivo approaches. Here, we report the characterization of FT1, a transcription factor, whose role was investigated during pancreas morphogenesis and throughout adulthood. Gene expression analyses demonstrated that FT1 expression is initiated at the early stages of embryonic pancreas development and is maintained throughout the entire adult life. In order to gain further insight into the role and function of FT1, we generated a transgenic mouse line allowing its specific inactivation in the pancreas from the first phases of organ development. The resulting animals were found to be viable, fertile, and did not exhibit any premature death. Combining functional studies, immunohistochemistry, lineage tracing, and electron microscopy approaches, we accumulated evidences suggesting a functional role of FT1 in pancreatic cells fate specification and phenotype maintenance. Importantly, using models of type I and II diabetes, we demonstrate that the sole loss of FT1 induces a protection against chemically-induced type I diabetes, but also against high fat diet-induced type II diabetes. Together, these results suggest that FT1 could represent a very important target in the context of type I and II diabetes research.

34 - NOVELLI Caterina– Axis 2

Hedgehog secretion mechanisms in Drosophila epithelial tissues

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Keywords : Drosophila melanogaster , Hedgehog, Cytonemes , Interference of Ihog, epithelial tissues

In our laboratory, we are studying the Hedgehog (Hh) morphogen. In particular, I am interested in how this dually lipid modified molecule can travel in the extracellular environment. Currently, there are three main systems accounting for Hh transport: formation of Hh multimers, integration of Hh into lipoprotein particles (Lpp), and finally exovesicle mediated Hh secretion which requires the function of the ESCRT machinery. As an additional level of regulation, recently cytonemes, which are dynamic thin long cellular extensions rich in actin, were shown to be involved in the transport of Hh and its co-receptor interference of Hh (Ihog) within exovesicles. We investigate the role of Ihog, a transmembrane protein, in the stabilization of filopodia-like structures using two different models: the wing imaginal disc and the epithelial sheet in the pupal abdomen (called histoblast nests). Our goal is to explain the regulation of Hh released by Ihog/Boi proteins and cytonemes formation. This work will help us to understand the Hh secretion at molecular and cellular level. Moreover, it is going to clarify the Hh role in oncogenesis with further developed of novel therapies for Hh-cancer disease.

35 - PICCO Vincent– Axis 4

AKT1 activity restricts migration capacities of an oral carcinoma cell line harboring a constitutive active PI3 Kinase activity

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Keywords : Cellular morphology, Invasion, PI3K/AKT, Oral squamous cell carcinoma, Phenotypic screeening

The AKT/PKB protein kinase family comprises three members in mammals, namely AKT1, AKT2 and AKT3. These proteins are activated by the PI3-Kinase (PI3K), an oncogene involved in a wide variety of cancers. Constitutive activation of the PI3K/AKT pathway has been associated with tumorigenic properties such as uncontrolled cell proliferation and survival, angiogenesis, promotion of cellular motility, invasiveness and metastasis. However, AKT1 activity can also repress the invasive properties of breast cancer cells in specific contexts. We showed that this situation is not restricted to breast cancers and can be expanded to oral carcinomas that exhibit constitutive activation of the PI3K/AKT pathway. We performed confocal imaging, physical measurements of cell adhesion and invasion assays on CAL 33 oral carcinoma cells. In these non invasive cells, we showed that the abrogation of AKT1 functions induce an invasive phenotype in an otherwise non-invasive cell line. Our study strongly suggests that repression of invasion by AKT1 may be a general mechanism that has to be taken into consideration in current and future clinical trials involving AKT inhibitors.

36 - PUSHPALATHA Kavya Vinayan– Axis 3

Identification and characterisation of potential interacting partners in IMP granule assembly and function

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Keywords : RNP Granules, Axonal remodelling, IMP, CCT chaperonin, Lamin

The complexity exhibited by an organism at the level of organisation and behaviour requires strict spatial and temporal regulation of gene expression. One way of achieving such a rigorous control is by packaging the nascent transcripts into ribonucleoprotein (RNP) granules, which contain regulatory proteins and are dynamically regulated in vivo. In neuronal cells, RNP granules transport mRNAs to axons or dendrites, and control their local translation in response to external stimuli. Proper regulation of their dynamics and size is necessary for neuronal functions, as the formation of toxic RNP aggregates has been proposed to disrupt cell ribostasis, leading to neurodegenerative disorders. Thus, a proper understanding of the mechanisms underlying RNP assembly or clearance is essential, and may lead to the development of new therapeutic strategies.
In the lab, we have shown that Drosophila IMP, the fly ortholog of ZBP1, forms RNP granules in neurons. These granules are transported to axons and contain mRNAs coding for proteins involved in F-actin regulation, including profilin mRNA. Imp mutants show impaired regrowth of remodeling axons during metamorphosis. To find regulators of IMP granule assembly and function, we performed a mass-spec analysis of IMP complexes, and identified 69 potential interacting proteins. Among those are subunits of the CCT chaperonin complex, which may be involved in the assembly of Imp RNP complex components. Unexpectedly, we also identified components of the nuclear membrane which might reflect a role of these components in the maturation of IMP RNP complexes. To validate the interactions of these candidates with Imp, we are currently performing co-immunoprecipitation experiments with Flag-tagged constructs. We are also developing tools to inactivate these interacting partners, and test the impact of this inactivation on IMP granule size and dynamics, both *in vivo* and *in vitro*.

