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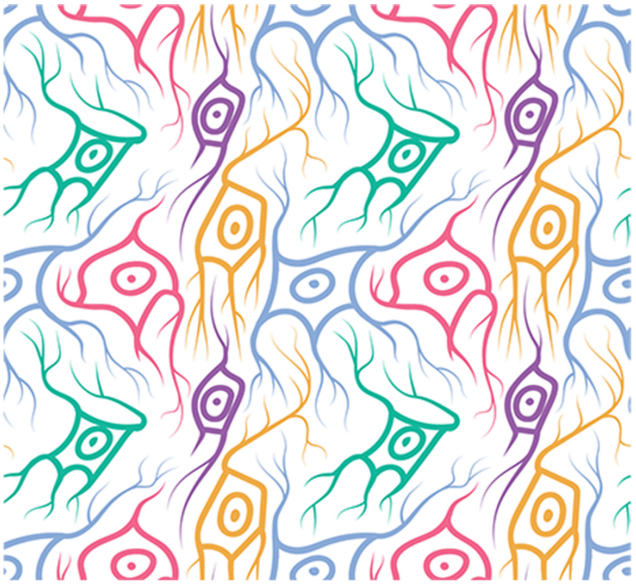
INAUGURAL SYMPOSIUM

Topics:

Functional networks in evolution and development

Neurons and muscles in pathology and ageing



14 16 OCT 2015

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Speakers: Jules Hoffmann (Nobel Prize in Medicine) | Margaret Buckingham Eytan Domany | Alessandra Carbone | Leonid Mirny | Edith Heard | Katja Wassmann William Martin | Philippe Lopez | Delphine Duprez | Alfonso Martinez Arias Michel Labouesse | Carmen Sandi | Jean-Louis Mandel | Antoine Triller Alexandre Mourot | Adam Antebi | Christian Neri | Brigitte Kieffer | Bruno Giros Laure Rondi-Reig | Jean-Claude Martinou | Etienne Jacotot | Hans Clevers

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IBPS INAUGURAL SYMPOSIUM

Program
October, 14-16, 2015

Jussieu Campus
Amphi 25

Functional networks in evolution and development
Neurons and muscles in pathology and ageing

14/10/2015

Inaugural session

17:00-17:05	**Michel Labouesse**, IBPS Director, *Welcome address*
17:05-18:00	**Jean Chambaz,** President of UPMC
	Catherine Jessus, INSB director, CNRS
	Etienne Hirsch, Director of the ITMO Neuroscience Department, Inserm
18:00-18:50	**Jules Hoffmann**, Nobel Prize, IBMC, Strasbourg (France). *Innate Immunity: from flies to humans*
18:50-19:40	**Margaret Buckingham**, CNRS gold medal Institut Pasteur, (Paris, France). *Skeletal muscle stem cells*
19:45	COCKTAIL

15/10/2015

Functional networks in evolution and development

Chairman: **Angela Falciatore**, UMR 7238, IBPS.

09:00-09:40 **Eytan Domany**, Weizmann Institute (Rehovot, Israel). *Pathway – Based Personalized Analysis of Cancer*

09:40-10:05 **Alessandra Carbone**, IBPS. *Coevolution analysis: a high resolution map of protein-protein interactions*

10:05-10:45 **Leonid Mirny**, MIT (Cambridge, USA), *Genome in 3D*

10:45-11:10 COFFEE BREAK

Chairman: **Stéphane Ronsseray**, UMR 7622, IBPS.

11:10-11:50 **Edith Heard**, Institut Curie Paris (Paris, France). *Dynamic X-chromosome structure and function during X-chromosome inactivation*

11:50-12:15 **Katja Wassmann**, IBPS. *How oocytes try to get it right: Spindle checkpoint control in meiosis*

12:15-13:30 LUNCH (Caves Esclangon)

13:30-14:30 Poster session (Caves Esclangon)

Chairman: **Paola Furla**, UMR 7138, IBPS.

14:30-15:10 **William Martin**, Institut für Molekulare Evolution (Düsseldorf, Germany). *Hydrothermal vents and the origin of life: A lot is going on*

15:10-15:35 **Philippe Lopez**, IBPS. *Using similarity networks in molecular evolution*

15:35-16:00 **Delphine Duprez**, IBPS. *Mechanobiology of foetal myogenesis*

16:00-16:20 COFFEE BREAK

Chairman: **Onnik Agbulut**, UMR 8256, IBPS.

16:20-17:00 **Alfonso Martinez Arias**, Cambridge University (UK). *Genetically supervised self organization in ensembles of mouse ES cells*

17:00-17:25 **Michel Labouesse**, IBPS. *Embryonic life under tension*

17:25-18:05 **Carmen Sandi**, Brain and Mind Institute, EPFL (Lausanne, Switzerland). *The brain on stress – mechanisms underlying increased risk to develop psychopathologies*

Chairman: **Hervé Chneiweiss**, UMR 8246, IBPS.

18:05:18:45 **Jean-Louis Mandel**, IGBMC (Strasbourg, France). *From rare to common diseases: what are the perspectives of genomics for predictive or personalized medicine?*

16/10/2015

Neurons and muscles in pathology and ageing

Chairman: **Sylvie Schneider-Maunoury**, UMR 7622, IBPS.

09:00-09:40 **Antoine Triller**, Ecole Normale Supérieure (Paris, France). *Synaptic stability and plasticity: a molecular movie*

09:40-10:05 **Alexandre Mourot**, IBPS. *Opto-chemical control of midbrain dopamine neurons*

10:05-10:30 COFFEE BREAK

Chairman: **Jamilé Hazan**, UMR 8246, IBPS.

10:30-11:10 **Adam Antebi**, MPI Biology of ageing (Köln, Germany). *Regulation of longevity by the reproductive system*

11:10-11:35 **Christian Neri,** IBPS. *Molecular dynamics of Huntington's Disease*

11:35-12:50 Poster session (Caves Esclangon)

12:50-13:50 LUNCH (Caves Esclangon)

Chairman: **Philippe Faure**, 8246, IBPS.

14:00-14:40 **Brigitte Kieffer**, Mc Gill University (Montréal, Canada). *Opioid receptors and brain function - mouse genetic approaches*

14:40-15:05 **Bruno Giros**, IBPS. *Molecular basis of vulnerability to depression*

15:05-15:30 **Laure Rondi-Reig**, IBPS. *Neural representation of space and Cerebellum*

15:30-15:50 COFFEE BREAK

Chairman: **Frédérique Peronnet**, UMR 7622, IBPS.

15:50-16:30 **Jean-Claude Martinou**, Geneva University (Geneva, Switzerland). *Role of the mitochondrial pyruvate carrier in neuronal function*

16:30-16:55 **Etienne Jacotot**, IBPS. *Caspase-2 as a target in acute and chronic neurodegeneration*

16:55-17:35 **Hans Clevers**, Hubrecht Institute (Utrecht, The Netherlands). *Lgr5 Stem Cells in self-renewal and cancer*

17:35 **Closing remarks**

ORAL PRESENTATIONS

Innate Immunity : From Flies to Humans

Jules Hoffmann
Institut de Biologie Moléculaire et Cellulaire, UPR 9022 du CNRS, 15 rue R. Descartes, F67084 Strasbourg Cedex, France, University of Strasbourg Institute for Advanced Study (USIAS), 5 allée du Général Rouvillois, 67083 Strasbourg, France.
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Life expectancy of humans has spectacularly increased since the second half of the 19th century, in large part through the progress in fighting infectious diseases. Whereas all animal species use the defense mechanisms of innate (first line) immunity devoid of memory, only vertebrates have developped the so-called adaptive (acquired) immune responses, a hallmark of which is memory which underlies the process of vaccination.

Insects make up some 80 % of present-day species on earth and are remarkably resistant to infections. They are devoid of adaptive immune defenses. Over several decades, we and others have attempted to unravel the mechanisms of the innate immune mechanisms which have so efficiently served insects (and the other invertebrates, i.e. 95 % of all species present to-day) to cope with microbial agressions. The presentation will review the major advances in these studies, particularly on the identification of effector polypetides with various antimicrobial activity spectra, on the control of expression of the corresponding genes during infections and on the recognition mechanisms of the infecting agents.

This progress will be put in parallel to that obtained by numerous laboratories investigating these aspects in mice and humans : it came as a major surprise to discover that many of the basic innate defense mechanisms are similar in mice and flies – and, as we now know, even in organisms as phylogenetically distant as sea anemones. However, in spite of these many compelling similarities, some significant differences are conspicuous and will be discussed during the presentation.

Taken together, the results obtained in flies and mice over the last decades have led to a paradigm shift in our views on the roles and mechanisms of innate immunity. These new developments are already having a notable impact in clinical settings.

Further reading :
Lemaitre B, Nicolas E, Michaut L, Reichhart JM, Hoffmann JA. Cell. 1996; 86 :973.
Hoffmann JA, Kafatos FC, Janeway CA, Ezekowitz RA. Science. 1999; 284: 1313.
Hoffmann JA. Nature. 2003; 426: 33.
Ferrandon D, Imler JL, Hetru C, Hoffmann JA. Nat Rev Immunol. 2007; 7: 862.
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Royet J, Gupta D, Dziarski R. Nat Rev Immunol. 2011; 11: 837.

Skeletal Muscle Stem Cells

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Skeletal muscle in the trunk and limbs derives from multipotent cells in the somites, segments of paraxial mesoderm that form along the anterior-posterior axis of the developing vertebrate embryo. Pax3 is an upstream regulator of myogenesis (see1). A screen for Pax3 targets in the mouse embryo has shown how this key transcription factor acts at different steps to orchestrate muscle stem cell behaviour, from controlling activation of the myogenic determination gene, Myf5, with consequent entry into the myogenic programme and muscle differentiation, to regulating survival, self renewal and migration of Pax3-positive myogenic progenitor cells. In the multipotent cells of the somite, perturbation of reciprocal genetic repression between Pax3 and Foxc2 affects cell fate choices (2). Thus activation of Notch signalling, for example, results in up-regulation of Foxc2 relative to Pax3 and acquisition of a vascular endothelial fate, at the expense of Pax3-dependent myogenic progenitors (3).

Regeneration of adult skeletal muscle depends on satellite cells, quiescent cells that are closely associated with muscle fibres. These cells are marked by the expression of Pax7 and derive from the Pax3-positive cells of the embryonic somite. When muscle is injured, satellite cells are activated, express myogenic factors and differentiate into new muscle fibres. Surprisingly, most quiescent satellite cells already transcribe the myogenic determination gene Myf5, which in the embryo leads to muscle formation. However, in the quiescent adult muscle stem cell, the Myf5 protein does not accumulate and the Myf5 messenger RNA is sequestered, with inhibitory microRNA, in ribonucleoprotein granules that prevent its translation. In response to injury, the granules breakdown rapidly, Myf5 accumulates and activated satellite cells enter myogenesis (4). This mechanism is of general interest in the context of adult tissue stem cells since it ensures tissue identity and a rapid regenerative response.

Another feature of muscle stem cells that we have investigated recently is their metabolic status. The level of reactive oxygen species (ROS) is controlled by Pitx2/3 transcription factors (5), where Pitx2 is a Pax3 target in the embryo. Fine-tuning of ROS is important for the onset of muscle differentiation, whereas excessive ROS leads to DNA damage and apoptosis, or senescence in the adult.

(1) Buckingham and Rigby, (2014), Dev. Cell; (2) Lagha et al., (2009), Dev. Cell; (3) Mayeuf-Louchart et al., (2014), PNAS; (4) Crist et al., (2012), Cell Stem Cell; (5) L'honoré et al., (2014), Dev. Cell.

