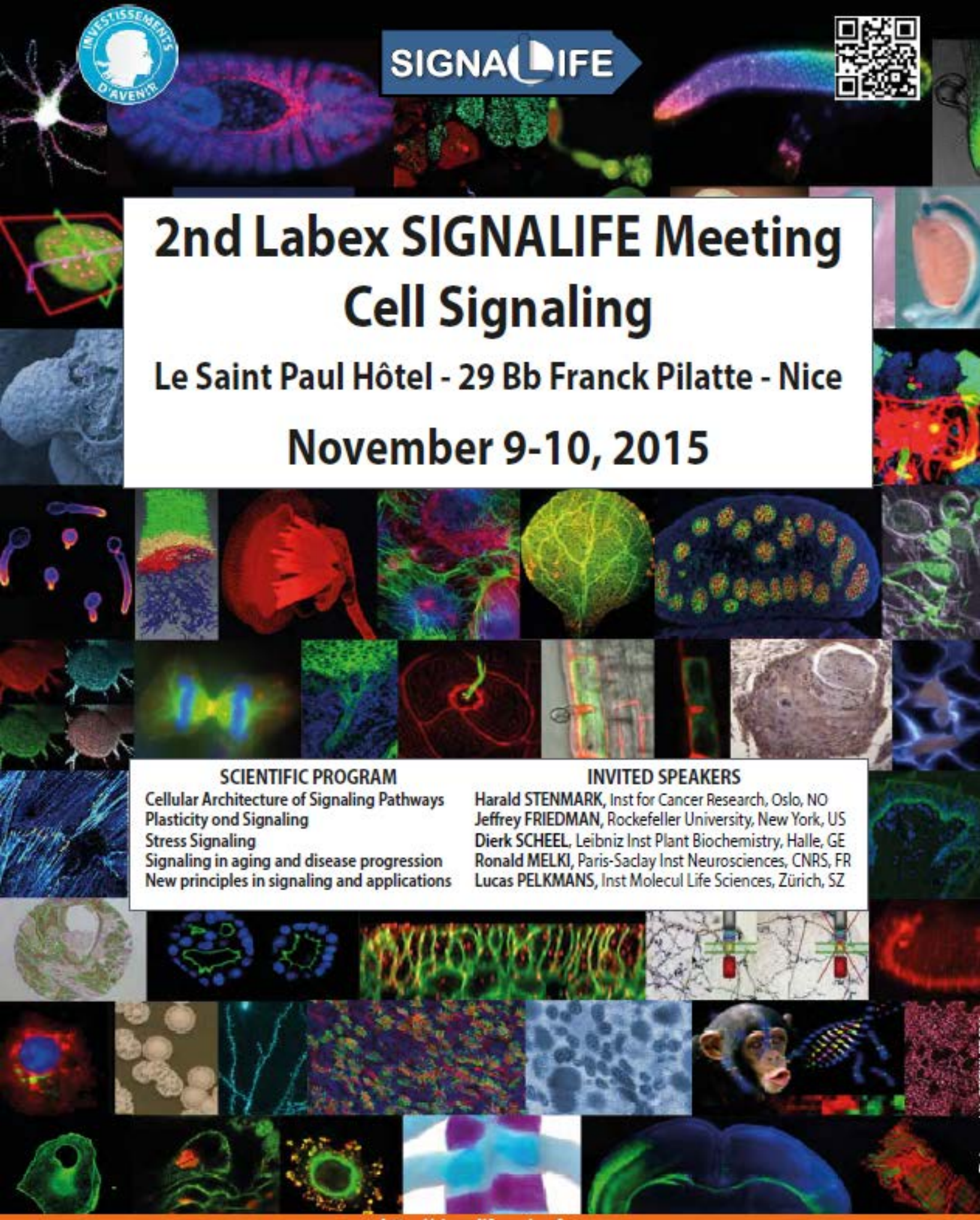

SIGNALIFE

2nd Labex SIGNALIFE Meeting
Cell Signaling

Le Saint Paul Hôtel - 29 Bb Franck Pilatte - Nice

November 9-10, 2015

SCIENTIFIC PROGRAM

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

INVITED SPEAKERS

Harald STENMARK, Inst for Cancer Research, Oslo, NO
Jeffrey FRIEDMAN, Rockefeller University, New York, US
Dierk SCHEEL, Leibniz Inst Plant Biochemistry, Halle, GE
Ronald MELKI, Paris-Saclay Inst Neurosciences, CNRS, FR
Lucas PELKMANS, Inst Molecul Life Sciences, Zürich, SZ

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Many thanks to all SIGNALIFE PhD Students

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PROGRAM OVERVIEW

2nd labex SIGNALIFE meeting November 9-10, 2015, Le Saint Paul Hôtel, Nice (Day 1)

	Monday 9 November
13:15 - 14:00	Registration
14:00 - 14:15	*Welcome* by **Stéphane Noselli**
	Session I, Axis 1: Cellular Architecture of Signaling Pathways chair: E. Lemichez
14:15 - 15:00	*Invited Keynote Lecture:* **Harald Stenmark,** Institute for Cancer Research, Oslo, Norway " ESCRTs of life"
15:00 - 15:30	*SIGNALIFE Keynote* : **Pascal Thérond**, iBV "Vesicular transportation of signaling molecules within the extra-cellular space: the Hedgehog example"
15:30 - 15:50	**Thomas Juan**, iBV "ESCRT proteins are essential for the function of the Zebrafish Left/Right organizer"
15:50 - 16:10	**Bin Wan**, ISA "Parasitoid wasp venom extracellular vesicles specifically transport RhoGAPs toxins inside Drosophila host lamellocytes"
16:10 - 16:40	Coffee Break
	Session II, Axis 2: Plasticity and Signaling chair: C. Dani
16:40 - 17:25	*Invited Keynote Lecture:* **Jeffrey Friedman**, Rockefeller University, NY, USA "Leptin and the Neural Circuits Controlling Food Intake and Metabolism"
17:25 - 17:55	*SIGNALIFE Keynote :* **Patrick Collombat**, iBV "Induction of pancreatic beta-like cell neogenesis"
17:55 - 18:15	**Andhira Viera**, iBV "Neurog3 misexpression in adult pancreatic duct cells reveals their plasticity"
18:15 - 18:35	**Diana Andrea Fernandes de Abreu**, ISA "Non-coding RNAs as inter-individual signaling molecules"
18:35 - 21:30	***Wine and Cheese Poster Session***

2nd labex SIGNALIFE meeting November 9-10, 2015, Le Saint Paul Hôtel, Nice (Day 2)

	Tuesday 10 November
	Session III, Axis 3: Stress Signaling chair: R. Ballotti
09:00 - 09:45	*Invited Keynote Lecture:* **Dierk Scheel**, Leibniz Institute of Plant Biochemistry, Halle, Germany "Signaling in plant immunity"
09:45 - 10:15	*SIGNALIFE Keynote:* **Eric Gilson**, IRCAN "The double life of telomeric proteins"
10:15 - 10:45	Coffee Break
10:45 - 11:05	**Laurent Boyer**, C3M "Bacterial virulence sensing by the innate immune system"
11:05 - 11:25	**Vincent Picco**, Centre Scientifique de Monaco "MAPK signaling in coral stress response"
	Session IV, Axis 4: Signaling in aging and disease progression chair: J.-E. Ricci
11:25 - 12:10	*Invited Keynote Lecture:* **Ronald Melki**, Paris-Saclay Institute of Neurosciences, CNRS, Gif-sur-Yvette, France "Prion-like propagation of protein aggregates in neurodegenerative proteinopathies"
12:10 - 12:40	*SIGNALIFE Keynote :* **Sophie Tartare-Deckert**, C3M "Microenvironmental influences in melanoma: a SPARC-ling affair"
12:40 - 14:00	Lunch Buffet
14:00 - 14:20	**Andrew Rallis**, iBV "Hedgehog signalling in lifespan determination"
14:20 - 14:40	**Bastien Vergoni**, C3M "DNA damage & the activation of the p53 pathway in adipocytes contributes to adipose tissue inflammation during obesity"
	Session V, Axis 5: New principles in signaling and applications chair: B. Bardoni
14:40 - 15:25	*Invited Keynote Lecture:* **Lucas Pelkmans**, Institute of Molecular Life Sciences, Univ Zürich, Switzerland "Cell-intrinsic adaptation of lipid composition to local crowding drives social behaviour"
15:25 - 15:55	*SIGNALIFE Keynote:* **Florence Besse**, iBV "Combining approaches to study the regulation and function of neuronal RNA granules"
15:55 - 16:25	Coffee Break
16:25 - 16:45	**Simona Catozzi**, Institut Non Linéaire de Nice "Control and prediction of the direct and retroactive propagation flow in a signaling cascade model"
16:45 - 17:05	**Loris Pratx**, ISA "Identification of epigenetic marks in the plant parasitic root-knot nematode Meloidogyne incognita"
17:05 - 17:15	*Poster awards* by the Scientific Committee
17:15 - 17:30	*Concluding remarks*

ORAL COMMUNICATIONS

Session I, Axis 1
Cellular Architecture of Signaling Pathways

Chair : E. Lemichez

Invited Keynote Lecture : Harald STENMARK

ESCRTs of life

Harald STENMARK

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Keywords : endosome, endocytosis, nuclear envelope, mitosis, ESCRT

The endosomal sorting complex required for transport (ESCRT) machinery was identified for its importance in sorting membrane proteins into intraluminal vesicles of endosomes/vacuoles. This machinery consists of four subcomplexes with distinct functions, termed ESCRT-0, -I, -II and -III. ESCRT-0 sequesters ubiquitinated cargo into endosomal microdomains, ESCRT-I and -II mediate involution of the endosome membrane and transfer cargo into the resulting invaginations whereas ESCRT-III (together with accessory proteins) mediates scission of the forming intraluminal vesicles. It turns out that parts of this elegant mechanism are used for many other, topologically related purposes, including virus budding, cytokinetic abscission, plasma membrane repair, neuronal pruning and surveillance of nuclear pore complex assembly. Recently, we discovered an additional mechanism controlled by ESCRT-III, namely sealing of holes in the reforming nuclear envelope during mitotic exit. The multiple functions of ESCRT-III raise the questions of how ESCRT-III proteins are recruited to the various membranes to execute their specific functions, and by which kinetics such recruitment occur. We are currently trying to address these issues.

Signalife Keynote Lecture : Pascal THÉROND

Vesicular transportation of signaling molecules within the extra-cellular space: the Hedgehog example

Pascal THEROND

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(corresponding author : therond@unice.fr*)*

Keywords : cell-cell communication, exovesicles, morphogen, Hedgehog, patterning

The Hedgehog (Hh) morphogen plays an instructive role in various developmental processes (Briscoe and Thérond, 2013). Malfunction of both Hh signaling and secretion leads to severe developmental disorders from fly to human. Although the molecular pathway of Hh signaling in the receiving tissue is quite well investigated, how this highly hydrophobic molecule dually lipidated by a palmitic acid and cholesterol is secreted and travels from the producing cells in the extracellular environment is still poorly understood. Current models for secretion and transport include Hh multimerisation, long filopodia-mediated transport, or binding to lipoprotein particles. However the possibility of Hh transport via exo-vesicles released by cells has never been functionally explored.
We recently provided evidence that Hh secretion is dependent on the Endosomal Sorting Complex Required for Transport (ESCRT) function. Interfering with ESCRT activity in Hh-producing cells in vivo leads to a specific loss of Hh long-range activity and Hh and ESCRTs are found at distance from their source of production, spreading together in common particles. Moreover we were able to trap Hh and ESCRT containing particles at the external surface of recipient cells expressing the Hh receptor. Our findings reveal a novel function for ESCRT proteins in controlling morphogen activity (Matusek et al., 2014). They also provide evidence for a previously unidentified mechanism for Hh release and intercellular communication. We also obtained evidence showing that endocytosis and Rab4-dependent recycling of Hh in producing cells is necessary prior to the ESCRT-dependent secretion of Hh exo-vesicle (D'Angelo et al., 2015). In light of these data, I will discuss the exo-vesicle transportation of Hh in comparison to other proposed models, such as long filopodia (cytonemes) and liprotein particles.

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

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Presentation 1 : Thomas JUAN

ESCRT proteins are essential for the function of the Zebrafish Left/Right organizer

Thomas Juan(1), Morgane Poulain (1), Sophie Polès (1), Marie-Alix Derieppe (1) & Maximilian Fürthauer (1)

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Keywords : Zebrafish, ESCRT, Cilia, Left/Right Organizer, Exovesicles

The establishment of Left/Right (L/R) asymmetry represents an essential step for organ development during embryonic morphogenesis in bilaterians and L/R defects have been involved in diverse severe human pathologies. We use the Zebrafish as a model to study L/R establishment in vertebrates. L/R asymmetry in Zebrafish is initiated through the action of a transient L/R organizer, Kupffer's vesicle (KV), an epithelial vesicle in which motile cilia are generating a circular, counter-clockwise, fluid flow. While it is well established that KV flow is essential for L/R asymmetry, the mechanism through which the flow triggers symmetry breaking remains to be elucidated. We have recently contributed to show that extracellular vesicles (exovesicles) that are generated by the action of the Endosomal Sorting Complex Required for Transport (ESCRT) can ensure the extracellular transport of signaling molecules during Drosophila development (Matusek et al, Nature 2014). Here we show that the Zebrafish ESCRT component CHMP1B is enriched on exovesicles that are present in the KV lumen. Moreover, depletion of a second ESCRT component, VPS4B, reduces the number of CHMP1B-positive exovesicles and leads to organ laterality defects. These data raise the question whether the KV fluid flow could promote the directional transport of symmetry-breaking signaling molecules in ESCRT-positive exovesicles. In order to address this issue, we have started to quantitatively analyze exovesicle transport dynamics in the L/R organizer. These measurements have allowed us to show that in spite of its overall circular geometry, the L/R organizer fluid flow can indeed ensure a global left-ward enrichment of material within the organ lumen. Surprisingly, our quantitative analysis of KV flow transport dynamics has moreover allowed us to identify a simple measureable parameter that can be used to predict the appearance of L/R asymmetry defects. Altogether, our findings are compatible with a scenario according to which ESCRT-positive exovesicles may ensure the directional transport of symmetry-breaking signals in the Zebrafish L/R organizer.

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

Presentation 2 : Bin WAN

Parasitoid wasp venom extracellular vesicles specifically transport RhoGAPs toxins inside Drosophila host lamellocytes

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Keywords : Drosophila melanogaster, parasitoids, RhoGAPs, lamellocytes, immunology

Leptopilina parasitoid wasps develop inside D. melanogaster larvae by consuming the tissues. They ensure parasitism success by injecting venom, together with the egg, at oviposition. Venom factors notably inhibit the fly immune response, i.e. the cellular encapsulation of the parasitoid egg, by targeting the main hemocyte type involved, the lamellocytes, inducing changes in their morphology. A main factor involved is a venom secreted RhoGAP protein, LbGAP, that in vitro targets Drosophila Rac1 and Rac2. A recent "omic" analysis identified eight other secreted RhoGAPs in L. boulardi venom, the second most abundant being LbGAP2. We demonstrate here that LbGAP and LbGAP2 are associated with the vesicular fraction of the venom and more specifically with a specific type of extra-cellular vesicles (EVs). The two proteins are detected in high amounts in parasitized hosts, and 15h and 24h post-parasitism, they can be immunolocalized in lamellocytes, most of them showing the expected typical change in shape. In parallel, the purified vesicular fraction of parasitoid venom was fluorescently labeled and microinjected in D. melanogaster larvae, and the hemocytes were collected at different times (4h, 15h, 20h). A strong colocalization of fluorescent vesicles and LbGAP or LbGAP2 was observed, showing that these toxins remain associated with the vesicles once inside the lamellocytes. Results suggest that the parasitoid venom extra-cellular vesicles act as "shuttles" that transport specific toxins (key signalization factors) and target them into the host immune cells, thus ensuring parasitism success. Our future experiments will aim at identifying "specific" lamellocyte receptors and understanding the mechanism of entry of the parasitoid vesicles inside these host cells.

This work is funded by the ''Investments for the Future" LABEX SIGNALIFE: program reference ANR-11-LABX-0028, and the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement No. 613678 (DROPSA).

Session II, Axis 2
Plasticity and Signaling

Chair : C. Dani

Invited Keynote Lecture : Jeffrey FRIEDMAN

Leptin and the Neural Circuits Controlling Food Intake and Metabolism

Jeffrey FRIEDMAN

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Keywords : Leptin, Insulin, Glucagon, Body Weight, Diabetes

The discovery of leptin has led to the elucidation of a robust physiologic system that maintains fat stores at a relatively constant level. Leptin is a peptide hormone secreted by adipose tissue in proportion to its mass. This hormone circulates in blood and acts on the hypothalamus to regulate food intake and energy expenditure. When fat mass falls, plasma leptin levels fall stimulating appetite and suppressing energy expenditure until fat mass is restored. When fat mass increases, leptin levels increase, suppressing appetite until weight is lost. By such a mechanism total energy stores are stably maintained within a relatively narrow range.