37 - ROGER Estelle– Axis 4

Microrna involvement in the control of brown adipose tissue activity in a model of predisposition to type 2 diabetes

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Keywords : malnutrition , diabetes, BAT, activity, microRNAs

In humans and animals maternal malnutrition predisposes the offspring to the development of metabolic disorders and diabetes. In the maternal low protein (LP) diet model, the hypoinsulinemic but normoglycemic rat progeny suffers from age-dependent deterioration of glucose homeostasis. We recently show that Brown Adipose Tissue (BAT) is a decisive physiological determinant of the onset of metabolic dysregulation, suggesting that unfavorable intrauterine environment could reprogram BAT physiology and metabolism. As microRNAs (miRNAs) are related to epigenetic mechanisms we hypothesize that they could control BAT adaptation in aging LP progeny.
To address this, we performed a miRNA profile in BAT of young normoglycemic and old hyperglycemic LP progenies. Amongst the 723 miRNAs screened, 58 are misexpressed in young normoglycemic LP progeny with hyperactive BAT. MiRNAs differentially expressed are mainly upregulated, and this is associated to an increased expression of miRNA biogenesis genes. Importantly, when BAT activity decreases and hyperglycemia appears with aging, the expression of misexpressed miRNAs drops to levels seen in control progeny. Concomitantly, the expression level of miRNA biogenesis genes of LP progeny returns to that of the control one. Next, we performed a miRNA profile in BAT of rats having been exposed to chronic treatment with an adrenergic β-3 receptor agonist (CL316, 243) to activate BAT. We also found that misexpressed miRNAs were upregulated with augmented expression of miRNA biogenesis genes. While both CL and LP rats show hyperactive BAT only three miRNAs are commonly dysregulated. Hence, upregulation of miRNA expression appears to be correlated to hyperactive BAT, but not specifically to the adrenergic pathway in LP rats. Using bioinformatic analysis focused on metabolism, we selected 10 miRNA candidates for ongoing investigation in vitro and in vivo. To sum up, we provide preliminary evidence to suggest that microRNAs participate to the compensatory response of BAT to maintain normoglycemia in young hypoinsulinemic LP progeny. We expect that, identification of miRNAs tuning BAT activity will offer novel opportunities for diabetes prevention and/or treatment.

38 - ROVERA Christopher– Axis 4

Melanoma educates fibroblasts of the distant lymph node pre-metastatic niche

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Keywords : metastasis, melanoma, lymph node, fibroblast reticular cell, extracellular matrix

The behaviour of cancer cells is largely influenced by their microenvironment, including stromal cells and extracellular matrix (ECM). Fibroblasts Associated with Cancers (called CAF) play a key role in tumorigenesis and metastasis. They secrete pro-tumorigenic growth factors and remodel the extracellular matrix (ECM). CAF are constitutively activated by factors secreted by tumor cells. Our team is particularly interested in the crosstalk between cancer cells and their microenvironment in melanoma, an aggressive form of skin cancer characterized by its high metastatic competence. The Lymph Node (LN) is the first tissue targeted by metastatic melanoma and is composed of very specific resident fibroblasts called Fibroblastic Reticular Cells (FRC). FRC regulate the LN architecture, as well as the recruitment and survival of immune cells, but little is known about their role in a metastatic context. Tumors are known to educate the microenvironment of their future metastatic niche before their arrival, through secreted factors. Our goal is to understand the implication of FRC in the invasion, proliferation, survival and immune escape of melanoma in the LN metastatic niche. We analyse (A) the effect of factors secreted by melanoma cells on FRC and the ECM they produce and (B) the role of these modifications on their interactions with immune and tumor cells. Our research is conducted in vitro on human primary FRC and melanoma cell lines. We observed that factors secreted by melanoma cells affect the proliferation and the actomyosin contractile phenotype of FRC, and modify the thickness, assembly and composition of the ECM. Furthermore, the secretome of melanoma-educated FRC attracts more immune cells than naïve FRC. Our results show that factors secreted by melanoma cells strongly modify FRC leading to modulation of their interactions with immune cells. Our aim is now to identify candidates involved in FRC education in the LN pre-metastatic niche. Our work will bring a more comprehensive view of tumor-stroma communication and a better understanding of both the melanoma biology and the LN tumoral niche. Our findings might have potential clinical implications for identification of novel biomarkers, potential targets and management of melanoma.