Pathway-based personalized analysis of cancer

Eytan Domany
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I will present a “systems approach” to analysis of high throughput large cancer datasets. The basic idea is to make use of existing knowledge, taking the golden path between “ignorance-based” machine learning approaches and the “all details are essential” view of many biologists. This philosophy has been implemented in Pathifier – an algorithm that infers pathway deregulation scores for each individual tumor sample, on the basis of expression data (1). This score is determined in a context-specific manner for every particular data set and type of cancer that is being investigated. The algorithm transforms gene level information into pathway level information, generating a compact and biologically relevant representation of each sample. We demonstrated (1) the algorithm’s performance on three colorectal cancer datasets, two glioblastoma multiforme datasets, and on a very extensive dataset on breast cancer (2). We showed that our multi-pathway-based representation is robust, preserves much of the original information, and allows inference of complex biologically significant knowledge, such as identifying pathways that were robustly associated with survival. We also discover new cancer sub-classes, that were not seen in direct straightforward analyses of the corresponding expression data.

(1) Pathway-based personalized analysis of cancer. Yotam Drier, Michal Sheffer, and Eytan Domany, PNAS 110, 6388 (2013)
(2) Pathway-based personalized analysis of breast cancer data. A, Livshits et al, Molecular Oncology 2015 (in print.

Coevolution analysis: a high resolution map of protein-protein interactions

Alessandra Carbone
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A novel computational approach of coevolution analysis allowed us to reconstruct the protein-protein interaction network of the Hepatitis C Virus at the residue resolution. For the first time, coevolution analysis of an entire virus was realised, based on a limited set of protein sequences with high sequence identity within genotypes. The identified coevolving residues constitute highly relevant predictions of protein-protein interactions for further experimental identification of HCV protein complexes. The method can be used for interaction predictions for other viral protein interaction networks.

Genome in 3D

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DNA of the human genome is two meters long and is folded into a structure that fits in a cell nucleus. Recently developed Chromosome Conformation Capture technique (Hi-C) provides comprehensive information about spatial genome organization and its reorganization during the cell cycle. I will present our analysis of Hi-C data and polymer modeling of chromosome organization for human, yeast and bacteria. In interphase, organization of human chromosomes is characterized by multi-level domain architecture, which correlates with sequence features and local chromatin states. In metaphase, the organization is homogeneous, common to all chromosomes, and is consistent among cell types, suggesting a general principle of metaphase chromosome structure. Using polymer simulations we built 3D models of metaphase and interphase chromosomes, and suggested mechanisms of chromosome organization and reorganization.

Dynamic X-chromosome structure and function during X-chromosome inactivation

Edith Heard
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X-chromosome inactivation (XCI) entails the mitotically heritable silencing of most genes on one of the two X chromosomes during early development in female mammals. This process represents a paradigm of epigenetic regulation. The XCI process is triggered by a non-coding RNA, Xist, that results not only in chromosome-wide gene repression, but also in major chromatin changes as well as 3D reorganization of the inactive X chromosome (Xi). How most X-linked genes are silenced and yet others escape from X inactivation remains unclear. We are investigating the expression status, chromatin structure and 3D organization of the X chromosome during pre-implantation development and in differentiating embryonic stem cells, before and after inactivation of one X chromosome. Our insights into the role of Xist RNA and the relationship between X-chromosome structure and gene activity on the inactive X chromosome will be presented.

How oocytes try to get it right: spindle checkpoint control in meiosis

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2CNRS, IBPS-UMR 7622 Developmental Biology Lab, 75005 Paris, France.
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The generation of a viable, diploid organism depends on the formation of haploid gametes, oocytes and spermatocytes, with the correct number of chromosomes. Halving the genome into two requires the execution of two consecutive specialized cell divisions, named meiosis I and II. Unfortunately, and in contrast to male meiosis, chromosome segregation in oocytes is error prone, with human oocytes being extraordinarily «meiotically challenged». Aneuploid oocytes, that is with the wrong number of chromosomes, give rise to aneuploid embryos, when fertilized. In humans most aneuploidies are lethal, and result in spontaneous abortions. But some trisomies survive to birth or even adulthood, such as the well-known trisomy 21, which gives rise to Down syndrome. A staggering 20-25 % of oocytes ready to be fertilized are aneuploid in humans. If this were not bad enough, there is an additional increase in meiotic missegregations as women get closer to menopause. A woman above 40 has a risk of more than 30 % of getting pregnant with a trisomic child.

To understand why errors occur so frequently during the meiotic divisions in oocytes, we try to elucidate the molecular mechanisms at works to control chromosome segregation during meiosis. An important mitotic control mechanism, namely the spindle assembly checkpoint or SAC, has been adapted to the special requirements of the meiotic divisions, and it has been shown that the abundance of certain SAC proteins in oocytes decreases with age. My talk will focus on our current work on SAC control in mammalian oocytes to understand why segregation errors occur in female meiosis. Using conditional, oocyte-specific knock-out approaches in the mouse we have demonstrated the essential roles of several SAC proteins for female meiosis and therefore fertility. Knowledge on how chromosome segregation is regulated in mammalian oocytes should help identify risk factors important for questions related to human reproductive health, both age-related and independent of age.

Hydrothermal vents and the origin of life: A lot is going on

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Life is the harnessing of chemical energy in such a way that the energy harnessing device makes a copy of itself. The talk outlines an energetically feasible path from a particular inorganic setting for the origin of life to the first free-living cells. The sources of energy available to early organic synthesis, early evolving systems and early cells stand in the foreground, as do the possible mechanisms of their conversion into harnessable chemical energy for synthetic reactions. With regard to the possible temporal sequence of events, we will focus on: (i) alkaline hydrothermal vents as the far-from-equilibrium setting, (ii) the Wood–Ljungdahl (acetyl-CoA) pathway as the route that could have underpinned carbon assimilation for these processes, (iii) biochemical divergence, within the naturally formed inorganic compartments at a hydrothermal mound, of geochemically confined replicating entities with a complexity below that of free-living prokaryotes, and (iv) acetogenesis and methanogenesis as the ancestral forms of carbon and energy metabolism in the first free-living ancestors of the eubacteria and archaebacteria, respectively. In terms of the main evolutionary transitions in early bioenergetic evolution, we will focus on: (i) thioester-dependent substrate-level phosphorylations, (ii) harnessing of naturally existing proton gradients at the vent–ocean interface via the ATP synthase, (iii) harnessing of Na+ gradients generated byH+/Na+ antiporters, (iv) flavin-based bifurcation-dependent gradient generation, and finally (v) quinone-based (and Q-cycle-dependent) proton gradient generation. Of those five transitions, the first four are posited to have taken place at the vent. Ultimately, all of these bioenergetic processes depend, even today, upon CO2 reduction with low-potential ferredoxin (Fd), generated either chemosynthetically or photosynthetically, suggesting a reaction of the type ‘reduced iron —> reduced carbon’ at the beginning of bioenergetic evolution.

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Lane N, Martin WF (2012) The origin of membrane bioenergetics. Cell 151:1406–1416 (2012).
Martin W, Baross J, Kelley D, Russell MJ (2008) Hydrothermal vents and the origin of life. Nature Rev. Microbiol. 6:805–814.

Using similarity networks in molecular evolution

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Evolution is more than just divergence from a common ancestor, since many evolutionary processes (like recombination, horizontal transfer or endosymbiosis) also combine existing evolutionary objects into new ones. Such processes, called introgressive, play a very important role in evolution, both quantitatively and qualitatively. As a result, many biological objects (be they genes, genomes or holobionts) are indeed composite entities, made of interacting heterogeneous parts that are brought together by reticulate processes. Describing the evolution of such complex objects, in particular the association, stabilisation, and transformation of biological elements resulting in novel higher level structures thus requires the development of network-based analytical tools and of increasingly flexible representations of life's history. In order to reach this conclusion, I will introduce some conceptual challenges raised by biological data and recent discoveries from microbiology and virology, and explain how these challenges encourage to expand the framework of evolutionary analyses. In particular, similarity networks, which map the resemblance between evolving objects, and bipartite graphs, which represent the distribution of lower level parts in higher level objects, constitute a very promising new data type for evolutionary studies.

Mechanobiology of skeletal muscle during development

Joana Esteves de Lima[1,2,3], Marie-Ange Bonnin[1,2,3] and Delphine Duprez[1,2,3]
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Skeletal muscle is essential for the mobility of the human body and consequently for the quality of life, health and survival. Skeletal muscle development, homeostasis and regeneration rely on muscle stem cells. Skeletal muscle is very plastic and adapts in size according to upload and download demands with hypertrophy or atrophy, respectively. Muscle atrophy is observed following immobility (or disuse) during development, adult life and ageing but also in disease-induced atrophy such as cachexia. Understanding the mechanisms underlying muscle atrophy remains a challenge. Both muscle fibres and progenitors respond to immobilisation, however, their respective contributions in muscle wasting are not well established. Moreover, the molecular mechanisms underlying the interplay between muscle fibres and muscle progenitors in the context of immobilization are not known. We analysed the molecular and cellular mechanisms underlying muscle wasting during development. We established that the activity of the NOTCH signalling pathway, known to be a central regulator muscle stem cells, was decreased in foetal muscles following immobilization. Moreover, the inhibition of muscle contraction mimicked a NOTCH loss-of-function phenotype, i.e. dramatically decreased the number of foetal muscle progenitors that engaged the differentiation process. Forced-NOTCH activation rescued the diminution in the number of foetal muscle progenitors in immobilized embryos. We further showed that muscle fibres rather than muscle progenitors first responded to the block of mechanical forces. We also provide molecular insights into how the muscle fibres sense the mechanical forces through the transcriptional co-activator YAP and affect the number of muscle progenitors via the NOTCH signalling pathway.

Genetically supervised self organization in ensembles of mouse ES cells

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The development of an organism from a zygote requires the establishment of global references, axis, which orient the cell diversification events and their organization into tissues and organs. Embryonic Stem (ES) cells are clonal derivatives from the mammalian blastocyst which can be differentiated in culture into most cell types of an organism. When differentiated in clumps, called Embryoid Bodies, they develop many cell types but in a disorganized manner. Cells in culture can be seen trying to recapitulate embryonic processes (1). Recently we have found that small aggregates of ES cells of defined sizes are able to organize themselves into structures that resemble the early mouse embryo and undergo processes that resemble gastrulation and axial extension (2-4). I shall discuss our progress to understand the mechanism of the early events that take place in these patterned aggregates and their relationship to events in the embryo.

(1) Turner DA, Rue P, Mackenzie JP, Davies E, Martinez Arias A. Brachyury cooperates with Wnt/ss-Catenin signalling to elicit Primitive Streak like behaviour in differentiating mouse ES cells. BMC Biol 2014;12:63.

(2) van den Brink SC, Baillie-Johnson P, Balayo T, Hadjantonakis AK, Nowotschin S, Turner DA, et al. Symmetry breaking, germ layer specification and axial organisation in aggregates of mouse embryonic stem cells. Development 2014;141:4231-42.

(3) Turner DA, Hayward PC, Baillie-Johnson P, Rue P, Broome R, Faunes F, et al. Wnt/beta-catenin and FGF signalling direct the specification and maintenance of a neuromesodermal axial progenitor in ensembles of mouse embryonic stem cells. Development 2014;141:4243-53.

(4) Baillie-¬-Johnson P, van den Brink S, Balayo T, Turner DA, Martinez Arias A. Generation of aggregates of mouse ES cells that show symmetry breaking, polarisation and emergent collective behaviour. bioRxiv 2014;http://dx.doi.org/10.1101/005215.