Recessive mutations in the leptin gene are associated with massive obesity in mice and some humans. Treatment with recombinant leptin markedly reduces food intake and body weight. The low leptin levels in patients with leptin mutations are also associated with multiple abnormalities including infertility, diabetes and immune abnormalities all of which are corrected by leptin treatment. These findings have established important links between energy stores and many other physiologic systems and led to the use of leptin as a treatment for an increasing number of other human conditions including a subset of obesity, some forms of diabetes including lipodystrophy and hypothalamic amenorrhea, the cessation of menstruation seen in extremely thin women. Identification of a physiologic system that controls energy balance establishes a biologic basis for obesity

Leptin has recently been approved for the treatment of lipodystrophy, a severe form of diabetes associated with reduced fat mass and low endogenous leptin levels. These and other data have suggested that leptin can reduce glucose and lower insulin independent of effects on food intake. Further evidence suggests that leptin's effects on glucose metabolism are mediated by the hypothalamus. Recent studies have focused on the role of specific populations of glucose sensing neurons in the ventromedial and lateral hypothalamus. These studies have employed a novel technology for modulating neural activity using radiowaves or magnets. The results of these studies have highlighted the critical role of the CNS to control blood glucose and the levels of pancreatic hormones.

Signalife Keynote Lecture: Patrick COLLOMBAT

Induction of pancreatic beta-like cell neogenesis

Patrick COLLOMBAT

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Keywords : Diabetes, Regeneration, beta-cells, Reprogramming, Pax4

Type 1 diabetes results from the autoimmune destruction of insulin-producing pancreatic beta-cells. Cell replacement therapy, using cell differentiation/reprogramming, represents a promising avenue of research. Indeed, using the mouse as a model, we previously showed that embryonic glucagon-producing cells can regenerate and convert into insulin-producing beta-like cells through the misexpression of a single gene, Pax4 (a developmental gene involved in the embryonic specification toward the beta-cell fate). More recently, we also demonstrated that the misexpression of Pax4 in glucagon-expressing cells age-independently induces their neogenesis and conversion into beta-like cells.
The regenerative capacity of glucagon-producing cells and their potential of conversion into beta-like cells by the simple ectopic expression of Pax4 are of interest in the context of type 1 diabetes research. However, this transgenic approach would be an impractical in humans. We therefore initiated a number of screens aiming to discover small molecules/chemical compounds mimicking the effects of the ectopic expression of Pax4.

Here, we report the in vivo activities of the G8 compound in promoting the neogenesis of alpha-cells and their conversion into beta-like cells, such cells being functional and allowing the reversal of chemically -induced diabetes.

Presentation1: Andhira VIEIRA

Neurog3 misexpression in adult pancreatic duct cells reveals their plasticity

VIEIRA Andhira (1,2), COURTNEY Monica (1,2), DRUELLE Noémie (1,2), GJERNES Elisabet (1,2), HADZIC Biljana (1,2), BEN-OTHMAN Nouha (1,2), AVOLIO Fabio (1,2), NAPOLITANO Tiziana (1,2), FERRER Jorge (3) and COLLOMBAT Patrick (1,2)*

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Keywords : Diabetes , Insulin, Neurog3, Transdifferentiation, Pancreatic ducts

The pancreas can be divided into two tissue types: exocrine and endocrine. The endocrine tissue is organized into clusters of cells named islets of Langerhans, comprising five cell subtypes of which the two main (α and β) secrete respectively glucagon and insulin. Type 1 diabetes is an auto-immune disease resulting in the loss of pancreatic β-cells and, consequently, in chronic hyperglycemia. Current therapies are efficient but remain highly binding, leading current research to aim at deciphering the β-cell genesis and/or regeneration to potentially establish new therapies. Many studies characterized the specific cascade of transcription factors differentiating pancreatic progenitor cells during development, including Neurog3 specifying the endocrine lineage and Pax4 favoring the β-cell lineage. Previous results obtained in the lab led us to establish the hypothesis that pancreatic ducts may contain a potential source of progenitor cells, which could become endocrine cells through re-expression of Neurog3. Thus, we investigated the consequences of the ectopic misexpression of Neurog3 in pancreatic duct cells in vivo. Using this strategy, we observed a dramatic increase in islet size, due to an augmentation in all endocrine cells types. Lineage tracing allowed us to demonstrate that the new endocrine cells have a ductal origin, while physiological studies displayed functional insulin response upon a glucose bolus. Finally, our analyses also demonstrated that the fate of these newly generated endocrine cells could be modulated by acting on the Pax4 gene.

Presentation 2: Diana Andrea FERNANDES DE ABREU

Non-coding RNAs as inter-individual signaling molecules

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Keywords : RNA, Behaviour, Plasticity, Signaling, C.elegans

Sensory imprinting is a life-long attachment to environmental features experienced during a critical period of early development. Imprinting of this kind is highly conserved in evolution and is an important form of adaptive behavioral plasticity (K. Lorenz, 1970). The nematode Caenorhabditis elegans can undergo such adaptations. We have shown that when exposed to an attractive odorant during its early development, adult nematodes will exhibit an increased attraction towards this odorant and an increased egg-laying rate. This phenomena, known as an olfactory imprinting, is not only odor-specific, but it is also concentration-specific which pinpoints the existence of tightly regulated molecular mechanisms (JJ Remy and O. Hobert, 2005). Strikingly, we have shown that olfactory imprints are vertically transmitted from the odor-experienced generation to the naive progeny (JJ Remy, 2010). Furthermore, we report here that C. elegans worms are able to share other's experience. Indeed, the co-culture of olfactory imprinted worms with naïve ones leads the latter to adopt the imprinted chemosensory behavior. We show that horizontal transmission from experienced to naïve is achieved via feeding, suggesting odor-experienced worms release signaling molecules in the environment. In order to identify which molecular signals support such worm-to-worm communication, we screened a battery of candidate mutants to assess their capacity to horizontally transmit the olfactory imprints. It emerged from our genetic screen that a subtype of non-coding RNA seems to be the information carrier. We are currently trying to identify which members of this particular subtype of RNA could be involved in olfactory behavior plasticity.

This work is supported by the Agence Nationale de la recherche (ANR).

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Session III, Axis 3
Stress Signaling

Chair : R. Ballotti

Invited Keynote Lecture : Dierk SCHEEL

Signaling in plant immunity

Dierk SCHEEL, Lennart ESCHEN-LIPPOLD, Justin LEE

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Keywords : Arabidopsis thaliana, calcium, lipopolysaccharide, MAP kinase, Pseudomonas syringae

Plants detect potential pathogens in their environment via pathogen-associated molecular patterns (PAMPs) that are recognized by plant plasma membrane receptors. Typical PAMPs include the flagellin-derived flg22 peptide, the elf18 peptide of elongation factor EF-Tu, peptidoglycans and lipopolysaccharides, as well as chitin oligomers and glucan fragments. PAMP binding to their receptors initiates complex signaling networks that activate a multi-component defense response and thereby establish PAMP-triggered immunity.

One of the earliest detectable responses after PAMP perception is the activation of ion channels at the plasma membrane. Using a transgenic Arabidopsis line with the calcium reporter, aequorin, increases in cytosolic calcium levels are detected after PAMP application. To identify signaling network components, seeds of aequorin-expressing lines were mutagenized and the population screened for mutants with changed calcium elevation (cce) in response to different PAMPs (1). Besides several receptor complex components, a lectin S-domain receptor kinase was identified, which mediates lipopolysaccharide sensing (2).

MAPK cascades are essential for controlling defense responses. The elements that prevent erroneous signaling crosstalk may include expression patterns of the MAPK cascade components, the presence of pathway-specific protein complexes or the MAPK substrate diversity. Different strategies have been employed to isolate MAPK interacting proteins. Several VQ-motif containing proteins and tandem zinc finger proteins are MAPK substrates and regulate immune responses (3, 4). Pathogen effectors interfere with PAMP recognition and signaling to suppress PAMP-triggered defense responses. Some effectors of the bacterial pathogen Pseudomonas syringae pv. tomato specifically interfere with MAPK cascades and thereby attenuate plant resistance.

This work is supported by Deutsche Forschungsgemeinschaft

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Signalife Keynote Lecture: Eric GILSON

The double life of telomeric proteins

Eric GILSON

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Keywords : Telomere, Ageing, Cancer, Chromosome stability, Chromatin

Telomeric proteins bind telomeric DNA to protect chromosome ends from degradation and inappropriate DNA damage response activation. Interestingly, they are also able to localize outside telomeric regions, where they can regulate the transcription of genes involved in metabolism, immunity, and differentiation as well as preventing replicative damages in heterochromatin regions. We will discuss recent data suggesting that this multifunctionality of telomeric proteins is not simply a meaningless side effect of evolution but instead delineates an important mechanism of telomere signaling by which telomere changes control the ability of their associated factors to regulate genome-wide transcriptional programs and genome stability. This mechanism is expected to enable a greater diversity of cellular responses adapted to specific cell types and telomeric changes, and may therefore represent a pivotal aspect of development, aging, and telomere-mediated diseases.

Presentation 1: Laurent BOYER

Bacterial virulence sensing by the innate immune system

Garcia E(1), Munro P(1), Diabate M(1), Jacquel A(2), Michel G(1), Obba S(2) Goncalves D(2) Luci C(3), Marchetti S(2), Demon D(4), Degos C(5), Lamkanfi M(4), Auberger P(4), Gorvel JP(5) Stuart LM (6), Landraud L(1), Lemichez E(1), Boyer L(1)

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Keywords : innate immunity, virulence factors, host-pathogens interactions

Innate immune signaling pathways are hard-wired networks that result in activation of transcription factors and expression of the immune effectors essential for pathogen defense in many species. These pathways are triggered by pattern recognition receptors that recognize invariant molecular patterns expressed by microbes. Although the ligands that stimulate these receptors are shared between avirulent and virulent strains, the host demonstrates a remarkable capacity to tailor the response to the virulence of the invading microorgansim 1. However, how the innate immune system recognizes the array of structurally diverse virulence factors to achieve this specificity remains obscure. Using drosophila we have set out to identify defense mechanisms that respond to microbial virulence, focusing on those that target the RhoGTPases 2. We demonstrate that toxin induced activation of Rac is sufficient to initiate defense signals in the absence of other bacterial components and identify a conserved Rac-dependent immune pathway. Further, we demonstrate the capacity of the host to detect the activity of the RhoGTPase targeting toxin CNF1 of Escherichia coli during mice bacteremia 3. This mechanism of immune surveillance, based on monitoring the activity of virulence factors, provides a framework for a recognition system able to deal with the large number of highly varied microbial toxins targeting RhoGTPases. We anticipate that other targets of microbial virulence determinants will be guarded and that this is an evolutionarily conserved means by which pathogenicity is detected.

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Presentation 2: Vincent PICCO

MAPK signaling in coral stress response

COURTIAL Lucile (1), GROVER Renaud (1), CORMERAIS Yann (1), PAGES Gilles (2), FERRIER-PAGES Christine (1), PICCO Vincent (1)

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Keywords : stress , signaling, ecology, climate, change

Coral reefs are of major ecological and socio-economic interests. They are exposed to a variety of anthropic stresses such as ocean acidification, global warming and touristic activity. In the context of climate changes, a great effort has been made to try predict and prevent coral reefs degradation in response to stresses. Still, very little is known about the signaling pathways involved in stress response in these organisms. We have identified Mitogen Activated Kinase pathways as being responsive to thermal and UV stresses. In particular, the JNK pathway is activated when corals are exposed to a temperature increase or UVs in a way comparable to mammalian cells. Using a specific inhibitor, we show that JNK activity is required for corals to regulate temperature and UV-induced reactive oxygen species (ROS) production. Taken together, our results show that the function of an ancestral stress response pathway involving JNK is conserved from corals to mammals.

This work is supported by the Government of Monaco

Session IV, Axis 4
Signaling in aging and disease Progression

Chair : J.-E. Ricci

Invited Keynote Lecture : Ronald MELKI

Prion-like propagation of protein aggregates in neurodegenerative proteinopathies

Ronald MELKI

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Keywords : neurodegenerative diseases, protein aggregation, prion, aging, therapeutic

The accumulation of misfolded protein aggregates within the central nervous system is the hallmark of several progressive neurodegenerative disorders in man. The main protein constituent of these aggregates and the affected regions within the brain differ from one neurodegenerative disorder to another. Until recently, the vicious circle consisting of template-driven misfolding of like proteins over time, spread and accumulation within the central nervous system of misfolded proteins aggregates was thought to be restricted to the prion protein PrP. Recent reports suggest that a variety of protein aggregates spread and amplify within the central nervous system leading to distinct diseases.

I will present data illustrating the propagation propensities of alpha-synuclein and huntingtin protein aggregates that are the hallmarks of Parkinson's and Huntington's diseases, respectively. I will discuss the nature of protein assemblies that are infectious and the reasons they are toxic to cells. I will show how one protein, alpha-synuclein, takes advantage of its chameleon properties to assemble into structurally and functionally distinct assemblies, we believe associated to distinct diseases. Finally, strategies targeting the propagation of protein assemblies involved in age-related dementias will be presented and the open questions we are facing will be discussed.

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Signalife Keynote Lecture : Sophie TARTARE-DECKERT

Microenvironmental influences in melanoma: a SPARC-ling affair

Sophie TARTARE-DECKERT

C3M/INSERM U1065, Team Microenvironment, Signaling and Cancer, Nice, France.

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Keywords : Signaling, Cancer, Extracellular matrix, metastasis, targeted therapy

My laboratory is interested in understanding microenvironmental influences and signaling networks that drive tumor growth and dissemination. We have been particularly involved in studying the role of the tumor microenvironment in metastatic niche formation and response to therapy in melanoma, the most aggressive and lethal form of skin cancer. Recent work of our lab has been focused in deciphering how melanoma cells communicate with endothelial cells during tumor cell extravasation and drive changes in the ecology of the lymphatic metastatic niche and how the extracellular matrix, a key component of the microenvironment influences the response of melanoma cells to targeted therapies. I will present an overview of our data supporting a cell-autonomous and non-cell-autonomous role for the matrix-associated protein SPARC in tumor cell plasticity, therapeutic resistance and metastasis. I will also present our recent findings showing that the extracellular matrix provides topographic and molecular information that affects melanoma cell phenotype and favors drug tolerance.

Presentation 1: Andrew RALLIS

Hedgehog signalling in lifespan determination

Andrew RALLIS, Pascal THEROND

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Keywords : Neurodegeneration, Hedgehog signalling, Glia, Ageing, Neurons

A plethora of neurodegenerative disease increase in incidence with age. However the signaling pathways which link ageing as a causal factor to disease onset and progression have to a large degree yet to be determined. At present signaling pathways which reverse or de-accelerate the ageing process are currently under investigation. Here we report that overexpression of Hedgehog (Hh) is able to considerably extend lifespan by approximately 25% compared to Wild type flies and maintain healthy mobility in aged flies in Drosophila Melanogaster and that inhibition of neuronal expressed Hh almost completely abolishes the Hh-mediated lifespan extension phenotype and associated fitness . Concomitantly loss of function of Hh during adult life gives a drastically shortened lifespan phenotype, accompanied by dopaminergic neuronal loss, as well as increased sensitivity to oxidative stress, thermal stress, cold-shock and rotenone treatment. Furthermore we have also uncovered that the vast majority of cells expressing the highly conserved receiving module of the Hh morphogen (Patched, Smoothened and Ci) are in the Glia. Interestingly activating Hh signaling in the glia through overexpression of activated forms of Smo and Ci, also gives a lifespan overextension phenotype comparable to overexpression of Hh in Hh expressing cells and overexpression of an activated form of Ci in the glia can rescue the short-lived Hedgehog loss of function phenotype to those above wild type levels. Overall our studies suggest that neuron-astrocyte communication in the adult brain is the modus operandi by which the Hh signaling pathway is activated in the glia, which in turn is crucial in maintaining the cellular integrity of the adult brain providing sustained neuroprotection. It is probable that Ci acts in the glia to mediate the transcription of neuroprotective secreted factors. We conclude that activating Hh signaling in the glia is critical in lifespan determination.

Presentation 2: Bastien VERGONI

DNA damage and the activation of the p53 pathway in adipocytes contributes to adipose tissue inflammation during obesity

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Keywords : insulin signaling, type 2 diabetes, chemokines, adipose tissue, obesity

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 function 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 damage and activation of the p53 pathway in adipocytes. We demonstrated that 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 the development of adipocyte insulin resistance. In vitro, DNA damage in adipocytes increased the expression of chemokines and triggered the production of chemotactic factors for macrophages. Furthermore, insulin signaling and effect on glucose uptake and Glut4 translocation were decreased while lipolysis was increased. These events were prevented by p53 inhibition whereas its activation by nutlin-3 in adipocytes reproduced these adverse effects induced by DNA damage. This study reveals that DNA damage in obese adipocyte could trigger p53-dependent signals involved in alteration of adipocyte metabolism and secretory function leading to adipose tissue inflammation, adipocyte dysfunction and insulin resistance.