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KLF10 establishes the landscape of diurnal expression in the liver

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Keywords : Circadian Clock, Liver Metabolism, RNA-seq

The mammalian circadian timing system (CTS) rhythmically controls most aspects of physiology and behaviour over the 24-hour day. An increasing body of evidence suggests that energy metabolism and the CTS are intimately linked. Accordingly disruption or misalignment of the CTS leads to obesity and diabetes in mice and is associated with alteration of metabolic parameters in humans. Reciprocally a high fat diet impairs circadian coordination. We have previously shown using a systemic knockout mouse model that the transcription factor Krüppel-like Factor 10 (KLF10) is a link between the circadian clock and energy metabolism in liver. To address the specific role of hepatic KLF10, we have generated a hepatocyte specific knockout mouse model. The molecular clock is intact in these mice. To gain insights into the role of KLF10 in the circadian coordination of the hepatic physiology, we have profiled liver mRNA expression in hepatocyte specific KLF10 knockout *vs* control animals around the clock using RNA-seq. Following the identification of rhythmically expressed transcripts and phase set enrichment analysis, we found that while control mice display a cluster of oscillatory metabolic genes peaking during the active phase, deletion of KLF10 in hepatocytes leads to a marked disorganization of this pattern. This data supports the notion that KLF10 is important for the circadian timing of liver metabolism.

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40 - SABOURAULT Cecile– Axis 2

Plasticity and regulation of a cnidarian-Symbiodinium endosymbiosis

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Keywords : endosymbiosis, cell proliferation, proteomics, autophagy, exocytosis

Cnidarian-Symbiodinium endosymbioses have a key role in marine biodiversity as they form both the trophic and structural foundation of coral reef ecosystems. Symbiodinium cells are hosted in the gastrodermal tissue, in a phagosome-derived vacuole that mature in a symbiosome. The maintenance of this mutualistic association is the result of complex molecular and cellular interactions between the two partners. This includes mechanisms of recognition and phagocytosis, induction of host-cell immunity and symbiont tolerance, metabolic exchange, regulation of symbiont cell growth and proliferation. Mechanisms that regulate symbiont biomass and active transfer of photosynthetates to the host are thus crucial to maintain symbiosis homeostasis.
We report here the characterization of cellular and molecular pathways potentially involved in the maintenance of symbiosis in the sea anemone Anemonia viridis by a multidisciplinary approach, including flow cytometry, transmission electron microscopy, confocal imaging, and shotgun proteomics. We first showed that several cellular mechanisms, including autophagy and exocytosis, are involved in regulation of intracellular symbiont proliferation. Cell cycle progression of intracellular Symbiodinium cells was greatly controlled and lengthened in the G1 phase as compared to the cultured free-living Symbiodinium cells. Furthermore, we demonstrated that cell wall composition of intracellular symbionts is correlated with cell cycle progression. More interestingly, cell wall composition was also correlated with the expression of proteins involved in metabolic exchange, suggesting a modulation of the proteome expressed at the symbiosome interface, depending on symbiont life stage. By shotgun proteomics, we were able to identified 202 host proteins expressed at the symbiosome interface, including proteins involved in cell adhesion and recognition, cytoskeletal remodeling, metabolic exchange and stress response. Some of these proteins are human's orthologous proteins involved in cell growth, migration and invasion processes in tumor progression. Comparison of carcinogenesis process and regulation of intracellular Symbiodinium cells proliferation could then provide new insights about the biological role of the symbiosome membrane proteins and potentially pinpoint new actors in tumor proliferation.