Embryonic life under tension

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The importance of mechanical forces in biology is well accepted, yet an integrated view of their mode of action in vivo is lacking. In particular, our knowledge of the cellular processes influenced by mechanical forces remains fragmentary. I will present our efforts to address those issues by studying how C. elegans embryos elongate, a process that occurs in the absence of cell division or cell intercalation. Recent data have highlighted how non-muscle myosin II powers morphogenesis in different systems. By combining genetic analysis, laser nano-ablation to measure mechanical tension and modelling we find that myosin II is not the whole story, and that the extraembryonic sheet together with hydrostatic pressure play an equally important role. In particular we define the respective forces played by each type of forces and find that they to do not act in a homogeneous way along the axis of elongation. In a second part, I will recap recent findings illustrating how the mechanical tension originating from muscle cells promotes and influences epithelial morphogenesis through a mechanotransduction pathway involving a GIT-1/PIX-1/PAK-1 module. I will go on to touch on the issue of cell shape maintenance as epidermal cells become submitted to stretching and compression from the underlying muscles. Shape maintenance involves spectrin and the GIT-1/PIX-1/PAK-1 module as well as other actin binding proteins.

The brain on stress – mechanisms underlying increased risk to develop psychopathologies

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Stress can exert prominent effects in cognitive function and social behaviors, and it is a key predisposing factor for the development of diverse psychopathologies (i.e., anxiety disorders, depression). However, there are important individual differences in the vulnerability to stress, with trait anxiety being a remarkably relevant phenotype for the regulation of brain and behavioral responses to stress and a prominent risk factor for the development of anxiety disorders and depression. I will present work that links trait anxiety with behavioral stress coping vulnerabilities both in animals and humans, as well as evidence that highlights energy metabolism as a mediating mechanism. I will speculate on the importance of these findings to define individuals that show vulnerability vs. resistance to develop stress-induced psychopathologies.

From rare to common diseases: what are the perspectives of genomics for predictive or personalized medicine?

Jean-Louis Mandel
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The technological revolutions of the past 10 years in genomic and their application to analysis of human diseases (through GWAS and CNV studies, followed by exome and now whole genome sequencing on cohorts of increasing size, non-invasive prenatal diagnosis etc…) has been widely heralded as anticipating medical revolutions, from 2P (predictive and preventive) to 3P, 4P (Lee Hood) and now 5P (Obama), adding successively personalized, participatory and most recently precision medicine. Huge programs have been launched in UK or US (not much in France yet). While indeed much has been gained in diagnosis and understanding of rare monogenic diseases , in identifying key genes and their driver mutations in cancer at a much increased pace and for common diseases, in identifying numerous genetic risk factors for the vast majority of common illnesses, the actual therapeutic progresses have been much slower, apart from rare exceptions (gene therapy for immunodeficiencies and a few other inherited diseases, a very personalized and costly drug for cystic fibrosis, antiPCSK9 monoclonals for hypercholesterolemia and hopefully for coronary heart disease, bRAF inhibitors for melanoma). If prediction is indeed possible (with often uncertainty on severity) for “monogenic” diseases, their prevention poses ethical issues (prenatal or preconceptional screening). The case for personalized medicine is somewhat encouraging for cancer, as there are drugs that are designed to target specific mutations. For common diseases, in most cases the identification of genetic risk factors, most of which have very minor effects, has little or no actual predictive value in addition to classic clinical and laboratory investigations, and preventive value is also dismal in reality. Identification of rare variants with major risk effects is much more difficult than expected. One should soberingly remind that while genetic has brought major understanding of Alzheimer disease pathways, initially by the identification of major players such as APP (in 1991), ApoE (1993) and presenilins (1995), and the ensuing design of animal models, this has not (yet) resulted in a single novel therapeutic for AD. The likely distant prospects of genomic-based personalized or precision medicine for common diseases should not deter from improving prevention at the general population level.

Synapse stability and plasticity: a molecular movie

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The efficiency and accuracy of neurotransmission strongly depends on two apparently antagonist properties of synaptic membrane: the stability of its organization and its ability to adapt to plasticity events. In addition, the structural stability of synapses has to be reconciled with the notion that cell membranes are fluid. Membrane molecules are compelled to move within the membrane surface due to thermal Brownian agitation, which favors the homogeneous distribution of the molecules. As a result, neurons spend energy to stop or reduce these movements, and maintain molecules in certain locations via mechanisms that decrease this fluidity. We investigate the regulation of synaptic receptors dynamics by the different (structural and functional) elements that make the synapse. We have approached these conceptual paradoxes by developing new technological and analytical tools that allow the monitoring of the behavior of synaptic components at the molecular level and change of the scale of analysis. We demonstrated rapid exchanges between synaptic and extra-synaptic receptors and we showed that transient stabilization of receptors at synapses occurs by interaction with partners, such as scaffold proteins. Novel super-resolution imaging methods (PALM, STORM) gave us a precise insight on the organization of these postsynaptic structures. Thus combination of single particle tracking and super-resolution methods, open access to molecular counting and energy involved in receptor-scaffold interactions as well as on and off rate of molecular interactions. Thus beyond super-resolution methods is chemistry "in cellulo" accounting for the regulation of receptor number and consecutively that of synaptic strength. Ultimately, the dynamic regulations of receptor-scaffold and scaffold–scaffold interactions appear as a central tenet for the maintenance and plasticity-related changes of receptor numbers at synapses. These processes are likely to be deregulated in pathological situations such as in neurodegenerative diseases.

Opto-chemical control of midbrain dopamine neurons

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The brain delivers neuromodulatory signals such as dopamine (DA) or acetylcholine in spatially and temporally precise, pulsed, phasic or tonic patterns depending on the situation. These signals are fundamental to the development and adaptation of the nervous system. Most neuromodulators act on multiple receptor classes, with different subtypes able to exert diverse physiological effects through different intracellular signaling pathways. Remote-controlling specific receptor subtypes with millisecond precision in defined neuronal types and in living animals is unprecedented, yet it would be extremely valuable to produce a clearer picture of the function of neuromodulatory-driven signals in neural information processing and plasticity. To achieve this aim, we developed a versatile opto-chemical genetic strategy that enables mammalian receptors to be repeatedly turned off and on with great temporal precision, at a time scale compatible with fast synaptic transmission (1). The idea is to attach a synthetic photosensitive ligand onto a genetically engineered receptor to allow activation or inhibition of only that very receptor with light. Following this strategy, we have molecularly engineered light-activated and -inhibited nicotinic acetylcholine receptors (nAChRs) of different subtypes (2). We are now implementing strategies to use these tools in vivo. We are especially interested in understanding the role of the β2 nAChR in modulating the midbrain reward system. Midbrain DA neurons show two different firing patterns: a regular pattern associated with a tonic release of DA in the target structures; and a « burst » pattern associated with a phasic release of DA and involved in reinforcement learning and reward prediction. To assess the precise role of nAChRs in the spontaneous DA release and in the response to drugs, we combined in vivo extracellular recordings with optical control of β2 nAChRs. We showed that photo-inhibiting β2 nAChRs decrease the spontaneous bursting activity of DA neurons, but also the bursting activity that is induced by an intravenous injection of nicotine. Our findings, though preliminary, establish a causal role for β2 nAChRs in regulating the excitability of midbrain dopamine neurons.

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Regulation of longevity by the reproductive system

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The reproductive system not only promotes procreation of a species but can also affect longevity. Removal of germline precursor cells in C. elegans extends life and health span, in a manner dependent on signals emanating from the somatic gonad. Downstream of this, a number of somatic transcription factors establish the long-lived state, including the steroid receptor DAF-12/FXR, DAF-16/FOXO, PHA-4/FOXA, HLH-30/TFEB, and NHR-80, but how they work together is not well understood.

From genetic screens we identified novel modulators of gonadal longevity, namely the Myc-Mondo homolog, MML-1 and its heterodimeric partner MML-2/Max-like. These proteins are basic helix-loop-helix transcription factors of the Myc subfamily whose mammalian homologs, MondoA/Chrebp and Max-like, sense glucose and regulate glycolytic flux and lipogenesis. Consistent with a signaling role, C. elegans MML-1 is upregulated upon germline removal and overexpression can extend life span. MML-1/MXL-2 are not only required for gonadal longevity but are also responsible for longevity due to reduced insulin/IGF and TOR signaling, as well as reduced mitochondrial function. They are thus among a select handful of factors acting at the convergence of multiple longevity pathways. Another such transcription factor is the TFEB homolog, HLH-30, which promotes autophagy, lysosomal function, and fatty acid metabolism. Interestingly, we found that MML-1/MXL-2 regulate HLH-30/TFEB nuclear localization and activity in germlineless animals, via downregulation of TOR signaling. Accordingly, MML-1/MXL-2 affect other TOR outputs including S6K phosphorylation and autophagy. Transcriptome analysis reveals that MML-1/MXL-2 and HLH-30 have substantial overlap, but also have preferential outputs. Mammalian MondoA and Chrebp also regulate TFEB nuclear localization and activity in response to amino acid starvation, showing that the regulatory relationships are evolutionarily conserved. These studies suggest how transcriptional networks distribute responsibility and mutually enforce states geared towards reproduction or survival.

Molecular dynamics of Huntington's Disease

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The study of inherited forms of neurodegeneration such as Huntington's disease (HD) provides a promising path to undertanding how the brain may be able to compensate for misfolded protein expression and neuronal dysfunction in neurodegenerative diseases. This has potential for the design of disease-modifying strategies based on stress response and resilience. However, models describing how HD may work at the dynamic level in terms of pathogenicity and compensation are still to be constructed. We will show two models that describe how HD may work on a dynamic level including (i) a mathematical model that unveils the role of specific signalling pathways in casting the frame for the pathogenic process to develop in HD and (ii) a mixture model based on computational and experimental biology that describes how FOXO3a, a transcription factor that is key to longevity and that is neuroprotective in HD, is repressed during the earliest phases of HD and how this may negatively impact on the capacity of the brain to efficiently compensate for proteotoxicity and resist the disruption of neuronal activity in HD.

Opioid receptors and brain function - mouse genetic approaches

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Opiates have been used since thousand years for their pain-relieving and rewarding properties. Opiates produce their potent effects by activating opioid receptors in the brain, highjacking the endogenous opioid system. This neuromodulatory system includes three opioid receptors, mu, delta and kappa, normally stimulated by endogenous opioid peptides to control pain and stress responses, as well as emotional and addictive behaviors. All three receptors are coupled to inhibitory G protein and reduce neuronal activity, but their distributions throughout brain circuits differ, and each receptor fulfills distinct functions in the brain. Gene targeting approaches in the mouse have been instrumental to identify the role of each opioid receptor in brain physiology and disease. Using gene knockout, we have demonstrated that mu receptors mediate morphine analgesia and reward, as well as reinforcing properties of non-opioid drugs of abuse and natural rewards, and have further shown that deficient mu receptor signaling may lead to autistic-like behaviors. We have also demonstrated opposing roles for mu and delta receptors in the regulation of emotional responses and motor impulsivity, and positioned delta receptors as a potential target to treat mood disorders. On another front, we have achieved functional imaging of delta receptors in vivo, using an eGFP knock-in strategy. This is the first example of a G protein coupled receptor directly visible in vivo. This unique tool led us to visualize real-time trafficking of the functional fluorescent receptor in live neurons, and demonstrate the physiological relevance of receptor internalization for analgesic efficacy and tolerance. A similar approach targeting the mu opioid receptor reveals brain sites of mu/delta receptor co-expression, and potentially heterodimerization, in vivo. Finally, we recently developed non-invasive MRI-based imaging of live genetic mutants, and detected significant consequences of receptor deletion on whole brain functional connectivity. Our findings have both fundamental and therapeutic implications in pain, mood and addiction research, as well as for GPCR biology and disease.