This work was supported by SFD, EFSD, and AVIESAN

Session V, Axis 5
New principles in signaling and applications

Chair : B. Bardoni

Invited Keynote Lecture : Lucas PELKMANS

Cell-intrinsic adaptation of lipid composition to local crowding drives social behaviour

FRECHIN Mathieu (1), STOEGER Thomas (1), DAETWYLER Stephan (1), GEHIN Charlotte (2), BATTICH Nico (1), DAMM Eva-Maria (3), STERGIOU Lilli (3), RIEZMAN Howard (2), PELKMANS Lucas (1)

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Keywords : Pattern formation, Lipids, Cell adhesion signalling, Membranes, Tunable capacitors

Cells sense the context in which they grow to adapt their phenotype and allow multicellular patterning by mechanisms of autocrine and paracrine signalling. However, patterns also form in cell populations exposed to the same signalling molecules and substratum, which often correlate with specific features of the population context of single cells, such as local cell crowding. Here we reveal a cell-intrinsic molecular mechanism that allows multicellular patterning without requiring specific communication between cells. It acts by sensing the local crowding of a single cell through its ability to spread and activate focal adhesion kinase (FAK, also known as PTK2), resulting in adaptation of genes controlling membrane homeostasis. In cells experiencing low crowding, FAK suppresses transcription of the ABC transporter A1 (ABCA1) by inhibiting FOXO3 and TAL1. Agent-based computational modelling and experimental confirmation identified membrane-based signalling and feedback control as crucial for the emergence of population patterns of ABCA1 expression, which adapts membrane lipid composition to cell crowding and affects multiple signalling activities, including the suppression of ABCA1 expression itself. The simple design of this cell-intrinsic system and its broad impact on the signalling state of mammalian single cells suggests a fundamental role for a tunable membrane lipid composition in collective cell behaviour.

Signalife Keynote Lecture: Florence BESSE

Combining approaches to study the regulation and function of neuronal RNA granules

Florence BESSE

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Keywords : RNA granules, neuronal remodeling, RNA transport, imaging, Drosophila

In vivo, mRNAs are packaged together with regulatory proteins into ribonucleoprotein particles (RNP) that control their fate and undergo extensive remodeling in response to developmental signals or environmental stresses. Cytoplasmic RNPs of different sizes, composition and regulatory properties have been described, including large macromolecular complexes such as P-bodies, stress granules, or germ cell granules. In neurons, so-called neuronal granules have been implicated in the long-distance transport of mRNAs to axons or dendrites, and in their local translation in response to external cues. To date, surprisingly little is known about the molecular mechanisms controlling the assembly and regulation of RNP granules, specifically neuronal granules. To identify these mechanisms and test their physiological importance in vivo, we use as a paradigm RNP particles characterized by the presence of the conserved IMP protein. We combine different approaches, ranging from fly genetics and biochemistry to high-throughput imaging or modeling.

Presentation 1: Simona CATOZZI

Control and prediction of the direct and retroactive propagation flow in a signaling cascade model.

CATOZZI Simona (1), DI BELLA Juan Pablo (2), VENTURA Alejandra (2), SEPULCHRE Jacques-Alexandre (1)

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Keywords : systems biology, linear signaling cascades, direct signaling, retroactive signaling, drug therapy

Signaling cascades are part of a very complex molecular network orchestrating the whole process of signal transduction. They consist in an ordered sequence of proteins, coupled three by three, involved in phosphorylation-dephosphorylation reactions. The first protein is activated (phosphorylated) by an input signal, then each protein is activated by the previous one. Moreover, according to common drug therapies applied to cascades, we assume that the last protein can be inhibited by a compound (drug). Having the sequence length fixed to 3, we study the dynamical equilibrium of such a system according to the direction of the information flow along the cascade and as a function of the biochemical parameters (which are randomly sampled), like reaction rates, total concentrations, or substrate-enzyme affinities. Particularly, our investigation is based on the effect of two different stimuli, namely the input signal and the inhibiting drug, which generate different stimulus-response curves, where the response is the proteins' variation. These two curves are respectively associated to opposite working regimes: the downstream (direct) and the upstream (retroactive) propagation. Our analysis shows the probabilities for a cascade to work in several (even opposite) regimes, and highlights which choices of parameter values may promote specific signaling directions and dwindle other ones. We also develop a graphic representation of the seven possible working regimes, built from the concepts of saturation, sequestration and cycles' activation. Therefore, these results furnish interesting bases and precise data for making experiments in synthetic biology, and possibly further understanding some existing cascades and predicting their response (maybe related to side effects) to drug administration.

Presentation 2: Loris PRATX

Identification of epigenetic marks in the plant parasitic root-knot nematode Meloidogyne incognita.

Pratx Loris (1,2,3) , Perfus-Barbeoch Laetitia (1,2,3), Castagnone-Sereno Philippe (1,2,3), Cosseau Céline (4,5), Grunau Cristoph (4,5), Abad Pierre (1,2,3)

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Keywords : Plant parasitic nematodes, Plasticity, Adaptation, Environment, Epigenetics

Root-knot nematodes, such as Meloidogyne incognita, are obligatory plant parasites that constitute major agricultural pests worldwide. Our knowledge about M. incognita's genetics egulation has significantly increased since genome sequencing, transcriptomic analysis and gene annotations are now available (1). However, despite this knowledge, the "classical" genetics fails to understand some phenomena occurring in our model. M. incognita reproduces in an asexual way by parthenogenesis without meiosis. Genetically identical individuals develop from females and form clonal populations. Although these clones share the same genetic heritage, modifications of their phenotype can be observed when they are exposed to unfavorable environments. For instance, the virulence (i.e. capacity to parasite a resistant crop) is heritable but transmitted in a non-Mendelian way (not acquired by 100% of the "clonal daughters") and could not be associated to a modification in DNA sequence (2). Epigenetic modifications can drive phenotypes by other mechanisms than genetics. These modifications are heritable, but metastable, which could change phenotypes by modifying genomic expression. We propose to test role of epigenome in the generation of phenotypic variability and consequently for microevolution towards infection success. We detailed DNA methylation and nucleosome structure, carriers of epigenetic information. We also developed a ChIP-seq assay protocol to compare post-transcriptional histone modifications between virulent and avirulent parasites ; and between different developmental stages. Our preliminary data indicated that the genome of M. incognita is not methylated and confirmed the existence of histone modifications which represents important markers involved in gene activation or repression by modifying chromatin state. This study opens the way for analyzing the role of epigenetic mechanisms at a whole genome scale and identifying new biological processes involved in the generation of phenotypic variation in asexual organisms.

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POSTERS

Wine and Cheese Poster Session

LIST OF 39 POSTERS PRESENTATIONS				
Number	Last Name	First Name	Scientific Axis	Abstract title
1.1	ACOSTA LOPEZ	Maria Isabel	Axis 1 – Cellular architecture of signaling pathways	Novel regulatory mechanism of the E3 ligase HACE1 by phosphorylation.
1.2	AIRA DIAZ	Lazaro Emilio	Axis 1 – Cellular architecture of signaling pathways	Role of the inflammatory caspases in the context of psoriasis
1.3	COSTA	Tiago	Axis 1 – Cellular architecture of signaling pathways	Extraction and identification of nematotoxic compounds from seeds of Solanaes with biotechnological potentialace
1.4	DE GARAY	Tomás	Axis 1 – Cellular architecture of signaling pathways	Integrin-Mediated Stiffness Sensing Requires an Extracellular, Non-Exposed Cysteine of the Co-Receptor CD98hc
1.5	DELGADILLO	Roberto F	Axis 1 – Cellular architecture of signaling pathways	Kinetically and Thermodynamically control access to binding pocket in Plasmodium and Toxoplasma
1.6	MANNI	Marco	Axis 1 – Cellular architecture of signaling pathways	Phospholipid polyunsaturation and dynamin-mediated membrane fission
1.7	MILANINI-MONGIAT	Julie	Axis 1 – Cellular architecture of signaling pathways	Functional link between EFA6A and alpha-actinin in lumen formation during cystogenesis
1.8	PRIETO	NURIA	Axis 1 – Cellular architecture of signaling pathways	The Hox gen Abdominal-B and the development of the posterior region of Drosophila melanogaster male: relationship between last segment elimination and genitalia rotation.
1.9	VENTURA	Patrícia	Axis 1 – Cellular architecture of signaling pathways	Characterization of primary cell culture from the temperate symbiotic cnidarian, Anemonia viridis
2.1	DANI	Vincent	Axis 2 – Plasticity and Signaling	Symbiosome membrane characterization, or how to decipher molecular interactions between cnidarians and their dinoflagellate symbionts
2.2	DE CIAN	Marie-Cecile	Axis 2 – Plasticity and Signaling	Amplification of R-SPONDIN1 signaling induces granulosa cell fate defects and cancers in mouse adult ovary
2.3	DRUELLE	Noémie	Axis 2 – Plasticity and Signaling	Pancreatic somatostatin-expressing cells: An untapped source for beta-cell regeneration?
2.4	LE THUC	Ophélia	Axis 2 – Plasticity and Signaling	A new role for Monocyte chemoattractant protein 1/CCL2 in promoting weight loss through inhibition of melanin-concentrating hormone-expressing neurons
2.5	MEDINA	Clémence	Axis 2 – Plasticity and Signaling	Characterization of small regulatory RNAs involved in the establishment of giant cells induced by parasitic nematodes of genus Meloidogyne.
2.6	NOVELLI	Caterina	Axis 2 – Plasticity and Signaling	Hedgehog secretion mechanisms in Drosophila epithelial tissues
2.7	PEREA-GOMEZ	Aitana	Axis 2 – Plasticity and Signaling	NOTCH activation interferes with cell fate specification in the gastrulating mouse embryo
2.8	ROUMENGOUS	Solange	Axis 2 – Plasticity and Signaling	Reprogramming and Morphogenesis during Drosophila embryo development
2.9	RUIZ GARCIA	Sandra	Axis 2 – Plasticity and Signaling	Respiratory epithelium differentiation: looking inside the cell.
3.1	BOONE	Emilie	Axis 3 – Stress Signaling	Coupling Drosophila insulin-like peptide 8 expression with organ size sensing
3.2	BRGLEZ	Vesna	Axis 3 – Stress Signaling	On the regulation of group X sPLA2 in breast cancer cells and its role in cell survival via lipid droplet formation and modulation of lipid metabolism
3.3	DEVECI	Derya	Axis 3 – Stress Signaling	A genetic screen to uncover new signals controlling Drosophila juvenile-maturation transition
3.4	GARCIA	Elsa	Axis 3 – Stress Signaling	Innate immune sensing of the Rho GTPase activating toxin CNF1 is counteracted by the α-Hemolysin
3.5	NAESSENS	Elodie	Axis 3 – Stress Signaling	Aphids reroute one of their immune regulators to repress plant immune responses
3.6	TRUONG	Nhat My	Axis 3 – Stress Signaling	Characterization of root-knot nematode effectors targeting host nuclear functions
4.1	AL-QARAGHULI	Sahar	Axis 4 – Signaling in aging and disease progression	Role of Xeroderma pigmentosum fibroblasts in squamous cell carcinoma invasion
4.2	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
4.3	CEPPO	Franck	Axis 4 – Signaling in aging and disease progression	Involvement of the Tpl2 kinase in COX-2 expression and prostaglandin E2 production in adipocytes in response to inflammatory stimuli
4.4	EL HACHEM	Najla	Axis 4 – Signaling in aging and disease progression	Pro-tumorigenic role of HACE1 in melanoma
4.5	GALANTONU	Ramona Nicoleta	Axis 4 – Signaling in aging and disease progression	A link between steroid signaling pathways and L1 retrotransposition
4.6	GILLERON	Jerome	Axis 4 – Signaling in aging and disease progression	Rab4b as a master regulator of T cell biogenesis and function tunes adipose tissue inflammation and insulin resistance
4.7	GUAL	Philippe	Axis 4 – Signaling in aging and disease progression	CD44 is an important actor in non alcoholic steatohepatitis
4.8	KOOTAR	Scherazad	Axis 4 – Signaling in aging and disease progression	To understand the functional role of Hippocampal Glucocorticoid Receptor in Alzheimer's Disease.
4.9	LEBEAUPIN	Cynthia	Axis 4 – Signaling in aging and disease progression	ER stress induces inflammasome activation and hepatocyte death
4.10	PROD'HOMME	Virginie	Axis 4 – Signaling in aging and disease progression	Role of Lymph Node fibroblasts in the establishment of the pre-metastatic niche and drug resistance of metastatic melanoma
4.11	ROUANET	Sophie	Axis 4 – Signaling in aging and disease progression	Deciphering molecular events occurring in keratinocytes upon solar simulated radiations
4.12	SULTANA	Tania	Axis 4 – Signaling in aging and disease progression	Does the genomic context influences integration site selection by human L1 retrotransposons
5.1	ALMEIDA	Sofia	Axis 5 – New principles in signaling and applications	Modeling and coupling biorhythms
5.2	HASANOVIC	Anida	Axis 5 – New principles in signaling and applications	Patched as a new therapeutic target for adrenocortical cancer
5.3	LUKIANETS	Nikita	Axis 5 – New principles in signaling and applications	Cluster analysis in defining morphological neuronal identity

Poster Session I, Axis 1
Cellular Architecture of Signaling Pathways

ACOSTA LOPEZ Maria Isabel 1.1

Novel regulatory mechanism of the E3 ligase HACE1 by phosphorylation.

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Keywords : Phosphorylation, HECT ubiquitin Ligase, Rac1

Rac1 is a small GTPase involved in the regulation of actin cytoskeleton dependent cellular processes, like adhesion, migration and phagocytosis. It switches between an inactive GDP-bound state and an active GTP-bound state, where it is able to bind to its effectors. As expected for such a central signaling module, Rac1 is tightly regulated within the cell by interaction with activators (GEFS) and inactivators (GAPS). In addition, our team found a new mode of regulation of Rac1 consisting in the ubiquitination of its active form and its subsequent proteosomal degradation. We also identified HACE1 as the E3 ligase that targets active Rac1. HACE1 has been described as a tumour suppressor downregulated in several cancer types and a protective agent against oxidative stress. Furthermore, recent studies have shown that de-regulation of Rac1 ubiquitination through HACE1 inhibition is correlated to Rac1-driven cell transformation, which opens the possibility of using HACE1 as a target for cancer therapy and/or diagnosis. Despite this, little is known about HACE1 regulation or signalling context. Therefore, this work aims to identify how HACE1 is regulated by post-translational modifications, specifically by phosphorylation. We used mass spectrometry to identify phosphorylation sites of HACE1 that were regulated by RhoGTPases. We found that phosphorylation of HACE1 at S385 is induced by Rac1, Cdc42 but not RhoA activation and that this modification inhibits HACE1 ability to ubiquitinate Rac1 without reducing HACE1 affinity towards Rac1. Together these results point to a new post-translational regulatory mechanism of HACE1 and a more dynamic modulation of Rac1 by HACE1.

AIRA DIAZ Lazaro Emilio 1.2

Role of the inflammatory caspases in the context of psoriasis

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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. We showed that inflammatory caspases are expressed in lesional biopsies as compared to non-lesionnal skin area of psoriatic patients. In different model of psoriasis-like disease in mice, we also established that IL-1β but also inflammasome components are expressed in injured skin as compared to normal skin. Accordingly, when we induced a psoriasis-like disease in caspase-1 deficient mice, we observed a decrease in ear thickness, inflammatory cytokines expression and immune cells infiltration. Moreover, as we observed that keratinocytes were primed to secrete IL-1β when cultured in condition mimicking psoriasis (TNF-α+IL17A), we decided to generate chimeric mice deficient for caspase-1 either in the immune system or in keratinocytes/fibroblasts (by adoptive transfer) in order to decipher the respective contribution of each tissue compartment for the activation of inflammatory caspases during psoriasis-like inflammatory response. Our data showed that the presence of caspase-1 in the immune system is necessary for a full inflammatory response whereas the absence of caspase 1 in keratinocytes/fibroblasts had no or little effect. Our study indicates that inflammatory caspases are implicated in the pathogenesis of psoriasis.

COSTA Tiago 1.3

Extraction and identification of nematotoxic compounds from seeds of Solanaes with biotechnological potentialace

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Keywords : Nematotoxic, Plants, M. incognita, Natural products, Metabolites

Meloidogyne incognita species cause annual losses estimated millions of dollars to various important crops. Among the various methods used to control this phytoparasite, the most common consist in using synthetic nematicides provoking risks to human health and the environment. Our studies on particular plant extracts have shown their potential as nematicidal and nematostatic compounds. The discovery of natural compounds with nematotoxic specificity is considered a promising and alternative strategy to methods currently used in agriculture. Several Solanaceaus species, globally distributed and well represented in Brazil, have been identified and proved to be a rich source for the isolation of nematotoxic compounds. Preliminary greenhouse tests using Solanaceaes plants, challenged with the nematode species M. incognita, were performed and plant metabolites extracts were generated from seeds. Aqueous crude extracts and fractions from dialysis were directly confronted in vitro with M. incognita and nematode recovery assays were performed. Crude aqueous extracts were dialyzed to obtain ID (Internal dialyzed) and ED (External dialyzed) fractions. In vitro studies using seed aqueous crude extracts clearly showed nematostatic (100 - 300 µg.mL-1) and nematicidal (500 - 1000 µg.mL-1) activity. Both, ID and ED fractions, exhibited nematostatic activity starting from 25 µg.mL-1, whereas nematicidal activity was observed when applying 100 µg.mL-1. We have screened and identified Solanaceae plants with the potential to provide metabolites to control the phytopathogen M. incognita. Extracts from seeds were generated and subjected to analysis for the isolation of chemical compounds with nematotoxic activity. In the future, promising extracts will be further purified, tested on nematodes and analysed for their effects on root growth.