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41 - SCHOROVA Lenka– Axis 5

Regulation of the SUMOylation balance at the neuronal synapse

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Keywords : sumoylation, desumoylation, synapse, live-cell imaging, FRAP

An average mature synapse consists of thousands of proteins, which mediate proper synaptic function via the activity-dependent regulation of their interactions. Such regulatory processes occur both in a time- and space-dependent manner usually by post-translational modifications including sumoylation. Sumoylation is a three-step enzymatic pathway, by which the small ubiquitin-like modifiers (SUMO1, SUMO2 and SUMO3, ~11kDa) are reversibly conjugated to target proteins. In physiological conditions, a dynamic equilibrium between a sumoylated and non-sumoylated state of a protein must be constantly maintained as disruption to the sumoylation/desumoylation balance in neurons is clearly associated with major brain diseases such as Parkinson's, Huntington's and Alzheimers' (reviewed in Schorova & Martin, 2016, Front in Synaptic Neurosci.). Thus, it is crucial to understand how the sumoylation pathway is regulated in neurons and at synapses prior to envisaging potential therapeutic strategies.
Our laboratory has recently reported that the activity of the sole SUMO-conjugating enzyme Ubc9 is regulated via the activation of the mGlu5 receptor/PLC/PKC signaling cascade, which induces synaptic anchoring of Ubc9 to newly phosphorylated proteins at synapses leading to an increase in synaptic sumoylation levels and ultimately to the modulation of synaptic transmission (Loriol et al., 2014, Nature Commun.). However, nothing is known about the regulation of the desumoylation pathway at synapses.
Here, to further assess the regulation of the sumoylation/desumoylation balance at synapses we have used live-cell imaging approaches to unravel the synaptic regulation of the SUMO-deconjugating enzyme SENP1. We demonstrated that changes in synaptic activity alter SENP1 dynamics at excitatory synapses and provided strong evidence that there exists a differential regulation to the SUMO-conjugating and deconjugating pathways both at the signaling and time scale levels. This work therefore represents an important step towards the elucidation of the physiological consequences of the sumoylation/desumoylation balance in neurons.

42 - TANG Furong– Axis 2

Rspo1 in female sex determination

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Keywords : Rspo1, Wnt/beta-catenin signaling, ovarian development, gonadal somatic cells, sex reversal

R-spondin1-4 genes encode secreted proteins that can activate the canonical Wnt/beta-catenin signaling pathway. Mutations in Rspo1 or Wnt4 lead to female to male sex reversal of XX individuals, both in humans and mice. Rspo1 mediated activation of the canonical Wnt/beta-catenin signaling is required both for ovarian development and to repress the testicular male differentiation pathway.
However, the precise timing of this requirement during gonad development is not well defined. We have produced a new Floxed Rspo1 allele (Rspo1F) in order to conditionally delete Rspo1 specifically in the XX gonadal somatic cells at different times. To validate this new mouse model, we have first generated a total constitutive knockout, Rspo1 deleted (RSPO1D), starting from the Rspo1F mice. As expected from a RSPO1 loss of function, XX Rspo1D/D gonads show masculinized phenotypes around birth. Namely, total deletion of Rspo1 releases the female pre-granulosa cells from mitotic arrest and leads to their precocious differentiation into granulosa cells prior to their trans-differentiation towards the male Sertoli cell fate. In addition, only a few germ cells survived in the posterior gonad of XX Rspo1D/D animals. In order to delete Rspo1 specifically in the somatic cells of the gonad around the time of sex determination we have used the Sf1-Cretg transgenic mouse line. Conditional Rspo1 knockout XX mutants (Rspo1cKO: Rspo1F/F, Sf1-Cretg/+) do not show female to male sex reversal phenotypes at birth. Analysis of Rspo1cKO mutants at different stages is ongoing to confirm this observation. Our preliminary results indicate that RSPO1 might functionally effect on female sex determination at early stages of gonad development before the activation of the Sf1-Cre transgene, or in gonadal cells not targeted by this transgene such as the germ cells and some epithelial cells.

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43 - VIJAYAKUMAR Jeshlee– Axis 3