Molecular basis of vulnerability to depression

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Depressive disorders in human are devastating psychiatric conditions and represent one of the largest causes for health related disabilities and social costs. The mechanisms underlying the emergence of this disorder, at the cross-sections between genetic and environmental etiology, are poorly known. It is however striking to consider the large inter-individual differences that exist in term of resistance versus vulnerability to develop a depressive state. Such inter-individual differences can be modeled in animal: following a chronic social defeat during one week, about half of the mice are vulnerable and will become “depressed” as evaluated by their anhedonia state or their social interaction scores, whereas the other half of the mice are resilient and will not displays such deficits and behave exactly as control animals.

Dopamine neurons in the ventral tegmental area (VTA) have been shown to play a key role in controlling stress susceptibility and resilience. However, upstream mechanisms responsible for the functional control of these neurons remain unknown. In our recent studies, we focus our attention on noradrenergic (NE) neurons in the Locus Coeruleus; the noradrenergic system has been implicated in the pathophysiology of depression, and these neurons have direct anatomical and functional connections within the VTA. Using specific mice models genetically engineered for an absence of functional NE release as well as optogenetic manipulations of this NE release, we were able to demonstrate the role of these noradrenergic neurons in regulating susceptibility to social defeat versus resilience against social defeat via inhibitory control of VTA-dopamine neurons.

By demonstrating that NE neurotransmission from the LC is both necessary and sufficient to promote resilience against social defeat, we introduced a new way to trigger resilience to emotional stress by manipulating NE neurotransmission. This finding now opens a novel understanding for future therapeutic strategies against depression and stress-related disorders.

Neural representation of space and Cerebellum

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The Nobel Prize in Medecine or Physiology for 2014 has been awarded to three neuroscientists: John O'Keefe, May-Britt Moser and Edvard Moser who discovered that the specific firing of place and grid cells constitutes a neural representation of space and travelled distances. This discovery highlighted how neural activity sustains our ability to localize ourselves, as we navigate into the world. We now know that this neural activity is driven by external and self-motion information and is used to navigate efficiently.

A key question remains however unanswered: which brain system processes these sensory signals en-route to neural representations of space?

We obtained results showing that the cerebellum is a core structure of this system. We found that intact cerebellar synaptic plasticity is required for efficient hippocampal space coding and could be at the core of the stabilization and update of spatial representation. More generally we find a functional interaction between the hippocampus and the cerebellum during sequence-based navigation in both mice and humans. Thus, the cerebellar-hippocampal interaction could be an invariant process monitoring spatial representation and subtending navigation across species.

Role of the mitochondrial pyruvate carrier in neuronal function

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During my talk, I will discuss the structure and function of the mitochondrial pyruvate carrier and its role in cell metabolism, in particular in relation to neuronal function.

Caspase-2 as a target in acute and chronic neurodegeneration

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Cysteine-dependent ASPartate-specific proteASES (Caspases) are central effectors of apoptosis and inflammation. The Caspase family also contribute to non-apoptotic form of regulated cell death. Independently of cell death, accumulating lines of evidence have also shown that caspases participate to major physiological processes including differentiation, tumour suppression, neural development, axon guidance and aging. Among caspases, caspase-2 (Nedd2, Ich-1, Casp2) has emerged as a unique caspase with potential roles in maintaining genomic stability, metabolism, chronic and acute neurodegeneration, and aging. We have for instance established that Casp-2 is a key initiator of neuronal cell death in neonatal brain damage. We and others have also proposed that Casp2 is a potential therapeutic target in human diseases, possibly in acute brain damage or neurodegenerative disorders. We have developed a group II (Casp2, Casp3, Casp7) caspase inhibitor, TRP601, which turned out to be a lead candidate for neuroprotective strategy in a variety of perinatal brain injury conditions. However, there is still a lack of genuine Casp2 inhibitors to be used as selective probes for activity detection and drug development. With the aid of structural information on the Casp2 we are now developing new series of compounds harboring Casp2 selectivity. Combining these new tools and genetic approaches in microfluidic neuronal cultures we are currently exploring the role of Casp2 in cellular models of neurodegenerative stress.

Lgr5 Stem Cells in self-renewal and cancer

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The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. We originally defined Lgr5 as a Wnt target gene, transcribed in colon cancer cells. Two knock-in alleles revealed exclusive expression of Lgr5 in cycling, columnar cells at the crypt base. Using lineage tracing experiments in adult mice, we found that these Lgr5+ve crypt base columnar cells (CBC) generated all epithelial lineages throughout life, implying that they represent the stem cell of the small intestine and colon. Lgr5 was subsequently found to represent an exquisitely specific and almost 'generic' marker for stem cells, including in hair follicles, kidney, liver, mammary gland, inner ear tongue and stomach epithelium.

Single sorted Lgr5+ve stem cells can initiate ever-expanding crypt-villus organoids, or so called 'mini-guts' in 3D culture. The technology is based on the observation that Lgr5 is the receptor for a potent stem cell growth factor, R-spondin. Similar 3D cultures systems have been developed for the Lgr5+ve stem cells of stomach, liver, pancreas and kidney. Using CRISPR/Cas9 technology, the CFTR locus has been corrected in intestinal organoids of cystic fibrosis patients.

POSTERS

Drosophila Genetic and Epigenetic Laboratory (GED Lab)

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Small non-coding RNAs are at the core of a universal system of gene regulation and immune defence against invading exogenous nucleic acids. Using Drosophila melanogaster as a model, our lab is interested in understanding the biogenesis and the function of small non-coding RNAs in homeostasis and under pathological conditions.

(i) Transposable elements (TEs) are mobile element that can trigger genetic instability and need to be tightly regulated. Our lab is interested in one of the main regulation mechanisms which implies piwi-associated small RNAs (piRNAs). Recently, we have shown that TE transcriptional silencing by piRNAs during early development is maintained independently of Piwi until adulthood. Furthermore, we have shown that TEs escaping Piwi silencing are controlled by the siRNA pathway in adult somatic tissues. We propose a model where, in somatic tissues, two layers of regulation by piRNAs and siRNAs cooperate to regulate TE and maintain genome stability.

(ii) In an attempt to characterize the small RNA molecular mechanisms, we performed a genome-wide screen that allows us to identify 18 new genes involved in miRNA silencing pathway. Many of them are also required for siRNA or piRNA silencing further emphasizing the overlap between the three small non-coding pathways existing in flies. We pursue the characterization of one of those genes encoding a potential RNA methyltransferase. We are also interested in investigating its role in human, in the perspective of identifying therapeutics targets in pathologies linked to small RNA silencing pathways disorders.

(iii) A second main axis of the lab is to analyze the regulation of small RNA pathways upon infections. Over the past few years, it became clear that acute viral infection can trigger the activation of small RNA pathways which constitute one of the main defence mechanism used by insects. Much less is known about the influences of persistent viral infection on host gene regulation. Recently, the Nora virus, a persistent Drosophila virus, was identified to cause an asymptomatic infection. Interestingly, our lab has demonstrated that this virus encodes a potent suppressor of RNA interference. Our aim is to understand the long-term genetic and epigenetic impact of Nora infection on host cells. The use of Drosophila as a unique experimental model is expected to provide new insights into physiological changes upon viral persistence, which influence the infection outcome and potentially lead to the discovery of new ways to target viral associated pathologies.

The ARTbio bioinformatics facility

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Through 5 main axes, the ARTbio bioinformatics analysis platform provides support to biologists in their analyses, at the IBPS and beyond.

Galaxy servers maintained at state of the art.
We will maintain our Galaxy server instances in configuration close to the highest standards which continuously evolve thanks to the Galaxy development community. Users with sufficient skill to autonomously conduct analysis using Galaxy will directly benefit from our public Mississippi Galaxy server (http://mississippi.snv.jussieu.fr). Other private Galaxy instances such as Plastisipi are dedicated to specific projects.

Analysis project support.
We will support NGS analysis projects through the use of the Galaxy interface. Interacting with biologists through the Galaxy framework is currently one of the best ways to give them consistent access to bioinformatics tools or complex workflows and to help them to perform reproducible and transparent analyses. We have experience in this activity and we propose more effective support to projects focusing on:

Small RNA and RNA biology
Epigenetics analyses
Virus detection and discovery
Variant and snp analyses
Metagenomics

Tool development
In a competitive context of a growing offer for highly relevant standalone or online software, focusing development to our area of biological expertise is the best way to deliver outstanding tools. We will develop Galaxy tools for small RNA analyses or for specific needs of expert users.

Training.
Analyses are better performed with educated users. We will participate to Galaxy training efforts and work at tutorials to help users in their analyses.

Cloud Infrastructure.
We took the option of having a light local hardware infrastructure, while keeping a maximum of our means to focus on tool development and user analysis projects. This implies working at migrating our services in cloud infrastructures, which we are doing primarily in collaboration with the Institut Français de Bioinformatique (IFB).

Seed biology

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The team «Seed Biology» is investigating the cellular and molecular events that control seed germination and dormancy. The work of the Seed Biology team is focused on the role of reactive oxygen species (ROS) in seed biology and on the molecular regulation of seed germination and dormancy. We associate physiological (germination assays in various environmental conditions), biochemical (ROS chemistry, oxidative processes), molecular (gene expression, protein synthesis) approaches to cell imaging and high throughput technologies (transcriptome, metabolome) for addressing our biological questions. The «Seed Biology» team is working with sunflower, barley and Arabidopsis seeds but has also a strong background in translational biology with crop species as shown by the numerous contracts that have been established with private seed companies.

Functional ultrasound imaging of a spatial navigation task in mobile rat

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Hippocampal theta rhythm is the electrophysiological signature of active locomotion during spatial navigation. It is critically involved in spatial memory, both during a task and subsequent sleep, and also plays a role in hippocampal- cortical interactions. Using functional ultrasound imaging (fUS) we sought to reveal the metabolic events associated with locomotion theta in mobile rats.

We recorded from rats walking along a linear maze, to address how brain-wide networks activate during periods of hippocampal theta rhythm. Healthy Sprague Dawley rats ran on a 2.25m long, 0.2m wide linear track for water reward. A single imaging plane included dorsal hippocampus, cortex with somatosensory areas, and thalamus. In order to temporally resolve hemodynamics as the animal crossed the maze fUS compound frames were acquired at 500Hz for 12s. Acquisition was triggered when the animal turned around, and was followed by a 40s lapse to collect the data. As expected, hippocampal theta was consistently associated with locomotion. Distance travelled over time was slower (56-

64%) than in control, surgery-free, rats ($p<10^{-6}$). Yet, maximum speed was only slightly slower for the initial 15min, with the difference reducing to non-significant 1% thereafter. In order to analyze series of track crossing trials, we aligned them by setting each trial reference time when the rat crossed the middle of the maze.