DE GARAY Tomas 1.4

Integrin-Mediated Stiffness Sensing Requires an Extracellular, Non-Exposed Cysteine of the Co-Receptor CD98hc

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Keywords : mechanosensing, stiffness sensing, CD98hc (SLC3A2), integrins, adhesion

Stiffness sensing is the mechanosensing process through which cells can assess the mechanical properties of their environment. This process requires an interplay between cell's extracellular matrix (ECM) mechanosensors, the integrin receptors, and its actomyosin-based contractile cytoskeleton. CD98hc (SLC3A2) is an integrin co-receptor that simultaneously functions as the regulatory chain of a heteromeric amino acid transporter. CD98hc has recently been shown to be necessary for integrin-mediated stiffness sensing in skin. Its loss compromises ECM stiffness sensing, leads to a marked decrease of matrix rigidity and reduces tumor development. Here, we investigate the molecular mechanism underlying rigidity sensing by CD98hc. We assessed mechanosensing in WT or CD98hc KO mouse dermal fibroblasts by monitoring RhoA activation upon force application on integrin receptors using fibronectin-coated magnetic beads. Alternatively, we grew cells on compliant surfaces of different stiffness. Interestingly, a point mutation (C330S) within the extracellular domain (ED) of CD98hc, normally ascribed exclusively to the amino acid transport function, abrogates RhoA activation without affecting other CD98hc functions. We currently investigate the mechanistic insights of this regulation. This work points out an unexpected role of CD98hc ED on integrin-mediated stiffness sensing that we now ought to characterize in detail, to fully comprehend its mechanism(s) and implications.

DELGADILLO Roberto F 1.5

Kinetically and Thermodynamically control access to binding pocket in Plasmodium and Toxoplasma

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Keywords : Fluorescence, thermodynamics, kinetics, Toxoplasma, Plasmodium

Toxoplasma, Malaria and Coccidiosis are burden diseases in human and domestic animal caused by parasites from Apicomplexa phylum. The surface protein Apical Membrane Antigen 1 (AMA1) and Rhoptry Neck Protein (RON) are important for Toxoplama gondii (Tg), Plasmodium falciparum (Pf) and Eimeria tenella (Et) to form Moving Junctions (MJ) for successful cell infection. AMA1 proteins have a mobile domain II loop that acts as gatekeepers for the binding pocket however the kinetic, thermodynamics and reaction mechanism steps have not been studied for these difference species. In the present work, we have studied the association, dissociation, and binding equilibria of TgAMA1 and ΔDII-loop-TgAMA1 a construct where the DII loop was replaced by a short Gly-Ser linker (ΔDII-PfAMA1) to analyze the effect of this loop upon reaction with TgRON2 and Eimeria tenella (Et)RON2. Our results are contrasted with Pf DII function. The reactions were tracked by fluorescence anisotropy as a function of temperature and concentration and globally fitted to acquire the rate constants which provide the thermodynamic profile and binding mechanism. As observed for PfAMA1-PfRONsp complex, TgAMA1 and ΔDII-loop-TgAMA1 bind to TgRON2 and EtRON2 with two-steps sequential reversible reaction: A↔B↔C. The enthalpy and entropy of the reactions are affected by DII modification as well as when reacting with EtRON2 reveling the function of DII loop by interacting with the ligand. Importantly, the half-lifetime of the Tg complexes was longer than those of DII-Tg and Pf complexes. The elucidation of the binding mechanism and thermodynamic profile bring new strategies for ligand discovery against these apicoplexan diseases.

MANNI Marco 1.6

Phospholipid polyunsaturation and dynamin-mediated membrane fission

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Keywords : Polyunsaturated phospholipids, Dynamin, Endophilin, Fission,, Synaptic vesicles

The acyl chains of membrane phospholipids vary tremendously among organisms, tissues, and cell organelles. For example, there is a sharp increase in the amount of phospholipids containing polyunsaturated acyl chains (ω6 and ω3) in neurons, notably at the axon tip and in synaptic vesicles. However, the functional consequence of this enrichment is poorly known. The importance of PUFA could be explained by their particular properties. Indeed, they are extremely flexible and, akin to contortionists, adopt different shapes of similar energy, thereby softening various membrane mechanical stresses. A previous work showed that endophilin and dynamin are very efficient in shaping membranes containing phospholipids with the highly polyunsaturated acyl chain C22:6ω3. Given the importance of the ω6/ω3 ratio for health, I will perform a comprehensive study of the effect of phospholipid polyunsaturation on dynamin/endophilin mediated membrane fission. I will vary the unsaturation level, acyl chain asymmetry, cholesterol/phospholipid ratio, and polar head chemistry. This study will improve our understanding of the mutual adaptation between endocytic machineries and membranes under physiopathological conditions. I will use biochemical and biophysical techniques such as GTPase assay and light scattering to evaluate the influence of the above mentioned parameters in the activity of dynamin and endophilin. I will compare these results with electron microscopy studies.. I will also take advantage of the multidisciplinary expertise of the host group to broaden my study at the cellular scale and at the molecular scale (with experts in molecular simulations).

MILANINI-MONGIAT Julie 1.7

Functional link between EFA6A and alpha-actinin in lumen formation during cystogenesis

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Keywords : epithelial cell, epithelial polarity, lumen formation, alpha-actinin 1 and 4, EFA6A : arf6 exchange factor

Preliminary results in 2006 showing an interaction between alpha-actinin and EFA6A-C-terminal domain in a Y2H screen, and the well demonstrated role of EFA6A- C-Terminal on actin network remodeling encouraged us to analyze the functional relationship between EFA6A and the alpha-actinin.EFA6A plays an important role in the establishment of epithelial polarity by stabilizing the tight junctions and its associated apical actin ring (Luton et al. 2004) (1). EFAA6 activates specifically the small G protein Arf6 through its catalytic Sec7 domain, and regulates the cortical actin organization through its C-terminal domain. Both activities are required for polarity establishment in MDCK cell. Alpha-actinin is a well-known dimeric protein that bridges actin filaments. It is a F-actin bundling protein in stress fibers and in the apical acto-myosin contractile ring of epithelial cell. Alpha-actinin is also located underneath the plasma membrane where it binds PIP2 through its second Calponin Homology domain. The four-repeat spectrin rod-like domain was shown to act as a scaffold to recruit various structural and signaling molecules. Here, we demonstrate in vitro that EFA6A and alpha-actinin interact directly, and that in vivo EFA6A recruits alpha-actinin independently of F-actin. Studies of cystogenesis show that EFA6A regulates lumen formation at least at two levels: VACs/vesicule fusion and lumen expansion. The fusion stage is also enhanced upon alpha-actinin depletion, most likely because of an overall contractility inhibition shown by others to facilitate fusion. Our preliminary data suggest that EFA6A stimulatory effects on lumen expansion are blocked when the cells are depleted in alpha-actinin. Thus, alpha-actinin might act as an effector of EFA6 to contribute lumen expansion. (1) EFA6, exchange factor for ARF6, regulates the actin cytoskeleton and associated tight junction in response to E-cadherin engagement.

Luton F, Klein S, Chauvin JP, Le Bivic A, Bourgoin S, Franco M, Chardin P. Mol Biol Cell. 2004 Mar;15(3):1134-45.

PRIERTO Nuria 1.8

The Hox gen Abdominal-B and the development of the posterior region of Drosophila melanogaster male: relationship between last segment elimination and genitalia rotation.

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Keywords : Drosophila, Hox genes, Abdominal-B, abdomen, genitalia

Hox genes determine the development of different structures in most animals. In vertebrates, Hox9-13 genes specify the posterior region, while the orthologous Abdominal-B (Abd-B) gene does a similar function in Drosophila melanogaster. The posterior region of Drosophila is sexually dimorphic: only males lack the seventh abdominal segment (A7). This segment is eliminated during pupal stages under the control of Abd-B and the sexual determination pathway, requiring also the activity of genes like extramacrochetae (emc) and the down-regulation of the EGFR and Wnt pathways. Although the fly is a bilaterally symmetric organism, the male genitalia undergoes a 360º dextral rotation during pupa, giving rise to an asymmetric organ. This requires the class I myosin MyoID, whose expression is activated by Abd-B. The full rotation results from an additive process involving two ring-shaped domains, each one producing a 180° turn. Therefore, Abd-B controls both A7 elimination and the rotation of genital plate. Moreover, both processes occur only in males, partially overlap in time, and may have arisen in a coordinated manner in the evolution of the Diptera. Throughout the phylogenetic tree of these insects there is a trend towards the reduction of the abdomen, from 8 segments in mosquito to 5 segments in higher Diptera; as well as an increase in the degree of genital rotation, thus with the possibility of finding species with 0°, 180° or 360°. To analyze the mechanisms that may be common to both events, we have studied genitalia rotation in genetic combinations that reduce A7 suppression, giving rise to an A7. We have found that genetic conditions that prevent the complete extrusion of this segment, such as reducing emc expression or activating the EGFR pathway, also produce partial rotation events. Since emc codes for an HLH protein that inhibits transcription of target genes by forming inactive heterodimers with other HLH proteins, we are performing a screening searching for Emc partners in the seventh segment. Emc probably interacts here with daughterless, avoiding its binding to the DNA and therefore its function to develop the A7, given that changes in da and emc expression affect the development of the A7 and the rotation of the genitalia. Finally, we are also investigating the mechanisms of A7 elimination and how the interaction of the two tissues (posterior abdomen and genitalia) allows or avoids the rotation of the two ring-shaped genital domains.

VENTURA Patricia1.9

Characterization of primary cell culture from the temperate symbiotic cnidarian, Anemonia viridis

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Keywords : Primary cell culture, Cnidarians, Cell proliferation, Cell viability, Stem cells

Primary cell cultures issued from tentacles of the temperate symbiotic sea anemone, Anemonia viridis, have been recently made available and establish a new experimental model to investigate molecular and cellular events involved in the establishment and maintenance of the symbiosis. Here we propose the optimization of the protocol previously developed and the resulting characterization of isolated animal cells in terms of cell growth, cell viability and cell proliferation, molecular markers and morphological analysis. We found that cell growth is maximal after 10 days in culture and stays high after 17 days. From this moment on, cell growth is reduced as well as cell viability. Following these results, we used BrdU to detect cell proliferation, we tested different germ cell markers (PIWI, VASA) and we investigated the morphology and type of cells in culture using electron microscopy.

Poster Session II, Axis 2
Plasticity and Signaling

DANI Vincent 2.1

Symbiosome membrane characterization, or how to decipher molecular interactions between cnidarians and their dinoflagellate symbionts

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Keywords : symbiosis, proteomics,signaling,migration, recognition

Trophic endosymbioses between cnidarians and photosynthetic dinoflagellates form the key foundation of reef ecosystems. The establishment and maintenance of the symbiotic interaction is dependent on intimate molecular communications, including recognition and tolerance of symbionts, as well as adaptations for mutual transport and exchange of nutritional resources. Cnidarians host their photosynthetic dinoflagellate symbionts in the gastrodermal tissue layer, in a phagosome-derived vacuole called the symbiosome. Despite its critical role, little information is available on the molecular characterization of this symbiotic interface, especially the symbiosome membrane. We report here the results of a multidisciplinary approach to characterize the symbiosome membrane complex in the sea anemone Anemonia viridis, combinating transmission electron microscopy, confocal imaging, shotgun proteomics and MALDI mass spectrometry imaging1–3. We identified 202 proteins that were overexpressed in intact symbiosomes, including proteins involved in cell adhesion and recognition, cytoskeletal remodeling, metabolic exchanges and stress response. Preliminary results also showed that most of the proteins identified at the symbiotic interface are orthologous to human proteins involved in cell growth, migration and invasion processes during tumor progression 4,5. By comparing carcinogenesis and establishment of the symbiosis, these data could then provide greater insight about the biological role of the symbiosome membrane proteins but could also pinpoint new actors in carcinogenesis processes.
This work was supported by the French ANR grant ANR-12-JSV7-0009-01 (inSIDE project)

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2. Are Niemann-Pick type C proteins key players in cnidarian–dinoflagellate endosymbioses? Dani, V., Ganot, P., Priouzeau, F., Furla, P. & Sabourault, C. Mol. Ecol. 23, 4527–4540 (2014).
3. Proteomics and metabolomics provide insight into the Symbiodinium-Anemonia symbiotic interaction. Revel, J. et al. . Symbiosis (2015).
4. On guard: coronin proteins in innate and adaptive immunity. Pieters, J., Müller, P. & Jayachandran R.Nat. Rev. Immunol. 13, 510–518 (2013).
5. Alpha-enolase as a potential cancer prognostic marker promotes cell growth, migration, and invasion in glioma. Song, Y. et al.Mol. Cancer 13, 65 (2014).

DE CIAN Marie-Cécile 2.2

Amplification of R-spondin1 signaling induces granulosa cell fate defects and cancers in mouse adult ovary

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Keywords : RSPO1, WNT/CTNNB1 signaling, ovary, remnant follicles, cancer

R-spondin1 is a secreted regulator of WNT signaling, involved in both embryonic development and homeostasis of adult organs. During ovarian development, Rspo1 is a key factor required for sex determination and differentiation of the follicular cell progenitors (1). The importance of RSPO1 in this process was highlighted by the linkage of mutations of the RSPO1 gene to female-to-male sex reversal (XX men), palmoplantar hyperkeratosis and a predisposition to squamous cell carcinoma in patients (2). However the role of Rspo1 in the physiology of the adult ovary remained to be investigated. In healthy adult ovaries, Rspo1 is down-regulated and maintaining increased RSPO1 expression is associated with ovarian carcinoma. However, it is not clear whether it is a cause or a consequence of the tumorigenic process. To address the role of Rspo1 expression in adult ovaries, we took advantage of an Rspo1 gain-of-function mouse model. The Rspo1 mutant mice are sterile and exhibit abnormal ovarian structures ranging from follicular like lesions to cancers. Our data show that the ectopic expression of Rspo1 in ovaries hampers ovarian cell differentiation and consequently ovarian function. This promotes the persistence of abnormal follicles that eventually become tumors. Altogether, these results suggest that RSPO1 has to be tightly regulated to allow proper ovarian development and maintenance of the healthy ovary.

1 Chassot, A. A. et al. Activation of beta-catenin signaling by Rspo1 controls differentiation of the mammalian ovary. Hum Mol Genet 17, 1264-1277 (2008).
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DRUELLE Noémie 2.3

Pancreatic somatostatin-expressing cells: An untapped source for beta-cell regeneration?

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Keywords : diabetes, plasticity, somatostatin, Pax4, beta-cell

Affecting an expanding number of people, Type 1 Diabetes Mellitus (T1DM) is an autoimmune disorder which results in the loss of insulin-producing beta-cells in the islet of Langerhans. Therefore, approaches aiming at gaining further insight into the molecular mechanisms underlying beta-cell (neo)genesis, during pancreas morphogenesis and throughout adulthood, is of growing interest. Toward this goal, a network involving numerous transcription factors was found to progressively specify endodermal progenitor cells toward the pancreatic, endocrine, and ultimately islet cell fates. Among these, Arx and Pax4, were found to exert key roles for the allocation to the alpha-/PP- and beta-/delta-cell fates, respectively. Importantly, using the mouse as a model, we recently showed that adult alpha-cells can be regenerated and converted into functional beta-like cells upon the sole ectopic expression of Pax4. Surprisingly, an increase in the number of somatostatin-expressing delta-like cells was also noted in these animals, such cells not accumulating over time. One could therefore wonder whether delta-cells could also be regenerated and converted into beta-like cells. To this end, using two different transgenic mouse lines, delta-cell plasticity was investigated by focusing on two hypotheses: (1) Can somatostatin-expressing cells be converted into beta-like cells following Pax4 misexpression in alpha-cells? (2) Do somatostatin+ cells have the ability to convert into beta-like cells upon Pax4 misexpression? Combining lineage tracing experiments and immunofluorescence, we show that Pax4 misexpression in alpha-cells results in the neogenesis and conversion of delta-cells into beta-like cells, such cells exhibiting a ductal ontogeny. Furthermore, our latest results also suggest that the sole ectopic expressing of Pax4 directly in delta-cells is sufficient to induce a massive insulin-producing cell hyperplasia, a significant augmentation in cell proliferation being noted within the ductal epithelium. Our current work will be presented. Taken together, these findings demonstrate a hitherto unrecognized plasticity of adult delta-cells, such cells potentially representing a new source for beta-cell regeneration therapies.

LE THUC Ophélia 2.4

A new role for Monocyte chemoattractant protein 1/CCL2 in promoting weight loss through inhibition of melanin-concentrating hormone-expressing neurons

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Keywords : Feeding behavior, Hypothalamus, Neuroinflammation, Chemokine, MCH neuronal network

Injuries or infections induce endocrine, autonomic and behavioural changes known as “sickness behaviour”. Among them, fever and weight loss appear driven by hypothalamic cytokines, although the exact mechanism remains elusive. Our goal was to investigate the neuroimmunological events driving appetite and weight loss in systemic high-grade inflammation. To study the role of the hypothalamic inflammation in the inflammation-driven weight loss, we performed intracerebroventricular (ICV) injections of lipopolysaccharide (LPS) in C57Bl6/J male mice. Blood and cerebral tissues were collected: mRNA and protein levels of cytokines/chemokines and hypothalamic peptides involved in the regulation of food intake were measured. The effect of inflammatory factors on neuropeptidergic systems involved in food intake was investigated via experiments of hypothalamic neuropeptides release (perifusion) and by electrophysiology. A central injection of LPS provokes a temporal sequence linking activation of pro-inflammatory cytokines and chemokines (notably CCL2) to down-regulation of the orexigenic neuropeptide Melanin-Concentrating Hormone (MCH). CCL2 particular activation kinetics lead us to investigate whether CCL2 could mediate LPS effects. ICV-injected CCL2 triggers neuroinflammation, downregulation of MCH and weight loss. Furthermore, CCL2 reduces KCl-induced MCH release from perifused hypothalamic explants and hyperpolarizes MCH neurons. These effects are reversed by the CCR2 antagonist INCB3344 and in CCR2-deficient mice. Finally, the demonstration that MCH neurons expressed CCL2 receptor confirms that CCL2 could act directly on MCH-neurons promoting inflammation associated weight loss. In conclusion, CCL2 appears as a major intermediate between cytokine-producing cells and neurons in the cascade linking inflammation and eating disorders as LPS-induced weight loss is mediated by CCL2 up-regulation through modulation of the MCH neuronal network.