Role of the Prion-like domain of dImp in RNP granule regulation

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RNA Binding proteins (RBP) are key post transcriptional regulators, playing a pivotal role in the life cycle of mRNAs by regulating their stability, subcellular trafficking and translation. This regulation is often mediated through formation of RNA-Protein (RNP) granules which concentrate mRNAs and RBPs together with regulatory factors. In neuronal cells, transport RNP granules are implicated in the transport of specific mRNAs to axons or dendrites, and in their local translation in response to external cues. To date, little is known about the assembly and regulation of these granules in vivo. However, growing evidence indicates that the presence of Prion Like domains (PLD) within RNA-binding proteins favors multivalent protein – protein and protein-RNA interaction and promotes the transition of soluble protein, RNA complexes into RNP granules.
Our group has recently uncovered the conserved RBP Imp as a core component of RNP particles that are actively transported to axons upon neuronal remodelling in Drosophila (Medioni et al., 2014).
Furthermore, Imp function is required for axonal remodelling during Drosophila nervous system maturation. Here, we have explored the function of a PLD located at the C-terminus of Imp. We observed that in the absence of the PLD, the number and size of Imp granules increased in cultured cells. Proteins with scrambled PLD amino acid sequence accumulated in granules of size and number similar to those of wild-type proteins, implying that the degree of disorder of this domain, and not the sequence, is essential for granule homeostasis. Using fluorescence recovery after photobleaching (FRAP), we further showed that Imp PLD is important for maintaining the dynamics of these granules.
In vivo, this domain is essential, since mutant forms lacking the PLD are not transported efficiently to axons and do not rescue the axon remodelling defects observed upon imp loss of function. Interestingly, we found that a variant of Imp with the PLD at the N-terminus, accumulates into large granules, yet is efficiently transported to axons in vivo and supports axon growth and branching, revealing that the functions of Imp PLD in granule homeostasis and transport are uncoupled. Together, our results show that the PLD of Imp is not required for the assembly of RNP granules, but rather to restrict granule size and number. Furthermore, Imp PLD has essential functions in axonal transport and remodelling during nervous system maturation.

44 - WAKADE Rohan Sanjay– Axis 1

The Rab GTPase Ypt6 is critical for Candida albicans invasive growth and virulence

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Candida albicans dimorphic switch requires cytoskeleton reorganization and sustained membrane trafficking. Rab (Ras related in Brain) GTPases play a central role in membrane trafficking, yet little is known regarding their function and regulation during hyphal growth and virulence. In C. albicans, Sec4 and its activator Sec2 localize at the Spitzenkörper (1, 2) and Cdc28/Hgc1-dependent Sec2 phosphorylation is critical for hyphal growth (2). Golgi polarization during hyphal growth is also regulated via the Rab GAP (GTPase Activating Protein) Gyp1 (3). Here, we focused on Ypt6 and Ypt31, the human Rab6 and Rab11 homologs, respectively. Our results indicate that these two proteins are critical for cell wall integrity, yet only Ypt31 is critical for antifungal sensitivity. Furthermore, both Ypt31 and Ypt6 are required for invasive hyphal growth. During hyphal growth, we show that Ypt6 localizes to the Golgi while Ypt31 localizes predominantly to the Spitzenkörper. With respect to the ypt6 deletion mutant, we also show that it produces shorter hyphae and is reduced for virulence in two murine candidiasis models. Further characterization of this ypt6 mutant shows that this defect in hyphal growth maintenance is associated with an alteration of the endocytic site distribution, upon filament extension. We are currently investigating the molecular mechanism underlying this defect and Ypt6 regulators and/or effectors during hyphal growth.

(1) Jones & Sudbery, 2010, Euk. Cell, 9, 1455.
(2) Bishop et al., 2010, EMBO J., 29, 2930.
(3) Huang et al., 2013, Euk. Cell, 12, 998.