Hemodynamic changes ranged from -10 to +20%. As expected, theta band intra-hippocampal EEG power peaked at top animal speed, which was coincident with crossing the midline, with a mid-height theta peak width of 3.2+/-0.3s (n=8). In order to quantify functional activation during the task, we computed the maps of Pearson's correlation coefficient between power in the theta band and pixel intensity, for varying time lags. Averaging pixels across anatomical areas revealed hyper-perfusion in the somatosensory cortex, dorsal thalamus and hippocampus, and hypo-perfusion in the ventral thalamus. These correlations were consistent with fUS signal time course. Hyperemia peaked at 0.7-1.5s following the peak of hippocampal theta, which is compatible with signaling cascades that adapt blood flow to processing activation. Our data reveal a pattern of combined hippocampal and widespread cortical activation in a short time window around the navigation task, with coordinated dorsal thalamic activation and ventral thalamus suppression.

Optogenetic mapping of translaminar functional connectivity in the somatosensory cortex of rodents.

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While the six-layered structure of the neocortex is one of the most prominent features of the mammalian brain, the role of this laminar architecture in information processing is still elusive.

Multiple simultaneous intracellular recordings as well as glutamate uncaging and laser scanning photostimulation in brain slices allowed the emergence of a picture of the wiring diagram between cortical layers. However, these approaches do not allow evaluating the relationships between the strength of translaminar connectivity and the response properties to sensory stimuli of individual neurons.

We used in utero electroporation in mice to deliver ChannelRhodopsin-2 to layer 2/3 pyramidal neurons in the barrel cortex of mice. This technique allows the specic, fast and reliable control of the temporal pattern of activity in the transfected neurons, while recording simultaneously the spiking activity of several layer 5 cortical neurons in vivo.

We found that optogenetic stimulation of layer 2/3 pyramidal neurons enhances the activity of only a subset of layer 5 neurons, which have particular response properties to tactile stimulations.

Adaptive biology : Minimization of refractive index mismatch to improve axial resolution with novel mounting media

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Resolution, high signal intensity and elevated signal to noise ratio are key issues for biologists who aim to study the localisation of biological structures on the cellular and subcellular level with confocal microscopy. The resolution required to separate sub-cellular biological structures is often near to the resolving power of the microscope. When optimally used, confocal microscopes may reach resolutions of 150 nm laterally and 500 nm axially, however, axial resolution is often impaired by spherical aberration that may occur due to refractive index mismatches (1, 2). Spherical aberration results in broadening of the point-spread function (PSF), a decrease in peak signal intensity when imaging in depth and a focal shift that leads to the distortion of the image along the z-axis and thus in a scaling error.
In this study, we use novel high refractive index mounting media to eliminate the effects of spherical aberration. These mounting media are compatible with most common fluorochromes and fluorescent proteins. We compare their performance with conventional mounting media by estimating lateral and axial resolution with subresolution fluorescent beads. We show furthermore, that the use of our high refractive index media renders tissue transparent and improves considerably the axial resolution and imaging depth in immuno-labelled or fluorescent protein labelled fixed animal tissue (Fouquet et al., 2015). We propose thus to use those novel high refractive index mounting media, whenever optimal axial resolution is required.

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Live imaging identifies a novel mechanism of sensory organ formation whereby directed cell movements drive morphogenesis and axon emergence

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To form functional sensory neuronal circuits, neurons have to assemble into compact clusters to shape sensory organs and ganglia, and send out axons transmitting information to the brain. Very little is known about how these two processes are regulated and coordinated in vivo. We use the olfactory placode in zebrafish as a system to address the underlying mechanisms. We find that cell death and proliferation are dispensable for olfactory placode morphogenesis. Live imaging demonstrates that it is rather achieved through coordinated and directed cell movements. Interestingly, axon formation is concomitant with placode morphogenesis and is also driven by cell movements. Instead of resulting from the expected outgrowth of axons from static cell bodies towards the brain, it occurs by displacement of cell bodies away from axon tips attached to the brain surface. This work unravels a novel mechanism of sensory organ formation, whereby directed cell movements drive both the morphogenesis of a neuronal cluster and the emergence of axonal contacts with the brain. We are currently analysing cell protrusions (lamellipodia, filopodia) and actomyosin dynamics in placodal neurons. Our results suggest that some of the observed movements are active, ie powered by internal, cell-autonomous forces, whereas others rather represent passive displacements, likely triggered by external pulling or pushing forces. We plan to map the mechanical forces exerted within the rearranging placodal tissue, and to probe the influence of external mechanical stimuli on cell behaviours. This will be essential to fully understand the mechanisms of olfactory placode assembly and its coordination with axon formation.

JET2-Viewer: a web server predicting multiple protein-protein interaction sites for PDB structures

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High-resolution characterization of protein functional sites and molecular determinants remains rooted in heavy experimental mutational analysis. JET2 is a new tool (Laine and Carbone, 2015) that addresses these questions. It accurately predicts protein-protein interfaces, understanding their properties, origins and binding to multiple partners. The method uses three sequence- and structure-based descriptors of protein residues: evolutionary conservation, physico- chemical properties and local geometry. Appropriate combinations of these descriptors yield very precise predictions for a wide range of protein-protein interfaces and discriminates them from small-molecule binding sites. Beyond its predictive power, the approach permits to dissect interaction surfaces and unravel their complexity.

JET2 Viewer is a web server that reports the results produced by JET2 on more than 40 000 chains. These chains represent the structural diversity of more than 20 000 PDB structures and constitute the nonredundant set of non-homologous (<40% id) protein chains extracted from all PDB structures. They generated a very large knowledge base that will soon be made accessible to the community. The web site gives access to an online intelligent display of the predicted interaction sites on PDB structures, and to suitable PyMOL file recording JET2 analyses.

Availability: The web server is available at http://www.lcqb.upmc.fr/jet2_viewer/report/index.html.

Vulnerability of the neural circuitry involved in the expression of male sexual behavior to adult exposure to endocrine disruptors

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A general finding of the last decades is the increased incidence of diseases and reproductive system dysfunctions in humans. A decrease in male fertility or sperm quality, in association with exposure to certain endocrine disrupting chemicals was reported. Endocrine disruptors are natural or environmental pollutants produced by humans capable of interfering with endogenous hormones or their signaling pathways. If their effects and mechanisms of action peripherally are extensively studied, their impacts and mechanisms at the central level still need to be elucidated. In this context, we have recently shown that adult, and not perinatal, exposure to bisphenol A reduces male sexual behavior at the Tolerable Daily Intake (TDI) dose (the lower reference dose). The present study aims to determine whether the vulnerability to adult exposure to endocrine disrupters, an under-estimated period in endocrine disrupters, extends to other endocrine disrupters with anti-androgenic activity. Nonylphenol (NP) and di (2-ethylhexyl) phthalate (DEHP) are two emergent compounds widely used in the industry and day life. This results in a large environmental animal and human contamination. DEHP is described as an anti-androgenic molecule, while NP seems to act as estrogenic and antiandrogenic molecule. In males, testosterone controls the expression of reproductive behaviors and signals either directly through androgen receptors or indirectly through estrogen receptors after neural aromatization into estradiol.

In this study, adult males were orally exposed for 1 month to DEHP or NP at the TDI dose (50 µg/kg bw/d) and to lower doses close to the environmental human contamination (0.5 and 5 µg/kg bw/d). Behavioral analyses included sexual behavior, attractiveness, olfactory preference, ultrasonic vocalizations and other behaviors modulated by sex steroids and able to interfere with mating when altered (locomotor activity, anxiety-related behavior). As neuroendocrine analyses showed unaltered levels of testosterone and GnRH/kisspeptin system, we conducted neuroanatomical and molecular studies in the neural circuitry underlying sexual behavior in order to determine whether exposure to DEHP or NP affects expression of sex steroid receptor or other target genes related to these pathways. All these results will be presented.

Function of DSCR6 (Down Syndrom Critical Region 6) during vertebrate development

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One of the most challenging questions in developmental biology is to understand how a totipotent zygote differentiates into an organism containing all cell lineages. Our team focuses on the cellular and molecular events that control embryonic induction and establishment of dorso-ventral and anteroposterior axis in vertebrates. Our main goal is to understand common mechanisms between early development and human diseases. In this context, we focused onto genes localized in the human DSCR region (Down Syndrom Critical Region). This region located on the chromosome 21 in human is sufficient to reproduce in mouse transgenic models most of the features found in Down Syndrom patients. Dscr6 is localized in this region. We have shown that xdscr6 is a maternal determinant able to induce mesoderm in Xenopus embryo. It dorsalizes ventral mesoderm during gastrulation and induces a secondary embryonic axis. This ability could be explain by the fact that XDSCR6 physically and functionally interacts with polycomb proteins like XEZH2, preventing its accumulation in Polycomb bodies, releasing it from the chromatin, and antagonising its repressor activity. More recently we have also identified STAT3 as a protein partner of XDSCR6. This bona fide transcriptional regulator is important for dorso-ventral patterning in Xenopus embryo. Moreover, it has been recently shown that STAT3 activity is positively regulated by EZH2 in stem-like glioblastoma cells to promote their tumorigenicity, revealing the existence of a functional STAT-EZH2 complex in mammals. Thus, DSCR6 could be located at the interplay between chromatin regulators and transcriptional factors during development but also during oncogenesis in vertebrates. Our aim is to determine how a tripartite complex including XDSCR6, XEZH2 and XSTAT3 could act during axis formation and layers specification. We have already defined spatio-temporal profile for each protein in Xenopus embryos and shown that XEZH2, XSTAT3 and XDSCR6 assemble as a tripartite complex. Moreover, XDSCR6 like a dominant negative form of XEZH2, antagonises endogenous XSTAT3 transcriptional activity. Furthermore knockdown of XEZH2 activity in ventral region mimics axis duplication induced by XDSCR6. Our future researches will determine if the mechanisms occurring during Xenopus development can be generalize to mammals development and oncogenesis.

Functional ultrasound imaging of spontaneous absence seizure in awake rat

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Absence epilepsy seizures consist in bilateral spike-and-wave discharges occurring in the thalamocortical circuit. In genetic rat models seizures emerge from the somatosensory cortex. A vascular correlate has been described both by NIRS and fMRI experiments, suggesting that localized and/or anticipatory vascular events coincide with EEG discharges. We sought to reveal these events with improved sensitivity and spatiotemporal resolution, using functional ultrasound imaging (fUS).

We scanned through the brain of epileptic rats, to address the heterogeneous alterations in neuro-metabolic coupling during hypersynchronous seizure activity. Spontaneous generalized absence seizures were recorded from bilateral cortical electrodes in Genetic Absence Epilepsy Rats from Strasbourg (GAERS). The ultrasound acquisition sequence consisted in alternating 200ms to generate one compound mfUS image followed with 2.8s of processing. Multiple imaging planes were scanned for 10-15min each. In order to test the effect of the imaging procedure, we quantified both the relative time spent seizing and seizure duration, and found no significant difference between control and imaging conditions.

Hemodynamic changes in seizure-associated areas ranged from -10% to +20%. We found distinct patterns of correlation across structures along the antero-posterior axis. Hyper-perfusion in the somatosensory cortex and thalamus was concomitant with hypo-perfusion in the Caudate Putamen and no variation in the hippocampus. Although absence seizures are generalized throughout neocortex, vascular alterations showed spatial compartments, and lateralization in the frontal primary sensory cortex perfusion was observed in half of the animals. Furthermore, consecutive seizures with a similar bilateral cortical EEG profile could display distinct bilateral or unilateral perfusion course. Comparing the dynamics of cortical and thalamic areas coupled to seizure revealed synchronous oscillations in the perfusion pattern. Thus, the responses we observed across anatomical structures are compatible with EEG-fMRI experiments that found inversed electrographic-hemodynamic coupling between the cortex and CPu, and with time-resolved EEG-NIRS experiments that indicate blood flow fluctuations around seizures initiation. With the best of time and spatial resolution of these two techniques, fUS further points to cortical decoupling between electrographic activity and perfusion, with both static and transient components, in naturally occurring seizures.