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MEDINA Clémence 2.5

Characterization of small regulatory RNAs involved in the establishment of giant cells induced by parasitic nematodes of genus Meloidogyne.

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Keywords : Epigenetic, MicroRNA, Arabidospsis thaliana, Nematodes, Phytopathology

Plant response to bioagressors involves modifications of gene expression. Recently, microRNAs have been evidenced as crucial regulators of host gene expression during plants-pathogen interactions. Root-knot nematodes (RKN) are biotrophic plant parasitic worms that transform plant cells from root vascular cylinder into hypertrophied, multinucleate and highly metabolically active giant feeding cells. Since RKN are able to induce the formation of feeding cells in roots of almost all cultivated plants, they are thought to manipulate essential and conserved plant molecular pathways. Previous transcriptomic analyses evidenced that redifferentiation of root cells into giant feeding cells implies transcriptional reprogramming with a large repression of gene expression. Our study aims to investigate the role of microRNAs in the regulation of transcriptional repression observed during the redifferentiation into feeding cells. Small RNAs from Arabidopsis thaliana roots infected with the RKN model species Meloidogyne incognita were sequenced by SOLID technology. As a control, small RNAs from non infected roots were also sequenced. First, a catalog of microRNA expressed in healthy and infected roots was established. Then, microRNAs that are differentially expressed between healthy and infected roots were then identified by EdgeR statistical analyses. Preliminary results identified 24 microRNAs that are differentially expressed in infected roots and statistically relevant. Some of these microRNAs are known to be involved in plant responses to biotic and abiotic stress or in hormone-dependent process. Our results suggest that microRNAs are involved in the regulation of gene expression that results in redifferentiation of root cells into giant feeding cells.

NOVELLI Caterino 2.6

Hedgehog secretion mechanisms in Drosophila epithelial tissues

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Keywords : Hedgehog protein, Dosophila melanogaster, Abdomen epithelial sheet , Wing disc, ESCRT

Hedgehog (Hh) is a secreted morphogen that acts on receiving cells through a concentration gradient. It is covalently modified by two lipids, cholesterol and palmitate, which turn the molecule highly hydrophobic. It can be released through short-, and long-range transport mechanisms from the producing cells to the receiving cells in order to control the growth and the patterning during the development. Currently there are three main systems accounting for Hh transport in the hydrophilic extracellular environment: formation of Hh multimers, integration of Hh into lipoprotein particles (Lpp), and finally exovesicles mediated Hh secretion that requires the function of the ESCRT complex. Recent evidence from our laboratory points out an emerging role of ESCRT proteins in the long-range secretion of Hh. 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 Ihog within exovesicles. The questions are how Hh molecule is released from the producing cells and how the relationship between the different transport mechanisms allows Hh to reach the target cells. To address these questions we work on the epithelial sheet model in the abdomen of Drosophila melanogaster.

PEREA-GOMEZ Aitana 2.7

NOTCH activation interferes with cell fate specification in the gastrulating mouse embryo

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Keywords : NOTCH signalling , NODAL signalling, mouse embryo, mesoderm, anterior-posterior patterning

NOTCH signalling is an evolutionary conserved pathway involved in intercellular communication essential for cell fate choices during development. Although dispensable for early aspects of mouse development, canonical RBPJ-dependent NOTCH signalling has been shown to influence lineage commitment during embryonic stem (ES) cells differentiation. NOTCH activation in ES cells promotes the acquisition of a neural fate, while its suppression favours their differentiation into cardiomyocytes. This suggested that NOTCH signalling is implicated in the acquisition of distinct embryonic fates at early stages of mammalian development. In order to investigate in vivo such a role for NOTCH signalling in shaping cell fate specification, we use genetic approaches to constitutively activate the NOTCH pathway in the mouse embryo. Early embryonic development, including the establishment of anterior-posterior polarity, is not perturbed by forced NOTCH activation. In contrast, widespread NOTCH activity in the epiblast triggers dramatic gastrulation defects. These are fully rescued in a RBPJ-deficient background. Epiblast-specific NOTCH activation induces acquisition of neurectoderm identity and disrupts the formation of specific mesodermal precursors including the derivatives of the anterior primitive streak, the mouse organiser. In addition we show that forced NOTCH activation results in misregulation of NODAL signalling, a major determinant of early embryonic patterning. Our study reveals a previously unidentified role for canonical NOTCH signalling during mammalian gastrulation. It also exemplifies how in vivo studies can shed light on the mechanisms underlying cell fate specification during in vitro-directed differentiation.

ROUMENGOUS Solange 2.8

Reprogramming and Morphogenesis during Drosophila embryo development

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Keywords : Reprogramming, Morphogenesis, JNK, Polycomb, abdominal-A

At the end of Drosophila embryogenesis, dorsal closure (DC) consists of the migration of the two lateral ectodermal sheets and their perfect fusion at the dorsal midline. Perpendicularly to the leading edge (LE) progression, the groove cells form biophysical boundaries that delimitate the segments, each one being divided in an anterior compartment and a posterior one expressing the posterior determinant engrailed (en). As DC progresses, one specific anterior cell, called the mixer cell (MC), localized at the intersection between the groove and the LE, crosses the segment boundary to integrate the adjacent posterior compartment. Surprisingly, mixing only occurs in the abdominal segments A1 to A5. We previously showed that, just before mixing, MCs are reprogrammed to express en de novo in a JNK-dependent manner. Here we deciphered the mechanisms that regulate the mixing downstream of JNK signalling. FISH experiments indicated that MC transition from anterior to posterior fate is accompanied by a release of the en promoter from the repressing Polycomb bodies. We further showed using both loss-of-function and gain-of-function experiments that mixing is under the control of the Hox gene abdominal-A (abd-A), explaining the specific occurrence of the mixing in the central region of the embryo. Overall, these results revealed a intergenic model involving JNK, Pc, en and abd-A in the regulation of segment boundary remodelling, and give new insight on the mechanisms acting during developmental reprogramming, with the perspective to understand reprogramming occurring in pathologies.

RUIZ GARCIA Sandra 2.9

Respiratory epithelium differentiation: looking inside the cell.

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

The lung upper airways are mainly composed of 3 cell types: goblet (or secretory) cells, multiciliated cells and basal cells. Some respiratory diseases such as chronic obstructive pulmonary disease and pulmonary fibrosis, or the inhalation of toxic compounds can lead to the destruction of this epithelium. It is known that the epithelium can be regenerated through processes of proliferation and differentiation of basal cells. However, in case of chronic injuries, the epithelium is not fully restored, with a loss goblet and multiciliated cells, leading to a poorly functional tissue.

During regeneration, the exact steps and cell stages that basal cells go through are not characterized. Hence, our main goal is to clarify the different progenitor cells and molecular pathways that are involved in this process. We are taking advantage of a 3D in vitro model or human airway epithelium regeneration. In order to deal with the heterogeneity of this tissue, we developed a novel approach allowing us to identify the whole transcriptome of each single cell.

Our preliminary results show that this method is able to identify the main cell types of the epithelium once it has reached homeostasis. Indeed, multiciliated, goblets and basal cells can be clearly identified upon transcriptome data analysis. With this single cell approach we are now analyzing the airway epithelium at different stages during regeneration.

Our results at the single-cell resolution should decipher the exact stages of basal cell differentiation and identify novel molecular actors which could be critical to regeneration of an injured epithelium into a fully functional tissue.

Poster Session III, Axis 3
Stress Signaling

BOONE Emilie 3.1

Coupling Drosophila insulin-like peptide 8 expression with organ size sensing.

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Keywords : Hippo, Growth, Dilp8, Coordination, Yorkie

Growth of different body parts needs to be coordinated and scaled with the overall body size to give rise to adults of correct proportions. Since different organs follow autonomous growth programs and therefore grow at different speeds and during distinct stages of development, mechanisms must operate to ensure that each organ has reached an appropriate size before proceeding through developmental transitions. We recently identified Drosophila insulin-like peptide 8 in a genetic screen for molecules coupling organ growth with developmental transitions. Dilp8 is secreted from abnormally growing tissues and acts on the brain complex to delay pupariation. Interestingly, dilp8 expression levels drops at the end of larval development suggesting a direct coupling between autonomous organ growth programs and dilp8 expression. Identifying signals that regulate dilp8expression during normal development is therefore likely to provide a better understanding of organ size assessment mechanisms. The Hippo tumour suppressor pathway plays a major function in restricting organ growth by promoting cell cycle exit and apoptosis. Hippo signalling is highly responsive to the mechanical forces operating in growing organs making it an ideal candidate for assessing organ size. Activation of the Hippo pathway restricts nuclear translocation of the transcriptional co-activator Yorkie, which together with its DNA-binding partner Scalloped, regulates downstream growth-promoting target genes. We show here that Yorkie is necessary and sufficient for inducing dilp8 expression and the associated delay in pupariation. Using a molecular biology approach, we demonstrate that Scalloped/Yorkie binds directly to three Hippo Responsive Elements (HREs) located in the dilp8 promoter. Importantly, a minimum promoter encompassing the three HREs is sufficient to activate dilp8 transcription in vitro and in vivo. We propose that dilp8 is a direct target of the Hippo pathway and its expression levels inversely correlates with organ size allowing a coupling between autonomous organ growth programs and animal maturation.

BRGLEZ Vesna 3.2

On the regulation of group X sPLA2 in breast cancer cells and its role in cell survival via lipid droplet formation and modulation of lipid metabolism

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Keywords : phospholipase A2, cancer, lipid metabolism, epigenetics, proteolytic cleavage

Secreted phospholipases A2 (sPLA2s) are enzymes that catalyse the hydrolysis of membrane phospholipids. Of the 11 sPLA2s in humans, group X (hGX) sPLA2 is of special interest due to its involvement in many (patho)physiological processes, such as the regulation of lipid metabolism, obesity and cancer (1). The regulation of its expression, both on transcriptional and post-translational level, is, however, largely unknown. Similarly, it has only recently been shown that it has a prosurvival role in breast cancer (2), where it induces the formation of lipid droplets (LDs) by an unknown mechanism. The aim of this study was thus to determine the mechanisms of transcriptional, epigenetic and post-translational regulation of hGX sPLA2 in breast cancer, as well as the mechanism of cell death prevention in invasive breast cancer cells. Our results show that the expression of hGX sPLA2 differs in tumour and normal tissue biopsies as well as in breast cancer cell lines of different molecular subtypes. Its transcription is differentially regulated by DNA methylation and histone acetylation, especially in aggressive triple negative cells (3). Post-translationally, the protein is matured by the intracellular cleavage of its propeptide by proprotein convertase furin, as with studies both in vitro with recombinant proenzyme and in transfected HEK293 cells. In invasive breast cancer cells, our results reveal that hGX sPLA2 acts on cell membranes to release free fatty acids, and that its ability to hydrolyse phosphatidylcholine-rich membranes is important for the stimulation of LD formation and its prosurvival action. We also show evidence that hGX sPLA2-stimulated LD biogenesis is accompanied by up-regulation of fatty acid oxidation enzymes and the LD-coating protein perilipin 2, and suppression of lipogenic gene expression. Accordingly, basal and maximal respiration are increased in hGX sPLA2-treated cells. Our results show evidence for complex transcriptional regulation and identify furin as the major protease responsible for the maturation of prohGX sPLA2. We also establish hGX sPLA2 as a novel modulator of lipid metabolism and provide mechanistic details on its prosurvival effects in breast cancer cells.

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DEVECI Derya 3.3

A genetic screen to uncover new signals controlling Drosophila juvenile-maturation transition

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Keywords : Puberty, Growth, Drosophila, Genetics, Steroids

Deciphering the regulatory mechanisms controlling final body size is a fundamental question in biology. In species with so called “determinate growth”, final body size is fixed at the transition from growing juvenile to sexually mature adult, a process known as juvenile maturation transition (JMT). Various external cues such as light, nutrition, oxygen and temperature play a role in the timing of this transition. However, it remains largely unknown which internal sensory mechanisms are involved in the coupling and integration of these cues for the subsequent activation of the cascade of events leading to JMT. In vertebrates, the onset of JMT is triggered by a peak of steroid hormones. In Drosophila melanogaster, and in various other holometabolous insects, a similar mechanism takes place. A peak of prothoracicotropic hormone (PTTH) produced by two pairs of neurons leads to the production of the insect steroid hormone ecdysone. PTTH is one of the first known signals to activate the cascade of events leading to juvenile maturation transition in D. melanogaster. If PTTH production is blocked, a delay is observed in this transition whereas this transition is accelerated upon PTTH overexpression, indicating the importance of PTTH neurons in the integration of internal and/or external cues (Yamanaka, Romero, et al. 2013, Rewitz, et al. 2009, McBrayer, et al. 2007). In order to understand the role of PTTH neurons in controlling JMT, we have conducted a biased RNAi screen in the PTTH neurons for genes whose knocked down delays JMT. By using Gene Ontology (GO) we have selected ~1300 predicted membrane associated protein encoding genes as well as transcription factors specifically expressed in the brain. In a primary screen, we used a strong Gal4 driver expressed in PTTH neurons as well as in some other neurons (NP0423-Gal4), from which we identified 270 hits. Next, we subjected these hits to a second round of screening using a driver specific for PTTH neuron (PTTH-Gal4), which markedly narrowed the number of positive hits to 36. We obtained 6 hits with unknown function or domain, 9 hits involved in synapsis or neuronal function, 8 hits involved in protein modification, 4 hits with heterogeneous functions, 3 nuclear receptors and 9 hits with receptor function. The detailed study of putative receptors controlling the function of PTTH neurons should help us uncover new signals integrated by the PTTH neurons that control the JMT.

GARCIA Elsa 3.4

Innate immune sensing of the Rho GTPase activating toxin CNF1 is counteracted by the α-Hemolysin

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Keywords : Innate immunity, Bacterial virulence sensing, RhoGTPases, Bacterial toxins, Bacteremia

The detection of the activities of pathogen-encoded virulence factors by the innate immune system has emerged as a new paradigm of pathogen recognition(1). Using Drosophila we previously demonstrated that the CNF1 toxin-induced activation of Rac2 is sufficient to initiate an evolutionarily defense signal conserved from flies to mammals(2). Further, we addressed the importance of this innate immune mechanism during infection. We demonstrated the central role of the IL-1β signaling axis and Gr1+ cells in controlling the Escherichia coli burden in the blood of mice in response to the sensing of the Rho GTPase-activating toxin CNF1. Consistently, this innate immune response is abrogated in caspase-1/11-impaired mice or following the treatment of infected mice with an IL-1β antagonist. 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 Rac, ASC and caspase-1 in this pathway. Finally, we found that the α-hemolysin toxin inhibits IL-1β secretion without affecting the recruitment of Gr1+ cells(3). We provide here an example of anti-virulence-triggered immunity counteracted by a pore-forming toxin during bacteremia.

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NAESSENS Elodie 3.5

Aphids reroute one of their immune regulators to repress plant immune responses

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Macrophage migration Inhibitory Factors (MIFs) are pleiotropic cytokines that are produced by multiple cell types in animals to modulate the expression of inflammatory molecules, thus playing either a protective or deleterious role in the immune responses to different pathogens. The cytokines are also produced by parasites of vertebrates, including nematodes, ticks, and protozoa, but are widely absent from insects [1]. We found that a MIF protein is secreted with aphid saliva [2], suggesting a role for the cytokine in plant-aphid interactions. We show that the expression of MIF genes is crucial for aphid survival, fecundity, and feeding on a host plant. The ectopic expression of aphid MIFs in leaf tissues inhibits major plant immune responses, such as the expression of defense-related genes, callose deposition, and hypersensitive cell death. Functional complementation analyses demonstrated that MIF1 allows aphids to exploit their host plants [2]. These findings suggest a so-far unsuspected conservation of infection strategies among parasites of animal and plant species. They show for the first time that an immune-regulatory protein becomes an effector for the modulation of plant immune responses. Our ambition is now to elucidate the physiological activity of the aphid MIF inside host plants. Surprisingly, MIFs are also encoded by plant genomes. The Arabidopsis genome harbors 3 genes [3], and the encoded proteins have striking structural similarities with the secreted aphid MIF. Despite this structural conservation, our first functional analyses indicate that aphid and plant MIFs have antagonistic effects on the plant immune system. Data from these analyses will be discussed.