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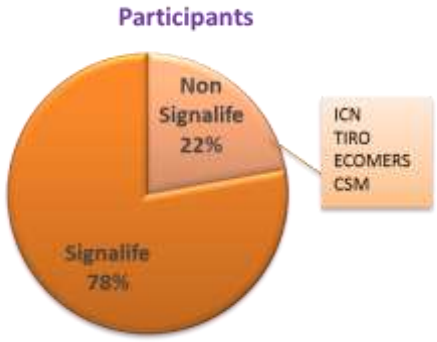
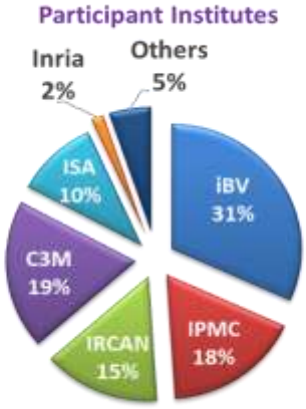
126	MATEGOT	Raphaël	C3M - Centre Méditerranéen de Médecine Moléculaire	Labex PhD Student	Raphael.MATEGOT@unice.fr	06 82 69 90 98	Yes		Poster	2
127	MENSCH	Maria	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	mensch@ipmc.cnrs.fr	176 59 68 49 06	Yes			
128	MEYER	Mickael	IRCAN - Institute for Research on Cancer and Aging, Nice	PhD student	meyermickael06@gmail.com	06 69 14 31 31	No			
129	MILORO	Giorgia	iBV - Institut de Biologie Valrose	Labex PhD Student	giorgia.miloro@unice.fr	06 67 77 95 74	Yes			
130	MOLINA JIMENEZ	Maria Dolores	iBV - Institut de Biologie Valrose	Post-doc	dmolina@unice.fr	07 77 94 60 52	No			
131	MULLER	margot	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	margot.muller@unice.fr	06 25 24 88 98	Yes			
132	MUNRO	Patrick	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	munro@unice.fr	04 89 06 42 63	Yes			
133	MUS-VETEAU	Isabelle	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	mus-veteau@ipmc.cnrs.fr	04 93 95 77 51 / 06	Yes	MEETING Program Committee		
134	NAHON	Jean-Louis	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	nahonjl@ipmc.cnrs.fr	06 35 28 32 92	Yes			
135	NAPOLITANO	Tiziana	iBV - Institut de Biologie Valrose	Labex PhD Student	tiziana.napolitano@unice.fr	07 81 73 48 33	Yes		Poster	2
136	NEDONCELLE	Karine	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	karine.nedoncelle@hotmail.fr	04 93 37 77 39	No			
137	NOVELLI	Caterina	iBV - Institut de Biologie Valrose	Labex PhD Student	cnovelli@unice.fr	06 20 59 12 36	Yes		Poster	2
138	PANABIERES	Franck	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	franck.panabieres@inra.fr	04 92 38 65 18	Yes			
139	PANDHARIKAR	Gaurav	ISA - Institut Sophia Agrobiotech	Labex PhD Student	gaurav.pandharikar@inra.fr	04 92 38 65 64	Yes			
140	PARASCHIVESCU	Cristina	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	paraschivescu@ipmc.cnrs.fr	06 50 94 03 76	Yes			
141	PARE	Martin	iBV - Institut de Biologie Valrose	Labex PhD Student	Martin.PARE@unice.fr	07 70 49 39 06	Yes			
142	PENDE	Mario	Institut Necker Enfants Malades, Paris, FR	Researcher / Lecturer	mario.pende@inserm.fr	06 32 83 18 39	No	Invited Keynote	Talk	4
143	PERALDI	Pascal	iBV - Institut de Biologie Valrose	Researcher / Lecturer	peraldi@unice.fr	04 93 37 77 04	Yes			
144	PEREA-GOMEZ	Aitana	iBV - Institut de Biologie Valrose	Researcher / Lecturer	apereagomez@unice.fr	04 92 07 64 18	Yes		Talk	2