Characterization of the expression patterns of genes coding for actors of the Wnt/Beta-catenin pathway in the medusa of clytia hemisphaerica

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The Wnt/β-catenin pathway is implied in the setting of the primary body axis during embryonic development in metazoans, and in its maintenance in adult cnidarian polyps. Medusozoan evolution involved events which led to the acquisition of a new stage in their life cycle: the medusa. This stage is characterized by the setting of an original body plan through post-embryonic development, with major differences observed between two main medusozoan lineages: hydrozoans and scyphozoans. However, up to now studies of signalling pathways in cnidarians have been focusing on planula larva and polyp stage. What can the expression of actors of the Wnt/β-catenin pathway in a medusa tell us about the origination(s) of this stage in medusozoans?

Here we reassess the orthologies between cnidarian and bilaterian Wnts through phylogenetic analyses involving increased taxonomic sampling compared to previous studies. The expression of most genes coding for potential actors and antagonists of the Wnt/β-catenin pathway has been analysed by in situ hybridisation in the medusa of the hydrozoan Clytia hemisphaerica. This study aims at bringing a better understanding of orthology relationships within the family of Wnt ligands at the metazoan level. It is furthermore a first step in tackling the issue of the acquisition of the medusa stage and more specifically the contribution of a major signalling pathway in the elaboration of this original body plan during medusozoan evolution.

Large-scale study of genetic exchange through bipartite graphs

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Genetic exchange events are recognized as an important driving force in the evolution of prokaryotes. Here, we implement a series of simple analyses to explore gene transmission between 382 prokaryotic genomes, thousands of plasmid and viral genomes using bipartite graphs.

With this strategy, we confirmed that gene transmission is neither random in terms of targets, nor in terms of functions of the transmitted genes. We unraveled high rates of gene externalization in prokaryotic genomes, with detectable differences in proportion and dynamics between bacteria and archaea, to the interesting exception of Haloarchaea.

We argue that these externalized genes produce extra-genomic paralogues, and constitute a major evolutionary outcome of gene transmission in the microbial world.

Pou3f4 plays essential roles in kidney development

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In Xenopus laevis, the pronephros is the functional kidney at larval stages. It is composed of a single nephron made up of the glomus, the tubule which is segmented along the antero-posterior axis, and the duct. The first sign of morphogenesis occurs at early tailbud stage with the pronephric anlage condensation. Then, the anlage is regionalized by the differential expression of various genes. This regionalization instigates nephron segmentation. After a functional differentiation, each segment of the nephron is characterized by the expression of specific solute transporters.

In mouse, during nephrogenesis, Pou3f3 is expressed in the prospective Henle's loop and distal convoluted tubule (functional analogs of pronephric intermediate and distal tubule). It is essential for the elongation and the differentiation of the developing Henle's loop. Pou3f3 is part of the POU domain transcription factor family characterized by a bipartite DNA binding. Among the four members of the class III POU genes, only pou3f3 expression and function in the developing kidney have been studied in mouse.

First, we determined which members of the class III POU genes were expressed in the developing pronephros by an in situ hybridization and RT-qPCR analysis of their spatio-temporal expression profile during the X.laevis development. We found that pou3f3 and pou3f4 present a pronephric expression as soon as the early taibud stage. At tadpole stage, pou3f3 is expressed, like in mouse, in the intermediate and distal tubule, and pou3f4 in the intermediate, distal tubule and duct.

To elucidate the role of Pou3f4 in pronephros development, we performed gain and loss of function experiments. Pou3f4 loss of function prevents intermediate tubule marker gene expression and leads to a decrease of terminal differentiation marker gene expression in the proximal and distal tubule. Pou3f4 gain of function induces an expansion of intermediate tubule marker gene expression and a decrease of terminal differentiation marker gene expression in the proximal and distal tubule. Pou3f4 plays a crucial role in tubule regionalization and terminal differentiation.

A role for odorant receptor mRNAs in axons of olfactory sensory neurons in mice?

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The axons of olfactory sensory neurons project from the olfactory epithelium in the nasal cavity to stereotyped targets within the olfactory bulb in the brain. Neurons that express the same odorant receptor project to a specic place in the bulb, resulting in an atypical discrete projection map depending on the identity of the axons in term of odorant receptor.
Thus, odorant receptors have at least two functions in olfactory sensory neurons in mice: the detection and transduction of odorant molecules, and the sorting and coalescence of axons in the brain. We previously demonstrated that odorant receptor messenger RNAs (mRNAs) are locally translated in axons, indicating that the odorant receptor proteins present in axons may have a local origin. Furthermore, we showed that odorant receptors promote adhesion of cells in a biophysical assay. We are now demonstrating the presence in the axons of olfactory sensory neurons of various components of the translation machinery. Moreover, we are characterizing 3' untranslated regions (3'UTRs) of odorant receptor mRNAs to address the regulation of their localization and translation. In future work, understanding the regulation of the local translation of odorant receptors will allow to further investigate their role in the formation and maintenance of the olfactory primary map.

Fine-tuning of Cdc6 accumulation by Cdk1 and MAP kinase is essential for completion of oocyte meiotic divisions

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In somatic cells, the protein Cdc6 is a major regulator of DNA replication and synchronizes S-phase with cell division by regulating the activation of the kinase Cdk1. While this protein is widely studied in somatic cells, its function and regulation during the female meiotic division remains elusive. Inn ovary, vertebrate oocytes are arrested in prophase of the 1st meiotic division and resume meiosis by activating Cdk1 upon hormonal stimulation. Oocytes then proceed through the 1st and the 2nd meiotic division without S-phase in between to become haploid. Although DNA replication does not take place, unfertilized oocytes acquire the competence to replicate DNA one hour after the 1st meiotic division by accumulating the single missing factor of the replicative machinery, Cdc6. Using Xenopus oocytes, we discovered that the turnover of Cdc6 is strictly regulated during meiosis by two main mechanisms: its interaction with Cyclins B that accumulate between the two meiotic divisions and the germ-cell specic Mos/MAPK pathway, which remains active after the 1st meiotic division. During meiosis resumption, Cdc6 starts to be expressed but cannot accumulate due to a proteasome-dependent degradation mechanism activated downstream Cdk1 activation.

During the 1st meiotic division, the interaction between Cdc6 and Cyclin B stabilizes the protein. However, Cdc6 cannot reappear because the Mos/MAPK pathway is activated and synchronizes its accumulation with the 2nd meiotic division. This timely expression of Cdc6 is essential for the normal progression of oocyte throughout meiosis since overexpressing Cdc6 inhibits Cdk1 reactivation and drives the oocyte into a replicative interphasic state. Hence, the ne-tuning of Cdc6 accumulation is required to ensure the two successive waves of Cdk1 activation required for the meiotic cell division and to avoid unscheduled DNA replication before fertilization.

Reprogramming GABA Metabolism towards GHB production decreases 5-hydroxymethylcytosine levels to repress malignant glioma cell growth

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Most neoplasms contain heterogeneous populations of cancer cells with varying degrees of aggressiveness notably in terms of proliferation and tumorigenic abilities. Considering the importance of metabolism reprogramming in supporting tumour growth, we envisaged the possibility that dened metabolic states restrict the tumorigenic potential of cancer cells. We addressed this question by exploring rst the changes in metabolism that accompany the differentiation of glioblastoma stem cells into poorly aggressive cells in response to miR-302-367 expression. We identied a reprogramming of the GABA metabolism resulting in enhanced GHB (g-hydroxybutyrate or 4-hydroxybutyrate) production. This reprogramming was driven by downregulation of the mitochondrial enzyme SSADH (succinic semialdehyde dehydrogenase) that switches GABA catabolism from succinate production towards GHB production.

Finding a positive correlation between mRNA levels of ALDH5A1 encoding SSADH, and tumorigenic properties in an independent published dataset of 78 human glioblastoma cell lines suggested that GABA metabolism reprogramming could be functionally relevant for cancer cell behaviour. Using cultures of glioma stem cells (GSC, n=13), each isolated from distinct malignant gliomas from adult or paediatric patients, we found that GHB represses cancer cell growth in all cases. GHB accumulation resulting from ALDH5A1 knock down or GHB treatment inhibited in turn the TET (Ten-Eleven-Translocation) dioxygenases, which catalyse the formation of the 5-hydroxymethylcytosine DNA epigenetic mark. We further show that either ALDH5A1 knockdown, GHB treatment or TET2 knockdown all decrease 5-hydroxymethylcytosine levels, trigger a nuclear exclusion of Nanog and reduce GSC growth, leading GSC to dierentiate into poorly aggressive cells. All acted on adult GSC as on paediatric GSC. Of note, GSC isolated from paediatric malignant glioma bear a H3.3K27M mutation that drives massive epigenetic deregulations. These results show that GHB acts as an anti-cancerous metabolite across a variety of genetic backgrounds.

Diatom responses to light: a tale of energy, rythms and colors

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Light is a key environmental signal for life on earth. It supplies energy for photosynthesis and represents a source of information from the environment, controlling physiological, adaptive and biochemical processes in most living organisms. Rhythmic light changes also synchronize basic biological mechanisms, allowing species to optimize their growth, propagation and survival. As on land, both irradiance and light quality change drastically in the different marine habitats, with blue light prevailing at increasing depths, this providing peculiar condition for life of marine organisms.

Diatoms are major components of eukaryotic phytoplankton standing at the crossroads of several evolutionary lineages and providing around 20% of global carbon fixation. The major objective of our research is to exploit novel genetic tools and genomic information to decipher light sensing and acclimation mechanisms, which synergistically control diatom growth and distribution in the marine environment. These analyses are revealing a surprising functional diversification of diatom photoreceptors and uncovering several novel nuclear factors regulating diatom growth and adaptive responses to light stress. It is becoming increasingly clear that differences in the light field have led to a variety of evolutionary adaptations in diatom light response regulators, which are without parallel in terrestrial systems. A summary of the latest results of the team will be presented.

Magnetic-Fluid-Loaded Liposomes (MFLs) for Selective Imaging and Treatment of Brain Tumors: example of combination of multi-scale approaches to validate in vivo magnetic targeting.

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Hybrid devices based on the association of iron oxides with lipid nanoscale particles play an increasing role for targeted delivery of chemotherapeutics, mainly due to their biocompatibility and intrinsic efficacy as contrast agents for in-vivo Magnetic Resonance Imaging (MRI). In this study, we aimed at demonstrating the targeting of glioblastoma, into the striatum of mice, using magnetic-fluid-loaded liposomes (MFLs). MFLs targeting was achieved with a magnetic field gradient, from a magnet placed onto the head of the mice.

In vivo MRI showed that MFLs were successfully delivered to glioblastoma cells via the vasculature. Brains were then processed for Transmission Electron Microscopy (TEM) and Chemical mapping using Energy-Filtered TEM (EFTEM). MFLs were identified as electron dense clusters of iron nanoparticles inside cells lining the vascular lumen or in the adjacent extracellular matrix space.

Challenge here was to localize 200 nm diameter particles randomly dispersed into a complex tissue (glioblastoma). To avoid looking for a needle in a haystack, we exploited the internal rhodamine labeling of MFLs to localize magnetic-fluid-enriched regions on 70 □m thick sections, prior to TEM or EFTEM preparation.

The results revealed MFLs as potent tools for selective targeting of malignant brain tumors, especially promising for therapeutic issue as it can be expected that healthy brain tissue will be spared upon treatments by deleterious anticancer drugs carried by MFLs.