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TRUONG Nhat My 3.6

Characterization of root-knot nematode effectors targeting host nuclear functions

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Keywords : plant, nematode, interaction, phytopathogene, development

Plant parasitic nematodes are microscopic worms, the most damaging species of which have adopted a sedentary lifestyle within their hosts. These obligate endoparasites are biotrophs that induce the differentiation of root cells into hypertrophied, multinucleate feeding cells. Effectors synthesized in the esophageal glands of the nematode are injected into the plant cells via the syringe-like stylet and may be required to modulate many aspects of plant cell morphogenesis and physiology leading to the establishment of the feeding giant cells. In a search for Meloidogyne incognita effectors targeting to the giant cell nuclei, we used bioinformatics and comparative genomics on EST and NGS datasets to identify genes encoding proteins potentially secreted upon the early steps of infection. We identified genes specifically expressed in the esophageal glands of parasitic juveniles that encode predicted secreted proteins and have a Nuclear Localization Signal and/or a DNA-Binding Domain. In planta nuclear localization of these putative effectors was confirmed using tobacco agro-infiltration, and siRNA soaking was used to silence these genes and study their role during parasitism. Using a yeast-two-hybrid approach and BiFC, we aim at identifying host nuclear functions manipulated by these effectors.

Poster Session IV, Axis 4
Signaling in aging and disease Progression

AL-QARAGHULI Sahar 4.1

Role of Xeroderma pigmentosum fibroblasts in squamous cell carcinoma invasion

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Keywords : squamous cell carcinoma, Xeroderma pigmentosum, Hepatocyte growth factor, nucleotide excision repair mechanisms, Carcinoma collective invasion

Squamous cell carcinoma (SCC) is the most frequent metastatic skin cancer. The etiology of skin SCC is linked to exposure to genetic stress, notably ultraviolet radiation (UVR). Xeroderma pigmentosum type C (XP-C) is a rare genetic disorder characterized by a severe susceptibility to particularly aggressive SCCs following minimal exposure to UVR, hence compromising the life expectancy of patients. XP-C cells are deficient in the nucleotide excision repair mechanism (NER) of DNA lesions introduced at bipyrimidine sequences upon UVR exposure. In addition, we reported that XP-C dermal fibroblasts constitutively expressed a phenotype resembling that of stromal fibroblasts associated to cancer cells (Carcinoma Associated Fibroblasts, CAFs) with accumulation of reactive oxygen species and over expression of matrix metalloproteinase 1. We further explored the phenotype of XP-C fibroblasts. We show here that they constitutively overexpress hepatocyte growth factor/scatter factor (HGF/SF). In organotypic skin cultures, XP-C fibroblasts promoted the invasion of SCC cells. Also scratch healing of SCC cells was enhanced in culture supernatants of XP-C fibroblasts through a mitogenic effect connected to increased ratio of SCC cells in the G2-M phase of the cell cycle. Blockage of c-MET activation prevented invasiveness of SCC cells within dermal equivalent through inhibition of p38 activation by XP-C fibroblasts culture supernatants. Our data indicated for the first time that absence of XPC in fibroblasts leads to overexpression of cell growth stimulators such as HGF and other factors (MMP1) responsible for the formation of a microenvironment permissive towards SCC cells proliferation and invasion. Therapies targeting XP-C fibroblasts may be considered as a way to control cancer in XP patients as well as in patients from the general population suffering from aggressive cancers.

BEN JOUIRA Rania 4.2

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

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Keywords : EMT, Melanoma, resistance, BRAFV600E, ECM

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 the tumor microenvironment in which the extracellular matrix (ECM) is a determinant factor. Both stromal and tumor cells contribute to ECM deposition and remodelling during disease progression. Here, we found that BRAF inhibitor (BRAFi)-resistant melanoma cells, but not BRAFi-sensitive cells, abundantly produced matrix proteins and remodelled a 3D ECM displaying fibronectin (FN) and collagen fibers. The deposition of tumor-derived ECM by BRAFi-resistant cells correlated with an exacerbated invasive mesenchymal phenotype characterized by increased expression of epithelial-to-mesenchymal transition (EMT) markers. The importance of tumor-derived ECM is underlined by the observation that migration and invasion of resistant cells is impaired by FN knock-down. In addition, BRAFi-resistant cells displayed enhanced beta 1 integrin/FAK and RHO GTPase signaling, two pathways involved in mechanotransduction. As a consequence, BRAFi-resistant cells exhibited increased cellular and biochemical response to matrix stiffness. Finally, we found that the 3D ECM produced by resistant cells is able to prevent the antiproliferative effect of the BRAFi Vemurafenib on therapy-sensitive melanoma cells. In conclusion, our results suggest that resistance to targeted therapy is associated with the production by tumor cells of a pathological matrisome that may affect tumor progression and therapeutic response.

CEPPO Franck 4.3

Involvement of the Tpl2 kinase in COX-2 expression and prostaglandin E2 production in adipocytes in response to inflammatory stimuli

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Keywords : obesity, Inflammation, adipocyte, macrophage, Prostaglandin

Obesity is associated with a state of low-grade inflammation of adipose tissue that contributes to its dysfunction. These alterations of adipose tissue predispose to insulin resistance development and to the onset of type 2 diabetes. Bioactive lipid mediators such as prostaglandins E2 (PGE2) have emerged as potent regulator of obese adipocyte inflammation and functions. PGE2 are produced by cyclooxygenases (COX) from arachidonic acid but inflammatory signaling pathways controlling COX-2 expression and PGE2 production in adipocytes remain ill-defined. Here we demonstrated that the MAP3 kinase Tpl2 controls COX-2 expression and PGE2 secretion in adipocytes in response to different inflammatory mediators. We found that pharmacological- or siRNA-mediated Tpl2 inhibition in 3T3-L1 adipocytes decreased by 50% COX-2 induction in response to IL-1beta, TNF-alpha or a mix of the two cytokines. PGE2 secretion induced by the cytokine mix was also markedly blunted. At the molecular level, NF-kappaB was required for Tpl2-induced COX-2 expression in response to IL-1beta but was dispensable for the TNF-alpha or cytokine mix response. In a co-culture between adipocytes and macrophages, COX-2 was mainly increased in adipocytes and pharmacological inhibition of Tpl2 or its silencing in adipocytes markedly reduced COX-2 expression and PGE2 secretion. Further, Tpl2 inhibition in adipocytes reduces by 60% COX-2 expression induced by a conditioned medium from LPS-treated macrophages. Importantly, LPS was less efficient to induce COX-2 mRNA in adipose tissue explants of Tpl2 null mice compared to wild-type and Tpl2 null mice displayed low COX-2 mRNA induction in adipose tissue in response to LPS injection. Collectively, these data established that activation of Tpl2 by inflammatory stimuli in adipocytes and adipose tissue contributes to increase COX-2 expression and production of PGE2 that could participate in the modulation of adipose tissue inflammation during obesity.

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EL HACHEM Najila 4.4

Pro-tumorigenic role of HACE1 in melanoma.

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Keywords : HACE1, RAC1, Migration, Melanoma,

RAC1 is the third most common somatic mutation in melanoma and is considered as an oncogene in this neoplasm. RAC1 functions in several key cellular processes, including cell migration. RAC1 also controls the MAP kinase, cell proliferation and survival. The activity of RAC1, small GTPase, is mainly controlled by GAPS, GEFs and E3 ligases. HACE1, a HECT-domain containing E3-Ubiquitin ligase that interacts preferentially with GTP-bound RAC1, catalyzes its polyubiquitylation and promotes its degradation. Therefore, by favoring the degradation of RAC1, HACE1 might act as a tumor suppressor, as this has been described in several human cancers. The role of HACE1 in melanoma has not been studied so far. In multiple melanoma cell lines and in primary melanoma cells, RNAi-mediated depletion of HACE1 does not affect cell proliferation, but inhibits cell migration. Overexpression of HACE1, increases the colony formation and migration of melanoma cells. Even though, we have been able to confirm that HACE1 target active RAC1 in melanoma cells, it seems that HACE1 behave as an oncogene rather than as a tumor suppressor, in melanoma cells. This hypothesis was confirmed by the analysis of public clinical data, showing that HACE1 expression correlates negatively with the survival of patients with melanoma. To gain further insights into the molecular mechanism downstream HACE1 in melanoma cells, we studied the effect of HACE1 inhibition on the main signaling pathways. HACE1-silencing decreases ERK and AKT phosphorylation that might explain the observed inhibition of migration, in the same conditions. Co-immunoprecipitation assays allowed us to identify new HACE1 interactors, providing thereby a direct molecular link between HACE1 and melanoma cell migration. Together, our results provide new insights into melanoma cell migration and establish a new potential role of the HACE1, E3 ubiquitin-ligase in this process. Our works support a critical tumorigenic role for HACE1 in melanoma progression.

GALANTONU Ramona Nicoleta 4.5

A link between steroid signaling pathways and L1 retrotransposition

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Keywords : retrotransposition, steroids, interaction, integration, 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 measure 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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GILLERON Jerome 4.6

Rab4b as a master regulator of T cell biogenesis and function tunes adipose tissue inflammation and insulin resistance

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Keywords : Rab proteins, Endocytic trafficking, Obesity-induced insulin resistance, T cell biogenesis, Differentiation

The small GTPase Rab4b was thought to be a major regulator of endosomal recycling. However, the role of this protein from cellular function toward the establishment and/or the maintenance of tissues and organisms remains to be determined. Several lines of evidence were proposing this protein as a key player in invertebrates and mammals immunity. Moreover, Rab4b is highly expressed in immune cells such as T cells. To elucidate the role of Rab4b in immunity, we generated mice invalidated for this protein specifically in T cells. Strikingly, the mice presented a deep lymphopenia due to apoptosis during thymic selection. Moreover, we evidenced that the T cells, that overcome the selection, failed to differentiate properly. Indeed, the invalidation of Rab4b in T lymphocytes skewed the differentiation of naïve Th0 towards Th17 at the expense of regulatory T cells. Outstandingly, this defect in T cells is sufficient to dramatically increase local inflammation within the adipose tissue leading to adipocyte differentiation failure and to a lack of adipose tissue expandability, which are responsible for the establishment of insulin resistance. Interestingly, we found that the expression of Rab4b is decreased in T cells isolated from blood circulation and adipose tissue of high fat diet-induced obese mice compared to lean control mice. On the one hand, this work thus reveals that Rab4b is a major regulator of T cell biogenesis and function, and on the other hand gives evidence that Rab4b could be involved in the development of obesity-induced insulin resistance.

GUAL Philippe 4.7

CD44 is an important actor in non alcoholic steatohepatitis

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Keywords : Liver complications, obesity, inflammation, macrophages

CD44 is expressed on many immune cells that contribute to inflammation. Mainly based on animal data, CD44 plays an important role in adipose tissue inflammation in obesity and hepatic leukocyte recruitment in a lithogenic context. However, its role in hepatic inflammation/fibrosis in mouse model of steatohepatitis (NASH) and its relevance in human have not yet been investigated. We here reported that liver injury (AST, ALT levels), steatosis, inflammation (inflammatory foci, MCP1, TNFα and IL1β expression) and hepatic infiltration of pro-inflammatory M1 macrophages (F4/80/CD11c+ cells) strongly decreased in cd44-/- mice compared with wild-type (Wt) mice upon methionine- and choline-deficient diet (MCDD) challenge. The silencing of CD44 strongly decreased the expression of MCP1 receptor (CCR2) in M1 macrophages. Neutralization of CD44 by specific antibody partially corrected the liver injury, hepatic inflammation (Inflammatory foci), M1 macrophages recruitment and MCP1 expression induced by MCDD. In line with decreased inflammation and liver injury, CD44 deficiency prevented liver fibrosis, stellate cells activation and hepatic expression of TGFβ, TIMP1 and Col1A1. In the context of human NAFLD, hepatic CD44 expression was strongly upregulated in NASH patients and correlated with NAS, ballooning and ALT and hepatic MCP1 and CD68 (marker of macrophages) expression. Correction of NASH by bariatric surgery was associated with a strong decrease in the hepatic CD44+ macrophages. In conclusion, human and experimental data suggest that CD44 is a key player in NAFLD pathogenesis and its targeting partially corrects NASH.

KOOTAR Scherazad 4.8

To understand the functional role of Hippocampal Glucocorticoid Receptor in Alzheimer's Disease.

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Keywords : Alzheimer's disease, Hippocampus, Synaptic plasticity, Corticosterone, Glucocorticoid receptors

It's well known that the hippocampus is one of the primary targets affected in early Alzheimer's disease (AD) leading to loss of memory and cognitive function. There has been substantial progress in the therapeutic approaches in AD but still many molecular mechanisms remain unclear to develop adequate treatments. There is strong evidence that both amyloid-beta (Ab) and the main stress hormone, cortisol (corticosterone (CORT) in mice), are abnormally elevated during the early phase of AD. Corticosterone is regulated by the Hypothalamus-pituitary-adrenal (HPA) axis through the mineralocorticoid and glucocorticoid receptors (MRs and GRs). Recent studies from the lab have shown high levels of CORT affects the episodic memory and synaptic plasticity in the hippocampus of 4 months old Tg2576 mice, a well-known AD mouse model. To understand better the role of GRs in the CA1 region of the hippocampus, we have crossed this model with the GR-floxed mice. As expected with the Tg2576 mice, the new transgenic mouse line shows an increase in CORT levels when compared to the control mice and exhibits synaptic dysfunction in the CA1 region of hippocampus. Using conditional genetic ablation of the GR in the CA1 by in vivo Cre virus injections, we observed down regulation of GR expression in this region by immunostaining and we are currently testing for rescue of the synaptic deficits in the absence of GR. Depending on these results we shall investigate the rescue of episodic like memory deficit upon down regulation of GR in the CA1 region of these transgenic mice. Together, these data shall indicate the importance of GR function in mediating the synaptic plasticity and memory deficits in this Alzheimer's disease mouse model.

This work is supported by the Labex SIGNALIFE, CNRS ATIP, Fondation Plan Alzheimer and France Alzheimer. 1.Subchronic glucocorticoid receptor inhibition rescues early episodic memory and synaptic plasticity deficits in a mouse model of Alzheimer's disease. Fabien Lante´ 1,2, Magda Chafai1,3, Elisabeth Fabienne Raymond1,3, Ana Rita Salgueiro Pereira1,3, Xavier Mouska1, Scherazad Kootar1, Jacques Barik1, Ingrid Bethus1 and Hélène Marie*1 (2015), Neuropsychopharmacology.

LEBEAUPIN Cynthia 4.9

ER stress induces inflammasome activation and hepatocyte death

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Keywords : ER stress, Inflammasome, Cell Death, Obesity, Chronic liver disease

Obesity is a major health problem which dramatically affects liver function and leads to Non-Alcoholic Fatty Liver Diseases (NAFLD) ranging from benign steatosis (hepatic triglyceride accumulation) to harmful non-alcoholic-steatohepatitis (NASH). Endoplasmic reticulum (ER) stress can lead to insulin resistance, inflammation and apoptosis, pathophysiological factors involved in NAFLD progression. Also, studies suggest the inflammasome plays a role in multiple manifestations of the metabolic syndrome. Nevertheless, the connection between ER stress and inflammasome signaling pathways remains unexplored in NAFLD. We hypothesized that ER stress could lead to NLRP3 inflammasome activation and hepatocyte death associated with steatohepatitis progression. Indeed, the analysis of human steatohepatitis liver biopsies showed a correlation between the upregulation of inflammasome and ER stress markers, as well as liver injury. In livers from obese mice, we showed that the administration of tunicamycin or LPS results in IRE1α and PERK activation, leading to the overexpression of CHOP. This, in turn, activates the NLRP3 inflammasome, subsequently initiating hepatocyte death. The central role of CHOP in mediating the activation of proinflammatory caspases and cell death was characterized by performing knockdown experiments in primary mouse hepatocytes. In contrast, the ER stress inhibitor TUDCA blocked tunicamycin and/or LPS challenges and notably led to CHOP downregulation, reduced caspase-1, caspase-11, caspase-3 activities, lowered interleukin-1β secretion and rescue from cell death. Thus, our data demonstrate that ER stress leads to hepatic NLRP3 inflammasome pyroptotic death, contributing as a novel mechanism of inflammation-mediated liver injury in chronic liver diseases.

PROD'HOMME Virginie 4.10

Role of Lymph Node fibroblasts in the establishment of the pre-metastatic niche and drug resistance of metastatic melanoma.

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Keywords : Fibroblastic reticular Cell, Lymph node, Metastasis, Melanoma, Therapeutic resistance

The behaviour of cancer cells is largely influenced by their microenvironment, including stromal cells and extracellular matrix (ECM). Our team is particularly interested in the crosstalk between cancer cells and the lymph node (LN) microenvironment in melanoma, an aggressive form of skin cancer characterized by its high metastatic competence and therapeutic resistance. Management of melanoma patients was revolutionized few years ago by the use of new therapies (Vemurafenib and Dabrafenib) targeting the most frequent mutation found in cutaneous melanomas, BRAFV600E. However, 30% of metastatic patients don't respond to these treatments and most responding patients relapse after a few months following acquisition of resistance. The LN is the first tissue targeted by metastatic melanoma and is composed of immune cells, endothelial cells and very specific resident fibroblasts called Fibroblastic Reticular Cells (FRC). Our goal is to understand the implication of FRC in the invasion, proliferation, survival, immune escape and therapeutic resistance of melanoma in the LN metastatic niche. Our preliminary data in an immune competent mice model of melanoma pointed out the activation of FRC in pre-metastatic LN. We observed in vitro that the actomyosin contractile phenotype, the cytokine/chimiokine secretion and the production of ECM proteins of human naïve FRC were modified following stimulation by melanoma secretome. In a panel of skin or LN melanoma patient biopsies, we then found that classical markers of activated fibroblasts associated to cancer distinguished very different profiles between Melanoma-Associated Fibroblasts (MAF) of skin or LN origins. Both biochemical and mechanical properties of the fibroblast-derived ECM also differed remarkably depending on the skin or LN origins of MAF. Notably, the matrix derived from LN fibroblasts was able to mediate resistance of BRAFV600E melanoma cells to Vemurafenib.
Our aim is now to identify candidates involved in the FRC activation in pre-metastatic LN and in drug tolerance mediated by the fibroblast-derived ECM in LN. Our work will bring a more comprehensive view of tumor-stroma communications 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.