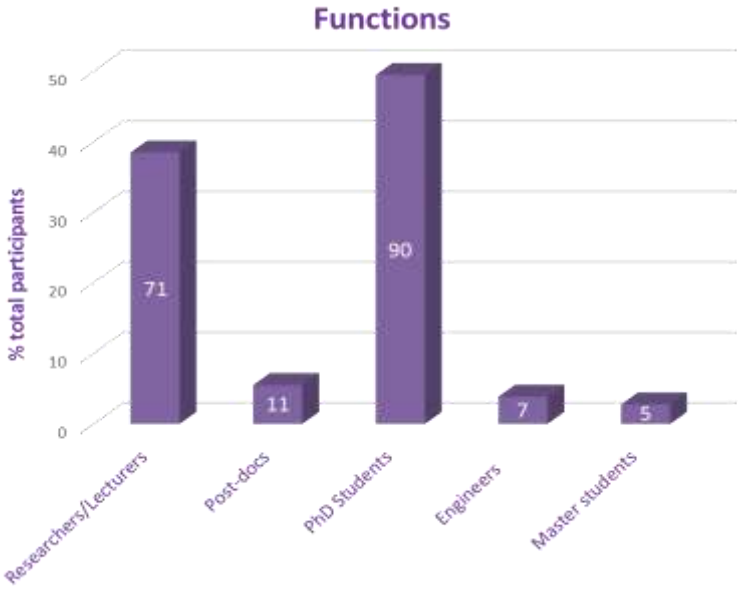
No.	Last Name	First Name	Research Institute or Laboratory	Function	Email	Phone	SIGNALIFE member	Special participant	Presentation	Axis
145	PERESSINI	Paula	IRCAN - Institute for Research on Cancer and Aging, Nice	Labex PhD Student	paula.peressini@unice.fr	06 69 01 38 63	Yes			
146	PHILIPPE	Claude	IRCAN - Institute for Research on Cancer and Aging, Nice	Engineer	claude.philippe@unice.fr	06 59 06 28 37	Yes			
147	PICCO	Vincent	CSM - Centre Scientifique de Monaco	Researcher / Lecturer	vpicco@centrescientifique.mc	377 97 77 44 15	No		Poster	4
148	PLOUVIER	Wouter	ISA - Institut Sophia Agrobiotech	PhD student	wouter.plouvier@inra.fr	07 89 41 83 68	No			
149	POIRIE	Marylene	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	poirie@unice.fr	04 92 38 64 09	Yes			
150	PRIETO	Marta	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	prieto@ipmc.cnrs.fr	06 14 39 58 86	Yes			
151	PROD'HOMME	Virginie	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	prodhomme@unice.fr	04 89 06 43 13	Yes			
152	PUSHPALATHA	Kavya Vinayan	iBV - Institut de Biologie Valrose	Labex PhD Student	kpushpalatha@unice.fr	07 82 65 78 90	Yes		Poster	3
153	RALLIS	Andrew	iBV - Institut de Biologie Valrose	Post-doc	arallis@unice.fr	06 25 30 12 88	No			
154	RAUZI	Matteo	iBV - Institut de Biologie Valrose	Researcher / Lecturer	matteo.rauzi@unice.fr	04 92 07 63 52	No			
155	RICHARDSON	Nainoa	iBV - Institut de Biologie Valrose	Labex PhD Student	nrichardson@unice.fr	07 68 49 68 39	Yes			
156	RISSO	Christine	ECOMERS - Ecosystèmes Côtiers Marins Et Réponses aux Stress	Researcher / Lecturer	Christine.RISSO@unice.fr	06 12 77 13 39	Yes			
157	ROBICHON	Alain	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	alain.robichon@inra.fr	04 92 38 64 19	Yes			
158	ROCHET	Nathalie	iBV - Institut de Biologie Valrose	Researcher / Lecturer	rochet@unice.fr	06 74 53 10 03	No			
159	ROGER	Estelle	IRCAN - Institute for Research on Cancer and Aging, Nice	PhD Student	estelle.n.roger@gmail.com	06 85 37 72 46	Yes		Poster	4
160	ROSSIN	Aurélie	iBV - Institut de Biologie Valrose	Researcher / Lecturer	rossin@unice.fr	04 92 07 64 49	No			
161	ROTTINGER	Eric	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	eric.rottinger@unice.fr	04 93 37 77 91	No			
162	ROUX	Jeremie	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	jeremie.roux@unice.fr	04 92 03 12 45	Yes			
163	ROVERA	Christopher	C3M - Centre Méditerranéen de Médecine Moléculaire	PhD Student	christopher.rovera@gmail.com	06 80 82 39 89	Yes		Poster	4
164	RUBERTO	Anthony	iBV - Institut de Biologie Valrose	Labex PhD Student	anthony.RUBERTO@unice.fr	06 58 40 33 69	Yes		Poster	4
165	RUIZ GARCIA	Sandra	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	ruiz-garcia@ipmc.cnrs.fr	04 93 95 77 59	Yes		Talk	5
166	SABOURAULT	Cecile	iBV - Institut de Biologie Valrose	Researcher / Lecturer	Cecile.Sabourault@unice.fr	06 98 78 30 84	No		Poster	2
167	SALLERON	Lisa	TIRO - Transporteurs, Imagerie et Radiothérapie en Oncologie	Post-doc	lisa.salleron@unice.fr	04 933 770 10	Yes			
168	SARASWATHY	Vishnu	iBV - Institut de Biologie Valrose	Labex PhD Student	vishnums007@gmail.com	07 55 80 33 26	Yes		Talk	1
169	SAUCET	Simon	ISA - Institut Sophia Agrobiotech	Post-doc	simonsaucet@free.fr	05 46 44 35 84	Yes			
170	SCHOROVA	Lenka	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	schorova@ipmc.cnrs.fr	06 22 93 19 85	Yes		Poster	5
171	SILVANO	Serena	iBV - Institut de Biologie Valrose	Labex PhD Student	ssilvano@unice.fr	06 63 22 04 08	Yes			
172	SIMON	Marie-Pierre	iBV - Institut de Biologie Valrose	Researcher / Lecturer	simonmp@unice.fr	06 18 15 71 93	No			
173	STUDER	Michèle	iBV - Institut de Biologie Valrose	Researcher / Lecturer	michele.studer@unice.fr	04 92 07 64 19	Yes			
174	TANG	Furong	iBV - Institut de Biologie Valrose	PhD Student	Furong.TANG@unice.fr	06 70 32 50 88	No		Poster	2
175	TANTI	Jean-François	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	tanti@unice.fr	04 89 06 42 37	Yes	Chair Labex Scientific Council		
176	TEBOUL	Michèle	iBV - Institut de Biologie Valrose	Researcher / Lecturer	teboulm@unice.fr	04 92 07 68 38	Yes			
177	TESTI	Serena	ISA - Institut Sophia Agrobiotech	Labex PhD Student	stesti@unice.fr	04 92 38 65 88	Yes		Talk	3
178	THEROND	Pascal	iBV - Institut de Biologie Valrose	Researcher / Lecturer	therond@unice.fr	04 92 07 64 46	Yes	Chair Labex Scientific Council		
179	TIBERTI	Marion	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	PhD student	tiberti@ipmc.cnrs.fr	06 31 83 23 68	No			
180	TSAI	Meng-Chen	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	tsai@ipmc.cnrs.fr	06 60 98 73 20	Yes			
181	VAN OBBERGHEN	Emmanuel	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	vanobbeg@unice.fr	04 93 37 77 85	Yes			
182	VAN OBBERGHEN-SCHILLING	Ellen	iBV - Institut de Biologie Valrose	Researcher / Lecturer	vanobber@unice.fr	06 75 08 17 46	Yes			
183	VAZQUEZ-ROJAS	Monserrat	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	PhD student	vazquez@ipmc.cnrs.fr	07 77 04 03 21	No			
184	VERGONI	Bastien	C3M - Centre Méditerranéen de Médecine Moléculaire	PhD student	bastien.vergoni@unice.fr	06 58 14 39 44	Yes			
185	VIAUD	Manon	C3M - Centre Méditerranéen de Médecine Moléculaire	PhD student	manon.viaud@unice.fr	04 89 06 42 35	No			
186	VIEIRA	Andhira	iBV - Institut de Biologie Valrose	Post-doc	avieira@unice.fr	06 23 47 17 02	Yes			
187	VIJAYAKUMAR	Jeshlee	iBV - Institut de Biologie Valrose	PhD Student	jvijayakumar@unice.fr	06 01 73 32 52	Yes		Poster	3
188	WAKADE	Rohan Sanjay	iBV - Institut de Biologie Valrose	Labex PhD Student	rwakade@unice.fr	06 52 73 89 03	Yes		Poster	1
189	WEBER	Vivien	IRCAN - Institute for Research on Cancer and Aging, Nice	PhD student	vivien.weber@unice.fr	06 11 53 72 83	Yes			
190	YAO	Xi	iBV - Institut de Biologie Valrose	PhD student	yaoxi65@126.com	07 87 14 35 53	No			
191	YAZBECK	Nathalie	IRCAN - Institute for Research on Cancer and Aging, Nice	Labex PhD Student	nyazbeck@unice.fr	04 92 03 12 43	Yes			
192	ZAGHRINI	Kristel	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	zaghrini@ipmc.cnrs.fr	06 30 91 45 55	Yes			
193	ZARAGOSI	Laure-Emmanuelle	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	zaragosi@ipmc.cnrs.fr	06 19 39 03 14	Yes	MEETING Program Committee		
194	ZERHOUNI	Marwa	C3M - Centre Méditerranéen de Médecine Moléculaire	Labex PhD Student	mzerhouni@unice.fr	06 76 29 49 17	Yes			