Reference

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

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Primary cell cultures from tentacles of the temperate symbiotic sea anemone, *Anemonia viridis*, have been recently made available in our laboratory. In order to propose a new suitable model to investigate molecular and cellular events involved in the establishment and maintenance of the Cnidarian-Dinoflagelatte symbiosis, the characterization of animal cultured cells is an essential step. By the optimization of the protocol previously developed, we measured/evaluated the cell growth capacity and viability of animal cells during maintenance and propagation of 31-day cultures. We showed that cell growth is maximal during the first two weeks in plate culture with a 20-fold increase of living cells. Cells in hanging drop culture also showed around 90% of viability all over the culture period but a very low rate of growth (0.5-fold increase). The cell type characterization identied by molecular analysis showed a gastrodermal signature.

Mechanotransduction underlying tendon cell differentiation

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Tendons are unique forms of connective tissue, which are components of the musculoskeletal system. Tendons are comprised of a dense extracellular matrix of type I collagen fibrils that are hierarchically organized to withstand tensile forces transmitted from muscle to bone. Tendon development, homeostasis and repair rely on specific combinations of mechanical parameters, transcription factors and growth factors that regulate the production and spatial organisation of type I collagen. Our objective is to decipher the mechanotransduction pathways underlying tendon cell differentiation during development, homeostasis and repair. Tendon mechanobiology was studied in vivo during development and in vitro using a murine cell line of mesenchymal stem cells (MSCs) in 2-dimensional (2D) cell culture systems but also in a 3-dimensional (3D) culture system that mimicks in vitro tendon formation.

The inhibition of muscle contraction in chick embryos led to a drastic decrease of the expression of the tendon marker Scx, while the expression of cartilage markers Sox9 and Aggrecan was increased in limbs. The mRNA levels of the mechanosensitive genes Egr1 and Srf were also downregulated in immobilized embryos.

We analysed the effect of molecular and mechanical parameters on the MSC tenogenic potential. Ectopic application of TGF-β2 or Egr1 induced Scx expression, while inhibiting cartilage marker expression. However, TGFβ2 decreased Tnmd expression, while Egr1 increased Tnmd expression.

Substrat stiffness and cell confluence also affected the tenogenic potential of MSCs, as well as the expression of bone- and cartilage-associated genes. The effect of mechanical stress on the tenogenic potential of MSCs was also assessed, using a bioreactor applying different strains to the cells.

MSCs were cultured in a 3D environment in fibrin gel constructs under tension, which mimicked tendon formation. The expression of tendon genes, Egr1, Srf target genes and TGFβ2 signalling was increased in 3D tendon constructs versus cells cultured in 2D. Tension release in 3D tendon constructs induced a drop of expression of the tendon genes, Egr1 and Tgfb2. Forced-expression of Egr1 was able to rescue tendon gene expression in addition to that of Tgbf2 in de-tensioned 3D tendon constructs.

All together, these results highlight the importance of the mechanical forces in cell differentiation during tendon formation. However, the precise relationship between forces, mechanosensitive transcription factors and signalling pathways remains to be further explored.

Snail factors, Escargot and Scratch, regulate neural commitment by repressing N-activity in Drosophila sensory organs

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How can neural precursor cells maintain their neural commitment in spit of the series of cell divisions that they undergo? We address this question in the cell lineage that gives rise to the mechanosensory organs of Drosophila. In this lineage a primary precursor cell (pI) undergoes a stereotyped sequence of oriented asymmetric cell divisions and generates a neurone and four other non-neuronal accessory cells forming the sensory organs. The division of pI cell produces two secondary precursor cells, a neural precursor cell (pIIb) and a non-neural precursor cell (pIIa). Later, pIIb divides to form a tertiary precursor cell (pIIIb) that divides and generates the neurone. Thus, as they repeatedly divide, pI cells transit through two different neural precursor states (pIIb and pIIIb) before acquiring a neurone identity. Using a combination of genetic and cell biology strategies, we show that Escargot and Scratch, two transcription factors belonging to the Snail superfamily, act redundantly to maintain neural precursor cell commitment in pI daughter cells by downregulating Notch pathway activity. Our results indicate that these factors repress transcription of Notch-gene targets by specific binding to their promoters. Since Snail factors are expressed in various precursor cell types in many organisms ranging from Drosophila to humans, these results should have important and general implications for the understanding of neural precursor cell maintenance and differentiation.

Phenotypic plasticity and regulation of chromatin structure in Drosophila

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Phenotypic plasticity describes the ability of a given genotype to produce different phenotypes in response to distinct environmental conditions. Many examples are known where fluctuations in abiotic (temperature, light, soil composition) or biotic (population density, presence/absence of predators or pathogens, nutrition) factors lead to phenotypic variation. This has major implications in medicine and agronomy and is thought to facilitate evolution as it broadens the range of phenotypes produced by a particular genotype. Phenotypic plasticity can also be an adaptation to fluctuating environments such as seasonal variations.

In Drosophila melanogaster, female abdominal pigmentation is temperature sensitive. It is thought to be adaptive as low temperature leads to darker pigmentation, which increases body temperature. We use this trait as a model of phenotypic plasticity to analyse how the environment affects gene regulation through chromatin structure.

We show here that temperature modulates expression of the pigmentation enzyme coding gene tan (t) in abdominal epidermis of freshly hatched females. Genetic experiments show that modulation of t expression by temperature plays a major role in female abdominal pigmentation plasticity. Temperature modulates the activity of a t abdominal enhancer, t_MSE. However, this enhancer has a similar opened structure at low and high temperature and the active histone mark H3K27ac is enriched but not modulated by temperature. In contrast, chromatin of t promoter is more opened at 18°C and the active mark H3K4me3 is strongly modulated by temperature. Reaction norms (pigmentation as a function of temperature) of mutants for the chromatin regulators involved in H3K4 methylation indicate that these mutations affect phenotypic plasticity of female abdominal pigmentation.

Altogether, our results show that regulation of chromatin plays a major role in female abdominal pigmentation plasticity. We are now reconstructing the gene regulatory network involved in t regulation in order to analyse how it is modulated by temperature.

Genetic and Epigenetic Regulation of Pancreas Development

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The pancreas is an interesting model recapitulating the fundamental mechanisms of development (cell lineage specification, cellular identity, migration, polarity...), with a medical relevance given the high prevalence of diabetes and the high morbidity of pancreatic cancer. Our goal is to understand the molecular mechanisms and the regulatory networks involved in differentiation of pancreatic endocrine and exocrine cells, in relation to human physiopathology. We study genetic and epigenetic control of pancreas organogenesis and function, using different mouse models allowing analysis of the role of transcription factors and epigenetic factors. We focus on the transcription factor Hnf1b and on the epigenetic factors histone deacetylases (HDACs), combining phenotypic, physiological and molecular analyzes. Our results and ongoing projects reveal their roles in proliferation of pancreatic progenitors, islet morphogenesis, acinar homeostasis and pancreas regeneration. Our findings are important to decipher the regulatory networks controlling these processes and also to contribute to development of new therapeutic approaches for diabetes and pancreatic cancer treatment.

Spastin short isoform acts as a downstream target of the Neuropilin 1 receptor during zebrash spinal motor neuron development

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Hereditary Spastic Paraplegia (HSP) is a heterogeneous group of neurodegenerative disorders characterized by progressive spasticity of the lower limbs due to the degeneration of the cortico-spinal tracts. Among the numerous Spastic Paraplegia Genes, SPG4, encoding the microtubule-severing spastin, is mutated in the most frequent form of autosomal dominant HSP. MT-severing by spastin has been involved in diverse cellular processes such endosomal tubulation, ER shaping and cytokinesis, and is essential for axonal development, maintenance and transport homeostasis. SPG4 transcript directs the synthesis of two spastin isoforms through the usage of alternative translational start sites: a long one of 68kDa and a short one of 60 kDa showing dierent structural domains, subcellular distributions and binding partners. However, their specic role and respective contribution to HSP pathogenesis remain largely unknown.

To unravel the neuronal function of these two isoforms, we performed loss-of-function experiments during zebrash development using antisense morpholino oligonucleotides targeted against each spastin translation start sites. We showed that each knockdown dierentially aects zebrash morphology, mobility and axon pathnding of spinal motor neurons (SMN).

Interestingly, zebrash larvae lacking the short isoform exhibit morphological and SMN defects that strikingly mimic those observed in larvae depleted of the Semaphorin receptor Neuropilin1a (Nrp1a). Furthermore, the double knockdown of Nrp1a and Spastin short isoform (but not the long form) signicantly aggravates SMN defects while overexpression of Spastin short isoform partially rescues the SMN defects of Nrp1a-depleted larvae.

Altogether, our results reveal that the two main Spastin isoforms play dierential roles in zebrash spinal motor axon targeting in vivo and demonstrate the specic involvement of the short isoform in the Semaphorin/Neuropilin pathway.

COMMA: fully automated tool for dissecting protein architecture

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Proteins adapt their shape and motions due to changes in environmental conditions. Characterising protein conformational dynamics is increasingly recognised as necessary to decipher the function of proteins. Given a conformational ensemble, computational tools are needed to extract in a systematic way pertinent and comprehensive biological information. We have developed a tool, Communication Mapping (COMMA), that identifies the dynamical architecture of proteins from all-atom molecular dynamics (MD) simulations in explicit solvent (1). COMMA extracts the dynamical properties of the protein at the residue level from conformational ensembles and employs them to identify communication routes (pathways) between residues. It defines communication blocks, that are groups of residues with high communication propensity and strong non-covalent interactions and maps this information on the structure of the protein. We show the utility and capabilities of COMMA by applying it to three archetypal proteins, namely protein A, the tyrosine kinase KIT and the tumour suppressor p53. COMMA is useful to identify residues playing a key role in protein allosteric regulation and to explain the effects of deleterious mutations in a mechanistic way. It enables us to detect the key pathways on the structure of the proteins. COMMA is a fully automated tool with broad applicability. It is freely available to the community at www.lcqb.upmc.fr/COMMA.

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Dissecting how mechanical forces impact on cellular processes

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The general goal of the lab is to achieve a global (mesoscopic) view of the mechanical forces that drive embryonic morphogenesisusing *C. elegans* embryos as a model. These embryos elongate four-fold along their anterior-posterior axis, in the absence of cell division and cell intercalation. Elongation entails lengthening of some adherens junctions, shortening of others, shortening of actin filaments, and remodelling of hemidesmosomes. The first half of elongation depends solely on epidermal cells, whereas the second depends on an interaction between the epidermis and the underlying muscles, which provide a mechanical input. We will illustrate some of the approaches that we are implementing.

To understand how mechanical forces lengthen the embryo, we are examining whether the apical extracellular matrix could play a role by characterizing proteins located with the so-called embryonic sheath, which covers the embryo. Our data indeed suggest that this layer could help distribute the tension originating from non-muscle myosin-2 and from muscle myosin. To understand how the mechanical tensile input brought by muscles influences embryo lengthening, we have carried out genetic screens for mutants affecting elongation, and in particular junction remodelling. To analyse how these mutants act, we use SPIM and spinning disk microscopy. We are also implementing TIRF microscopy to monitor actin and microtubule dynamics at the single molecule level, and plan to use TIRF to examine the trafficking of junctional proteins.

Some of our key findings include: 1/ the identification of a mechanotransduction pathway whereby muscle tension activates a protein kinase acting on intermediate filaments; 2/ the characterization of the mechanical role of the apical extracellular matrix in morphogenesis; 3/ the characterization of a pathway to reorganize junctions.