This work is supported by the Fondation ARC and the Fondation de France.

ROUANET Sophie 4.11

Deciphering molecular events occurring in keratinocytes upon solar simulated radiations

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Keywords : Xeroderma pigmentosum, carcinogenesis, UV, chronic irradiations,

Xeroderma pigmentosum (XP) is a rare, recessive genodermatosis characterized by an extreme photosensitivity and a high susceptibility to the development of malignant epidermal carcinomas in photoexposed skin. In absence of photo protection, young patients present aggressive tumors before the age of 8, leading to compromised health conditions and life expectancy. This disease is due to defective nucleotide excision repair of DNA lesions occurring upon solar radiation. XP-C is the most frequent form of the disease in our countries. In our laboratory, we use XP-C primary skin keratinocytes to model genomic hypermutability as well as molecular and cellular events leading to aggressive cutaneous cancers. As chronic solar irradiations are responsible for the majority of SCC, which relative frequency is much higher in XP patients than in general population, we analyzed the effects of chronic solar simulated radiations (SSR) on WT and XP-C keratinocytes in culture, using chronic low dose of single SSR per week for 8 weeks (100 J UVB/m²). We have shown the emergence of atypical clones of XP-C keratinocytes populations while SSR irradiation of WT cells resulted in clonal transition. Atypical clones exhibited significant increase in growth and clonogenic potential compared to the WT suggesting a selective advantage of growth after iterative irradiation (IRR) of XP-C cells (from 10% after 4 IRR to 25% after 8 IRR). Karyotype analyzes of XP-C clones revealed normal chromosomal distribution, suggesting occurrence of point mutations rather than gross genetic rearrangement. Cell cycle analyses of those clones showed higher rates of cells in G2/M phases. We are currently analyzing 1) the genetic status of 400 oncogenes and tumor suppressor genes frequently mutated in tumor cells, and 2) the patterns of gene expression in those clones. Deciphering molecular and cellular modifications occurring in cells during iterative exposure toward UV carcinogenesis will be a great help to better diagnose the evolution of skin cancers and to develop drugs targeting the specific pathways affected in both XP patients and in individuals of the general population.

SULTANA Tania 4.12

Does the genomic context influences integration site selection by human L1 retrotransposons

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Keywords : Retrotransposons, L1 target site preference, ATLAS-seq

Retrotransposons are mobile genetic elements that employ an RNA intermediate and a reverse transcription step for their replication. Long Interspersed Nuclear Elements-1 (LINE-1 or L1) form the only autonomously active retrotransposon family in humans. Although most copies are defective due to the accumulation of mutations or deletions, each individual genome contains an average of 100 retrotransposition-competent L1 copies, which contribute to the dynamics of our contemporary genome. The core retrotransposition machinery is a ribonucleoprotein particle (RNP) containing the L1 mRNA, and with endonuclease and reverse transcriptase activities. It initiates reverse transcription directly at genomic target sites upon endonuclease cleavage, a process known as target-primed reverse transcription (TPRT). The sequence specificity of the endonuclease, as well as base-pairing between the L1 mRNA and the target site, contributes to L1 target choice. However, whether L1 exhibits a preference for specific genomic locations beyond small sequence determinants is currently unknown. To address this question, we induce retrotransposition by transfecting a plasmid-borne L1 element into human cell lines. This copy contains an artificial sequence tag, which allows us to discriminate novel L1 insertions from existing ones. The chosen cell lines have been extensively studied in the context of the ENCODE project. Hence large ChIP-seq data for various histone modifications or transcription factor binding sites are publicly available. De novo integration events are then mapped by deep-sequencing using a dedicated method developed in the laboratory (ATLAS-seq). Finally, new integration sites will be compared to genomic features (such as gene body, introns, exons, promoters, histone marks, transcription factor binding sites, transcription start sites, replication origins, DNAse sensitivity, etc). This study will highlight how the genomic context influences L1 target site preference in vivo.

Poster Session V, Axis 5
New principles in signaling and applications

ALMEIDA Sofia 5.1

Modeling and coupling biorhythms

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Keywords : cell cycle, circadian clock, mathematical modeling, signaling pathways, coupled oscillators

Biorhythms such as the cell cycle and the circadian clock are essential to guarantee the proper functioning of the mammalian cell. These are controlled and regulated by a series of signaling pathways, that arise from a variety of biological mechanisms. We focused on identifying the main mechanisms behind cell cycle rhythms and propose a mathematical model to describe them. The model is successful in reproducing oscillatory behaviors consistent with cell cycle periods, while maintaining a good connection with the reality of biological phenomena. We analyze the main properties of this model and perform sensitivity analysis. The cell cycle is here interpreted as a cellular oscillator that may later be coupled with the circadian clock oscillator.

This work is supported by Laboratory of Excellence Labex SIGNALIFE “Network for Innovation on signal Transduction Pathways in Life Sciences”, Grant ANR-11-LABX-0028-01.

HASANOVIC Anida 5.2

Patched as a new therapeutic target for adrenocortical cancer

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Keywords : adrenocortical cancer, Patched, multidrug transporter, drug efflux, doxorubicin

Adrenocortical cancer has very poor prognosis with an estimated survival rate of 35% in 5 years and until today pharmacological therapy is based on mitotane in combination with doxorubicin, cisplatin and etoposide. Unfortunately, this treatment has very low response rate and high toxicity on various organ systems. We have showed that members of Hedgehog pathway and its receptor Patched are overexpressed in human adrenocortical H295R cells. This was also proved by a team of clinicians on cohort of 99 patients. We have showed that Patched is a multidrug transporter involved in the resistance of cancer cells to chemotherapy. Therefore, our laboratory is interested in developing a new treatment for adrenocortical cancer by blocking drug efflux activity of Patched. During the past few months we have done the screening of compounds from the chemical library in combination with doxorubicin on human adrenocortical H295R cells and yeast expressing human Patched. We observed that some compounds inhibit doxorubicin efflux activity of Patched and increase the effect of doxorubicin on viability, proliferation, clonogenicity and apoptosis of H295R cells. Ongoing project is testing these compounds in vivo.

LUKIANETS Nikita 5.3

Cluster analysis in defining morphological neuronal identity

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Keywords : clustering, machine learning, neuronal identity, neuron morphology, brain development

The diversity of cell morphology present within a given substructure of the central nervous system reflects a part of its computational complexity. Neuron morphology is a spatial fingerprint that determines organizational principles of the brain by directly influencing connectivity and a signal integration properties. Different parameters of the neuron morphology are commonly used by neuroanatomists as one of the discrimination and classification features of cell populations. For example, characterization of dendritic architecture is important as it represents the input region of the neurons and describes a complex computational unit. Another example of such distinctive features is the soma size, which could define local integration capability, or the number of branching points that directly impact neuron backpropagation properties. In this work, we present a numerical approach using semiautomatic image reconstruction and data clustering techniques to define the morphological identity of different cortical pyramidal cell subclasses. One of our objectives is to study the morphological features of cells co-expressing molecular markers of projection neurons in the somatosensory cortex. Overall, our methodology allowed identifying and linking morphology to molecular identity of cells in a robust and unbiased manner.

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24	BIANCHINI	Laurence	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	laurence.bianchini@unice.fr	04 93 37 70 09	No			
25	BJORDAL	Marianne	iBV - Institut de Biologie Valrose	Post-doc	bjordal@unice.fr	04 92 07 64 58	Yes			
26	BONCHE-JOUTEUR	Raphaël	iBV - Institut de Biologie Valrose	PhD student	rbonche@unice.fr	06 45 61 55 94	No			
27	BOONE	Emilie	iBV - Institut de Biologie Valrose	Researcher / Lecturer	eboone@unice.fr	06 07 95 36 03	Yes		Poster	3
28	BOSCARI	Alexandre	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	alexandre.boscari@sophia.inra.fr	04 92 38 66 37	Yes	Scientific Committee		
29	BOSSOWSKI	Józef	C3M - Centre Méditerranéen de Médecine Moléculaire	Labex PhD Student	jpbossowski@unice.fr	07 58 29 34 21	Yes			
30	BOST	Frédéric	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	bost@unice.fr	04 89 06 42 29	Yes			
31	BOUGET	Gwenaelle	C3M - Centre Méditerranéen de Médecine Moléculaire	Labex PhD Student	gwenaelle.bouget@unice.fr	04 89 06 42 34	Yes			
32	BOURDELY	Pierre	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	bourdely@ipmc.cnrs.fr	06 50 82 83 43	Yes			
33	BOUROUIS	Marc	iBV - Institut de Biologie Valrose	Researcher / Lecturer	bourouis@unice.fr	06 08 06 79 85	Yes			
34	BOYER	Laurent	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	boyerl@unice.fr	04 89 06 42 44	Yes	Scientific Committee	Talk	3
35	BREST	Patrick	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	brest@unice.fr	334 92 03 12 45	Yes			
36	BRGLEZ	Vesna	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Post-doc	brglez@ipmc.cnrs.fr	336 95 94 90 95	Yes		Poster	3
37	CABRAL DO NASCIMENTO	Danila	ISA - Institut Sophia Agrobiotech	PhD student	danila.cabraln@gmail.com	5567 91 27 98 02	Yes			
38	CAPOVILLA	Maria	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	maria.capovilla@sophia.inra.fr	06 33 93 29 54	Yes			
39	CASTAGNOLA	Sara	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	castagnola.sara@gmail.com	07 70 41 97 11	Yes			
40	CATOZZI	Simona	INLN - Institut Non Linéaire de Nice	PhD student	simona.catozzi@inln.cnrs.fr	06 98 22 90 95	No		Talk	5
41	CEPPO	Franck	C3M - Centre Méditerranéen de Médecine Moléculaire	Post-doc	ceppo@ipmc.cnrs.fr	04 93 95 77 80	Yes		Poster	4
42	CHAVIGNY	Pascal	ISA - Institut Sophia Agrobiotech	Engineer	pascal.chavigny@sophia.inra.fr	04 92 38 64 42	Yes	Organizing Committee		
43	CHOUGULE	Anil	iBV - Institut de Biologie Valrose	Labex PhD Student	anilmchougule@gmail.com	07 83 26 41 61	Yes			
44	COLLOMBAT	Patrick	iBV - Institut de Biologie Valrose	Researcher / Lecturer	collombat@unice.fr	04 92 07 64 16	Yes	SIGNALIFE Keynote	Talk	2
45	COLOMBANI	Julien	iBV - Institut de Biologie Valrose	Researcher / Lecturer	colomban@unice.fr	04 92 07 64 43	Yes			
46	CORMONT	Mireille	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	cormont@unice.fr	04 89 06 42 34	Yes			
47	COSTA	Tiago	ISA - Institut Sophia Agrobiotech	PhD student	skarlaos@gmail.com	06 42 14 73 35	Yes		Poster	1

No.	Last Name	First Name	Research institute or laboratory	Function	Email	Phone	SIGNALIFE member	Special participant	Presentation	Axis
48	COURTNEY	Monica	iBV - Institut de Biologie Valrose	Post-doc	monica.courtney@unice.fr	04 92 0764 56	Yes			
49	CZERKINSKY	Cecil	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	czerkinsky@ipmc.cnrs.fr	04 93 95 77 63	No	Organizing Committee		
50	D'ANGELO	Gisela	iBV - Institut de Biologie Valrose	Researcher / Lecturer	gisela.dangelo@unice.fr	04 92 07 64 58	Yes			
51	DANI	Christian	iBV - Institut de Biologie Valrose	Researcher / Lecturer	dani@unice.fr	04 93 37 7647	Yes	Chairman		
52	DANI	Vincent	SYMAR - Symbiose Marine	PhD student	vincent.dani@unice.fr	06 09 40 07 71	No		Poster	2
53	DE ALMEIDA-ENGLER	Janice	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	janice.almeida-engler@sophia.inra.fr	06 18 25 03 30	Yes			
54	DE CIAN	Marie-Cecile	iBV - Institut de Biologie Valrose	Researcher / Lecturer	mcdecian@unice.fr	06 22 10 80 36	Yes		Poster	2
55	DE GARAY	Tomás	IRCAN - Institute for Research on Cancer and Aging, Nice	Labex PhD Student	tdegaray@unice.fr	07 50 37 89 34	Yes		Poster	1
56	DEBREUIL	Julien	IRCAN - Institute for Research on Cancer and Aging, Nice	Post-doc	debreuil.julien@gmail.com	07 82 87 05 04	No			
57	DECKERT	Marcel	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	deckert@unice.fr	04 89 06 43 13	Yes			
58	DEGOUT	Marie	C3M - Centre Méditerranéen de Médecine Moléculaire	Technician	Marie.degout@unice.fr	04 89 06 43 43	No	Organizing Committee		
59	DELANOUE	Rénald	iBV - Institut de Biologie Valrose	Researcher / Lecturer	delanoue@unice.fr	04 92 07 64 43	Yes			
60	DELAUNAY	Franck	iBV - Institut de Biologie Valrose	Researcher / Lecturer	delaunay@unice.fr	04 92 07 68 38	Yes			
61	DELGADILLO	Roberto F	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Post-doc	delgadillo@ipmc.cnrs.fr	07 81 21 37 44	Yes		Poster	1
62	DEVAUX	Nadège	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Engineer	devaux@ipmc.cnrs.fr	04 93 95 77 50	Yes			
63	DEVECI	Derya	iBV - Institut de Biologie Valrose	Labex PhD Student	DeryaDeveci@gmail.com	07 82 83 78 39	Yes		Poster	3
64	DJERBI	Nadir	IRCAN - Institute for Research on Cancer and Aging, Nice	Technician	nadir.djerbi@unice.fr	04 93 37 70 17	Yes	Organizing Committee		
65	DRUELLE	Noémie	iBV - Institut de Biologie Valrose	PhD student	noemie.druelle@gmail.com	06 17 34 45 16	Yes		Poster	2
66	DUMORTIER	Olivier	IRCAN - Institute for Research on Cancer and Aging, Nice	Post-doc	olivier.dumortier@unice.fr	06 26 09 11 48	Yes			
67	EFTHYMIOU	Georgios	iBV - Institut de Biologie Valrose	Labex PhD Student	Georgios.EFTHYMIOU@unice.fr	07 70 38 63 46	Yes			
68	EL HACHEM	Najla	C3M - Centre Méditerranéen de Médecine Moléculaire	Labex PhD Student	najla.el-hachem@unice.fr	04 89 06 43 26	Yes		Poster	4
69	FABRIS	Gaia	IRCAN - Institute for Research on Cancer and Aging, Nice	Labex PhD Student	fabris.ga@gmail.com	07 70 37 98 31	Yes			
70	FALVEY	Aidan	ISA - Institut Sophia Agrobiotech	Labex PhD Student	Aidan.FALVEY@unice.fr	06 31 26 24 66	Yes			
71	FAVERY	Bruno	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	favery@sophia.inra.fr	04 92 38 64 64	Yes			
72	FAYAD	Racha	iBV - Institut de Biologie Valrose	Labex PhD Student	racha.fayad1@gmail.com	06 19 64 04 74	Yes			
73	FELSKE	Torsten	iBV - Institut de Biologie Valrose	Labex PhD Student	torstenfelske@gmx.de	49176 63 60 15 10	Yes			
74	FERAL	Chloe	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	chloe.feral@inserm.fr	04 93 37 76 18	Yes			
75	FERNANDES DE ABREU	Diana Andrea	ISA - Institut Sophia Agrobiotech	Post-doc	diana.fernandes@sophia.inra.fr	04 92 38 64 18	yes		Talk	2
76	FOLLETTE	Peter	iBV - Institut de Biologie Valrose	Researcher / Lecturer	follette@unice.fr	06 82 52 79 17	Yes			
77	FORCIOLI-CONTI	Nicolas	iBV - Institut de Biologie Valrose	PhD student	nforcioliconti@gmail.com	06 63 57 58 14	Yes			
78	FORMICOLA	Nadia	iBV - Institut de Biologie Valrose	Labex PhD Student	Nadia.formicola@unice.fr	3934 07 07 61 89	Yes			
79	FRIEDMAN	Jeffrey	The Rockefeller University, NY, USA	Researcher / Lecturer	friedj@mail.rockefeller.edu	121 23 27 88 00	No	Invited Keynote	Talk	2
80	FURLA	Paola	SYMAR - Symbiose Marine	Researcher / Lecturer	furla@unice.fr	04 92 07 68 30	No			
81	FÜRTHAUER	Maximilian	iBV - Institut de Biologie Valrose	Researcher / Lecturer	furthauer@unice.fr	04 92 07 64 39	Yes			
82	GAGGIOLI	Cedric	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	gaggioli@unice.fr	04 93 37 77 53	Yes			
83	GALANTONU	Ramona Nicoleta	IRCAN - Institute for Research on Cancer and Aging, Nice	Labex PhD Student	ramona.galantonu@unice.fr	06 34 48 69 82	Yes		Poster	4
84	GALLET	Armel	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	gallet@unice.fr	04 92 38 65 19	No			
85	GANOT	Philippe	Centre Scientifique de Monaco	Post-doc	pganot@centrescientifique.mc	+377 97 77 44 76	No			
86	GARCIA	Emilien	C3M - Centre Méditerranéen de Médecine Moléculaire	PhD student	egarcia@unice.fr	06 36 53 13 73	Yes			
87	GARCIA	Elsa	C3M - Centre Méditerranéen de Médecine Moléculaire	PhD student	elsa.garcia@unice.fr	04 89 06 42 44	Yes		Poster	3
88	GATTI	Jean-Luc	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	jean-luc.gatti@sophia.inra.fr	06 26 99 83 98	Yes	Scientific Committee		
89	GILLERON	Jerome	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	gilleron@unice.fr	04 89 06 42 34	Yes		Poster	4
90	GILLOT	isabelle	iBV - Institut de Biologie Valrose	Researcher / Lecturer	gillot@unice.fr	04 92 07 64 22	Yes			
91	GILSON	Eric	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	Eric.Gilson@unice.fr	06 07 27 29 73	Yes	SIGNALIFE Keynote	Talk	3
92	GIRARD	Christophe	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	christophe.girard@unice.fr	04 89 06 43 13	Yes	Scientific Committee		
93	GUAL	Philippe	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	gual@unice.fr	04 89 06 42 23	Yes		Poster	4
94	GUY	Nicolas	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Engineer	nguy@ipmc.cnrs.fr	04 93 95 77 57	Yes			
95	HALLIN	Johan	IRCAN - Institute for Research on Cancer and Aging, Nice	Labex PhD Student	johan.h.hallin@gmail.com	06 84 91 74 19	Yes			