MEETING STATISTICS

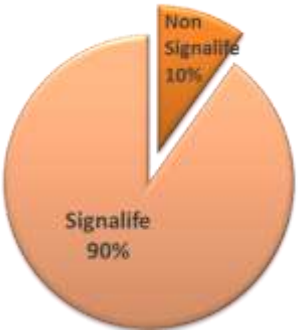
194 PARTICIPANTS
20 talks:
5 Invited
5 SIGNALIFE
10 PhD/Post-Docs/Researchers
44 Posters

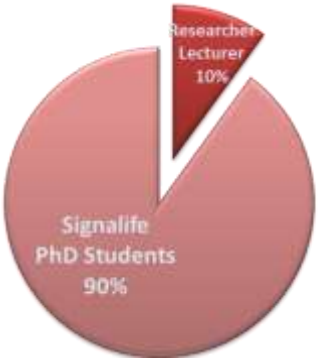




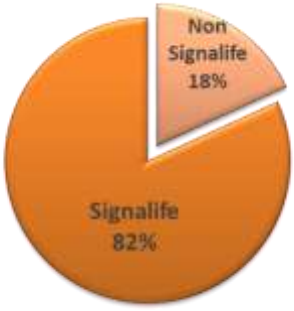


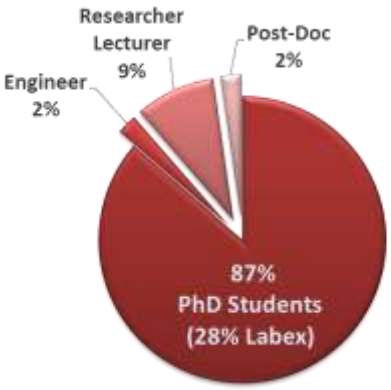
10 Talks





44 Posters





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