No.	Last Name	First Name	Research institute or laboratory	Function	Email	Phone	SIGNALIFE member	Special participant	Presentation	Axis
96	HASANOVIC	Anida	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	ahasanovic@unice.fr	07 82 72 40 95	Yes		Poster	5
97	HICHRI	Maha	TIRO - Transporteurs, Imagerie et Radiothérapie en Oncologie	PhD student	hichri.maha@gmail.com	06 08 85 14 78	No			
98	HINAULT	Charlotte	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	hinault@unice.fr	04 93 37 77 33	Yes			
99	HUEBER	Anne-Odile	iBV - Institut de Biologie Valrose	Researcher / Lecturer	hueber@unice.fr	04 92 07 64 47	Yes			
100	JAMECNA	Denisa	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	jamecna@ipmc.cnrs.fr	4219 10 26 28 07	Yes			
101	JAUBERT-POSSAMAI	Stéphanie	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	stephanie.jaubert@sophia.inra.fr	06 62 21 45 49	Yes	Scientific Committee		
102	JUAN	Thomas	iBV - Institut de Biologie Valrose	PhD student	thomas.juan@unice.fr	06 33 43 72 05	Yes		Talk	1
103	JUSTINO	Joana	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	joanafjustino@gmail.com	3519 36 11 69 14	Yes			
104	KAMINSKI	Lisa	C3M - Centre Méditerranéen de Médecine Moléculaire	PhD student	pinkounet@hotmail.fr	04 89 06 42 29	Yes			
105	KELLER	Harald	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	harald.keller@sophia.inra.fr	04 92 38 65 94	Yes	Scientific Committee		
106	KHOU	Sokchea	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	khousokchea@hotmail.com	07 53 40 01 28	Yes			
107	KIM	Chami	iBV - Institut de Biologie Valrose	Labex PhD Student	kim.chami@sophia.inra.fr	06 68 64 27 17	Yes			
108	KOOTAR	Scherazad	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	kootar@ipmc.cnrs.fr	06 08 05 61 31	Yes		Poster	4
109	KUZET	Sanya	IRCAN - Institute for Research on Cancer and Aging, Nice	Labex PhD Student	sanya.kuzet@unice.fr	07 70 45 28 20	Yes			
110	LAI	HueiYi	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	okook22@hotmail.com	06 66 59 82 20	Yes			
111	LALLI	Enzo	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	ninino@ipmc.cnrs.fr	04 93 95 77 55	Yes			
112	LE THUC	Ophélia	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	PhD student	lethuc@ipmc.cnrs.fr	04 93 95 77 41	Yes		Poster	2
113	LEBEAUPIN	Cynthia	C3M - Centre Méditerranéen de Médecine Moléculaire	Labex PhD Student	Cynthia.LEBEAUPIN@unice.fr	06 42 02 08 93	Yes		Poster	4
114	LEMICHEZ	Emmanuel	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	lemichez@unice.fr	06 65 72 90 60	Yes	Chairman		
115	LEOPOLD	Pierre	iBV - Institut de Biologie Valrose	Researcher / Lecturer	leopold@unice.fr	04 92 07 64 45	Yes			
116	LITI	Gianni	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	gianni.liti@unice.fr	07 78 81 09 67	Yes			
117	LOTOTSKA	Liudmyla	IRCAN - Institute for Research on Cancer and Aging, Nice	Labex PhD Student	Liudmyla.Lototska@unice.fr	04 93 37 70 74	Yes			
118	LOTTE	Romain	C3M - Centre Méditerranéen de Médecine Moléculaire	PhD student	lotte.r@chu-nice.fr	04 89 06 42 62	Yes			
119	LOUDHAIEF	Rihab	ISA - Institut Sophia Agrobiotech	PhD student	Rihab.Loudhaief@sophia.inra.fr	06 23 50 37 85	No			
120	LUKIANETS	Nikita	iBV - Institut de Biologie Valrose	Labex PhD	nikita.lukianets@unice.fr	07 52 62 60 26	Yes		Poster	5
121	LUTON	Frédéric	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	luton@ipmc.cnrs.fr	04 93 95 77 70	Yes			
122	MAGNALDO	Thierry	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	tmagnaldo@unice.fr	06 79 80 47 90	Yes	Scientific Committee		
123	MALLAVIALLE	Aude	C3M - Centre Méditerranéen de Médecine Moléculaire	Engineer	mallavia@unice.fr	04 89 06 43 13	Yes			
124	MANNI	Marco	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Post-doc	manni@ipmc.cnrs.fr	07 83 58 62 08	No		Poster	1
125	MARI	Bernard	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	mari@unice.fr	06 18 54 06 75	Yes			
126	MARIE	Helene	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	marie@ipmc.cnrs.fr	04 93 95 34 40	Yes			
127	MARTIN	Virginie	C3M - Centre Méditerranéen de Médecine Moléculaire	Technician	Virginie.MARTIN@unice.fr	04 89 06 42 69	No	Organizing Committee		
128	MARTIN	Stéphane	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	martin@ipmc.cnrs.fr	04 93 95 34 61	Yes			
129	MARTINET	Nadine	ICN - Institut de Chimie de Nice	Researcher / Lecturer	nadine.martinet@inserm.fr	06 98 28 86 06	No			
130	MATEGOT	Raphaël	C3M - Centre Méditerranéen de Médecine Moléculaire	Labex PhD Student	raphael.mategot@unice.fr	06 82 69 90 98	Yes			
131	MATUSEK	Tamas	iBV - Institut de Biologie Valrose	Researcher / Lecturer	tmatusek@unice.fr	04 92 07 64 43	Yes			
132	MEDINA	Clémence	ISA - Institut Sophia Agrobiotech	PhD student	clemence.medina@sophia.inra.fr	06 87 39 58 78	Yes		Poster	2
133	MELKI	Ronald	Paris-Saclay Institute of Neurosciences, CNRS, FR	Researcher / Lecturer	ronald.melki@lebs.cnrs-gif.fr	01 69 82 35 03	No	Invited Keynote	Talk	4
134	MENEGUZZI	Guerrino	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	meneguzz@unice.fr	06 84 19 29 37	Yes	Scientific Committee		
135	METTOUCHI	Amel	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	amel.mettouchi@unice.fr	04 89 06 42 61	Yes			
136	MILANINI-MONGIAT	Julie	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	milanini@ipmc.cnrs.fr	04 93 95 77 73	Yes		Poster	1
137	MOLINA JIMENEZ	Loli	iBV - Institut de Biologie Valrose	Post-doc	dmolina@unice.fr	07 77 94 60 52	No			
138	MONDRAGON-MARTINEZ	Laura	C3M - Centre Méditerranéen de Médecine Moléculaire	Post-doc	Laura.MONDRAGON-MARTINEZ@unice.fr	04 89 06 43 01	Yes			
139	MORATAL	Claudine	iBV - Institut de Biologie Valrose	PhD student	cmoratal@unice.fr	04 93 37 70 38	Yes			
140	MULLER	Margot	IRCAN - Institute for Research on Cancer and Aging, Nice	PhD student	muller.margot@gmail.com	06 25 24 88 98	Yes			
141	MUS-VETEAU	Isabelle	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	mus-veteau@ipmc.cnrs.fr	04 93 95 77 51	Yes			
142	NAESSENS	Elodie	ISA - Institut Sophia Agrobiotech	PhD student	elodie.naessens@sophia.inra.fr	06 52 97 21 82	Yes		Poster	3
143	NAHON	Jean-Louis	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	nahonjl@ipmc.cnrs.fr	04 93 95 77 53	Yes			
144	NAPOLITANO	Tiziana	iBV - Institut de Biologie Valrose	Labex PhD Student	tiziana.napolitano@unice.fr	04 92 07 64 56	Yes			

No.	Last Name	First Name	Research institute or laboratory	Function	Email	Phone	SIGNALIFE member	Special participant	Presentation	Axis
145	NEDELJKOVIC	Gordana	IRCAN - Institute for Research on Cancer and Aging, Nice	Post-doc	Gordana.NEDELJKOVIC@unice.fr	06 40 36 10 57	No			
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147	NOVELLI	Caterina	iBV - Institut de Biologie Valrose	Labex PhD Student	cnovelli@unice.fr	04 92 07 64 46	Yes		Poster	2
148	OBBA	Sandrine	C3M - Centre Méditerranéen de Médecine Moléculaire	PhD student	sobba@unice.fr	04 89 06 43 06	Yes			
149	PANABIERES	Franck	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	franck.panabieres@sophia.inra.fr	04 92 38 65 18	Yes			
150	PARE	Martin	ISA - Institut Sophia Agrobiotech	Labex PhD Student	paremartin1986@hotmail.com	450 348 8901	Yes			
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152	PELKMANS	Lucas	Inst Molecular Life Sciences, University of Zürich, SZ	Researcher / Lecturer	lucas.pelkmans@imls.uzh.ch	417 89 19 92 65	No	Invited Keynote	Talk	5
153	PERALDI	Pascal	iBV - Institut de Biologie Valrose	Researcher / Lecturer	peraldi@unice.fr	04 93 37 77 04	Yes			
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155	PICCO	Vincent	CSM - Centre Scientifique de Monaco	Researcher / Lecturer	vpicco@centrescientifique.mc	+377 97 77 44 15	No		Talk	3
156	PRATX	Loris	ISA - Institut Sophia Agrobiotech	Labex PhD Student	loris.pratx@sophia.inra.fr	04 62 38 64 94	Yes		Talk	5
157	PRESSE	Françoise	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	presse@ipmc.cnrs.fr	04 93 95 77 50	Yes			
158	PRIETO	Nuria	iBV and Centro Biologia Molecular Sevro Cohoa (CSIC)	PhD student	nprieto@cbm.csic.es	346 55 42 69 68	Yes		Poster	1
159	PROD'HOMME	Virginie	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	prodhomme@unice.fr	04 89 06 43 13	Yes		Poster	4
160	RALLIS	Andrew	iBV - Institut de Biologie Valrose	Researcher / Lecturer	arallis@unice.fr	07 52 12 33 35	Yes		Talk	4
161	RASSOULZADEGAN	Minoo	iBV - Institut de Biologie Valrose	Researcher / Lecturer	minoo@unice.fr	06 08 32 45 03	Yes			
162	RAZETTI	Agustina	Inria - Centre de Recherche Sophia Antipolis Méditerranée	Labex PhD Student	a.razetti@gmail.com	06 12 86 04 33	Yes			
163	REMY	Jean-Jacques	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	jean-jacques.remy@sophia.inra.fr	04 92 38 64 18	Yes			
164	REPETTO	Emanuela	C3M - Centre Méditerranéen de Médecine Moléculaire	Post-doc	erepetto@unice.fr	04 89 06 42 56	No			
165	RICCI	Jean-Ehrland	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	ricci@unice.fr	04 89 06 43 04	Yes	Chairman		
166	RICHARDSON	Nainoa	iBV - Institut de Biologie Valrose	Labex PhD Student	Nainoa.RICHARDSON@unice.fr	415 298 3376	Yes			
167	ROBICHON	Alain	ISA - Institut Sophia Agrobiotech	Researcher / Lecturer	alain.robichon@sophia.inra.fr	04 92 38 64 19	Yes			
168	ROGER	Estelle	IRCAN - Institute for Research on Cancer and Aging, Nice	PhD student	estelle.n.roger@gmail.com	06 85 37 72 46	Yes			
169	ROTTINGER	Eric	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	eric.rottinger@unice.fr	04 93 37 77 91	No			
170	ROUANET	Sophie	IRCAN - Institute for Research on Cancer and Aging, Nice	PhD student	srouanet@unice.fr	06 29 85 03 84	Yes		Poster	4
171	ROUMENGOUS	Solange	iBV - Institut de Biologie Valrose	PhD student	solange-85@hotmail.it	06 13 04 40 97	Yes		Poster	2
172	ROVERE	Carole	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Researcher / Lecturer	rovere@ipmc.cnrs.fr	04 93 95 77 41	Yes			
173	RUBERTO	Anthony	iBV - Institut de Biologie Valrose	Labex PhD Student	Anthony.RUBERTO@unice.fr	06 22 60 76 58	Yes			
174	RUIZ GARCIA	Sandra	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	ruiz-garcia@ipmc.cnrs.fr	04 93 95 77 59	Yes		Poster	2
175	SABOURAULT	Cecile	SYMAR - Symbiose Marine	Researcher / Lecturer	Cecile.Sabourault@unice.fr	04 92 07 68 95	No			
176	SARASWATHY	Vishnu	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	vishnums007@gmail.com	9196 65 14 26 96	Yes			
177	SAVASTA	Marc	Délégation Régionale INSERM PACA	Researcher / Lecturer	marc.savasta@inserm.fr	04 91 82 7039	No			
178	SCHEEL	Dierk	Leibniz Institute of Plant Biochemistry, Halle, GE	Researcher / Lecturer	dscheel@ipb-halle.de	49 345 55821400	No	Invited Keynote	Talk	3
179	SCHOROVA	Lenka	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	schorova@ipmc.cnrs.fr	06 22 93 19 85	Yes			
180	SCIMECA	Jean-Claude	iBV - Institut de Biologie Valrose	Researcher / Lecturer	scimeca@unice.fr	06 20 33 55 93	No			
181	SHARMA	Priyanka	iBV - Institut de Biologie Valrose	PhD student	psharma@unice.fr	04 92 07 64 40	No			
182	SIMOES DE SIQUEIRA	Kercya Maria	ISA - Institut Sophia Agrobiotech	Post-doc	kercyasimoes@hotmail.com	06 33 11 86 63	Yes			
183	STENMARK	Harald	Institute for Cancer Research, NO	Researcher / Lecturer	stenmark@ulrik.uio.no	47 90 60 82 40	No	Invited Keynote	Talk	1
184	STOBBE	Katharina	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Labex PhD Student	katharina.stobbe@gmail.com	49157 74 33 66 93	Yes			
185	STUDER	Michèle	iBV - Institut de Biologie Valrose	Researcher / Lecturer	michele.studer@unice.fr	04 92 07 64 19	Yes			
186	SULTANA	Tania	IRCAN - Institute for Research on Cancer and Aging, Nice	PhD student	tania.sultana@unice.fr	06 05 50 77 52	Yes		Poster	4
187	SZMIDT	Simon	IPMC - Institut de Pharmacologie Moléculaire et Cellulaire	Engineer	szmidt@ipmc.cnrs.fr	04 93 95 77 06	Yes	Organizing Committee		
188	TANTI	Jean-François	C3M - Centre Méditerranéen de Médecine Moléculaire	Researcher / Lecturer	tanti@unice.fr	04 89 06 42 37	Yes	Scientific Committee		
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196	VERGONI	Bastien	C3M - Centre Méditerranéen de Médecine Moléculaire	PhD student	bastien.vergoni@unice.fr	04 89 06 42 34	Yes		Talk	4
197	VIEIRA	Andhira	iBV - Institut de Biologie Valrose	Post-doc	avieira@unice.fr	06 23 47 17 02	Yes		Talk	2
198	VOURET-CRAVIARI	Valérie	IRCAN - Institute for Research on Cancer and Aging, Nice	Researcher / Lecturer	vouret@unice.fr	06 76 13 09 91	Yes			
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