Mass spectrometry and proteomics for your projects

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The mass spectrometry and proteomics platform offers its expertise to help you strengthen your existing research projects, or develop new ones, for the characterization and quantification of molecules and biomolecules. We can help you design and tailor your experiment for proteomics and mass spectrometry (MS), assist in or perform important parts of the sample preparation, and decipher the analysis results.

For sample preparation, we can assist in classical biochemistry: 1D SDS-PAGE or native gels, protein digestion and sample clean-up. We also develop liquid chromatography (LC) for protein digest fractionation before HPLC-MS/MS. We focus on reverse phase for orthogonal or diagonal 2D LC, and on phosphopeptide enrichment. Finally, our workflows can be adapted to quantitative measurements.

For MS, we are equipped with electrospray (ESI) and matrix-assisted laser desorption ionization (MALDI) sources. The MALDI-TOF De-Pro Voyager is readily available after a two days training for the rapid characterization of simple mixtures. The MALDI-TOF/TOF 4700 Proteomics Analyzer expands on that with the available MS/MS fragmentation to go deeper into molecular characterization. The ESI Q-Trap can characterize medium complexity mixtures by MS and MSn, offers the MRM mode for better sensitivity and quantification, and can be coupled to a microLC. The ESI LTQ Orbitrap XL allows high resolution and accuracy measurements, and multiple fragmentation modes. Coupled to a nanoLC separation, its high scanning speed can handle complex mixtures.

Data evaluation and processing will be performed in close collaboration with you. We want to make sure that you fully comprehend the data produced. Regarding proteomics, we will take care of the database search, the validation of the identifications and some proteome annotations. Classical quantification by isotopic labeling and statistical treatment can also be performed, and we are developing label-free quantification.

Persistent molecular associations in eukaryotes by fusion of genes from ancient prokaryote operons

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Eukaryogenesis (i.e the origin of eukaryotic cells) has been acompanied with major changes. Size population decreased, transcription/translation have been decoupled because of nucleus innovation, intron invaded genes… All these changes deeply impacted genome architecture. Notably, assuming that eukaryotes arose from the merging of one archaea and at least one eubacteria (i.e the ancestor of mitochondria), one could expect operons, a group of co-transcribed genes, a central structure in prokaryotic genomes, could be present in eukaryotic genomes, at least, as part of the DNA transferred from prokaryote ancestors. However, operons of prokaryotic origin are absents in eukaryotes. In this study, we found that some eukaryotic specific genes are fusions of genes colocalized in operon in extant prokaryotic species. Some of these fusions are widely distributed in eukaryotic supergroups and thus seem ancient, some others are lineage specific. Interestingly, a few number of these fusions have frozen, in the sense that the genes that composed the fusion are never found alone in the genome, suggesting strong functional constraints maintaining these genes fused.

De novo assembly pipeline for transcriptomic analysis

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High-throughput sequencing technologies generate unprecedented amounts of genomic data. These recent methodological breakthrough are particularly interesting to study the biology of non-culturable organisms for which there is no reference genome. This is the case for many of the marine planktonic organisms, in which symbiotic interactions between microalgae and a predator host (photosymbiosis) are frequently observed but remains poorly known. Our works propose the establishment of an original de novo assembly method for RNA-Seq data and the exploration of transcriptome. More specifically we will apply our methods to the study of the photosymbiosis processes in the marine plankton. The RNA-Seq de novo assembly allow to reconstruct most of the transcripts of an organism from its sequenced transcriptome. Our pipeline is based on this technique and process the analysis to carry out the exploration of the transcriptome and the annotation of the studied species. The originality of our program lies in its ability to merge the transcriptomes reconstituted by two different assembly programs (Trinity and Velvet / Oases), in order to take the best of both assemblers for a given dataset of raw sequences. We have tested our pipeline on an existing transcriptome from yeast to validate its performance. The success of the validation step led us to its application on RNA-Seq data in the context of the investigation on photosymbiosis in the marine plankton. Using our program we reconstructed the transcriptomes of four symbiotic microalgaes. The exploration of transcriptomes from the holobiont (mix host + symbiont) is still in progress. We developed a new methods to explored the transcriptomes of the symbiotic microalgae. This methods, based on sequence similarity networks applied to RNA-Seq data aims at classify sequences and having a support for partitioning our downstream analyzes on restreint groups of sequences. Ultimately, our analysis will promote the understanding of processes involved in marine photosymbiosis.

Bio-scaffolding regenerative matrices for combinatory approaches for traumatic spinal cord repair

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Recent progress in the production of novel biomaterials offers a particularly promising perspective for the development of combinatorial therapeutic strategies for spinal cord injury (SCI) repair that will include implantation of such biomaterials into the lesion site, functioning both as extracellular matrix substitute, and as bioactive support structure.

Accordingly and as first step, we developed a therapeutic strategy based on the use of chitosan polymer, that exhibits ideal characteristics for tissue engineering. Thus, after evaluation of various structures, we were able to determine the formulation that appears the best suited for implantation into the SCI lesion site. Our experimental paradigm is a thoracic dorsal hemisection in adult female rat, with or without implantation of polymer directly after the lesion.

The bio-scaffolds lead to an important reduction of astrogliosis, impeding glial scar formation, tissue necrosis, and hence reducing the cavity formation. Astrocytic remodeling is accompanied by vigorous axon regrowth into the chitosan matrix, and newly formed, functional blood vessels colonizing the interior of the chitosan polymer. These results are evidence for the specific chitosan formulation creating a permissive, dynamic microenvironment for neural tissue regeneration. Finally, the partial locomotor recovery (BBB test) observed in rodents after a spinal cord hemisection, is significantly improved in animals that received a polymer implant.

We currently investigate whether the therapeutic potential of our initial regenerative strategy using chitosan-based hydrogels can be further enhanced from combination with cell therapy and with administration of molecule reported to have protective effect for neural cells.

Role of organic cation transporter 2 (OCT2) in long-term antidepressant response

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Mood disorders represent widespread disorders, with up to 16% of the world population affected by various symptoms of the depression. However, current antidepressant treatments do not relieve symptoms in a large fraction of patients, due to individual resistance and low efficacy. Our recent work identified OCT2 as a potential pharmacological target for mood disorders therapy. OCT2-/- mice displayed an altered sensitivity to acute treatments with NE- and/or 5-HT-selective transport blockers (i.e. venlafaxine, reboxetine and citalopram) in the forced-swim test. These acute "behavioral despair" tests, although useful to screen antidepressants, do not reproduce the complete spectrum of cognitive and emotional dysfunctions found in depression. We thus used a validated chronic depression model induced by corticosterone exposure, which mimics distinct symptoms of depression such as anhedonia, anxiety and social aversion, to test the effects of classical antidepressants in wild-type and OCT2 mutant mice. In this model, we showed that OCT2 is required for the long-term effects of fluoxetine on several behaviors including: anhedonia, spatial memory, social interaction and stress-sensitive spontaneous behavior. To determine the mechanisms underlying the role of OCT2 in the response to antidepressant, we characterized by quantitative Western blot intracellular signaling pathways implicated in antidepressant response. We obtained evidence that in dorsal hippocampus (and in some cases prefrontal cortex) of wild-type mice, there is a strong modulation of the activation state of ERK1/2, GSK3β and mTOR signaling by chronic corticosterone treatment, and these effects are reversed by fluoxetine. However, the effects of long-term fluoxetine on GSK3β and mTOR (both mTORC1 and mTORC2), but not of ERK1/2 signaling, were significantly attenuated in OCT2-/- mice brain. Altogether, our findings indicate that OCT2 is a major actor in the long-term action of SSRI/SNRI antidepressants and that GSK3β and mTOR signaling pathways could underlie antidepressant resistance in OCT2-/- mice.

Detection of Composite Genes in Large Similarity Networks

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Evolutionary combinatorial processes, such as fusion and recombination of DNA segments derived from (un)related gene families, are involved in the creation of composite genes [1]. These saltatory mechanisms are a source of new genes, involved in adaptations and phenotypic changes in organisms [2][3]. These processes have been well studied in eukaryotic genomes but little is known about their impact on soil, marine, gut microbial communities or mobile genetic elements [4][5]. Moreover despite their high adaptive potential, where and how composite genes are created in the environment is poorly understood. An increasing amount of molecular data with a considerable genetic diversity is now available from metagenomics projects, allowing to address these fundamental issues in uncultivable microorganisms.

Bioinformatics methods, like FusedTriplets 2.0 and MosaicFinder [6], are available to detect composite genes and families of composite genes, respectively, in sequence similarity networks, where each node represents a unique sequence and each edge represents a similarity between connected sequences. Here we present COMPOSITEFinder, a new software implemented in C++, which is more memory-efficient and faster, for the detection of composite genes and families of composite genes in very large similarity networks, e.g. with several millions of nodes and hundreds of millions edges. Furthermore, we developed a user-friendly tool that computes a quality score for each family of composite genes allowing one to select the most conserved composite genes from metagenomic and genomic data, or to discard dubious candidate composite genes.

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Appearance and xation of Alternative Splicing Events during Evolution and their Impact on the Protein Structures

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Alternative splicing (AS) is the mechanism by which several distinct proteins, or isoforms, are produced from the same gene. AS is common in higher eukaryotes and is recognized to be essential for the functional diversication of the proteome. Although AS mechanisms have been widely studied at the genomic level, its role in the evolution of protein structures and functions remain largely uncharted.

We have developed a computational method to infer evolutionary scenarios that can explain transcripts observed within a set of species. The method combines a transcripts phylogeny reconstruction algorithm with a protein structure prediction routine. It is implemented in an automated tool called transPhyl. By applying transPhyl to the c-Jun N-terminal kinases (JNKs) family, we were able to propose a plausible evolutionary scenario explaining the transcripts observed in seven species, ranging from nematode to human. In particular, we could date the appearance and xation of an ASE that resulted in the production of isoforms diering by two mutually exclusive exons. These isoforms were shown to have dierential binding anity to their substrates. By mapping this ASE onto the predicted structural models we could identify and characterize at atomic level the molecular determinants of the selectivity of JNKs isoforms to their targets.

Trans-generational epigenetics linked to non-coding small RNAs in Drosophila: functional properties, molecular mechanism, influence of environmental factors and impact on genome expression

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Our group investigates gene regulations whose variations are epigenetically transmitted over generations. A new type of non-coding small RNAs, called Piwi-Interacting RNAs (piRNAs), has recently been discovered in Drosophila. They are produced by around 140 loci and mostly repress transposable elements (TEs) in the germline, but also some genes in somatic tissues. piRNA mediated repression can show strong trans-generational effects. Our group firstly investigates the mechanisms of induction of production of piRNAs by a genomic locus. This induction does not appear to be genetically determined in the germline. We have shown that induction of piRNA production by a locus can be induced by maternal cytoplasmic inheritance of homologous piRNAs, resulting in an epigenetic conversion process called paramutation. This activated state is then perfectly stable over generations (n>100). Moreover, we have shown that similar piRNA locus activation can be mediated by a thermic stress. This induction is then stably maintained over generations in the absence of stress. Second, we characterize the properties and mechanisms of piRNA mediated repression during germline development, and identify and analyze a cellular memory process which links embryonic primordial germ cells to ovarian adult germline stem cells. Third, we investigate the structure of a telomeric piRNA producing locus and the impact of such telomeric piRNAs on genome expression. Indeed, a number of genes carries fragments of telomeric sequences. In conclusion, the piRNA machinery provides the molecular support for an epigenetic trans-generational transfer of information which protects the genome from mobile DNA, can be used to mediate gene regulation and can memorize environmental-induced gene expression changes over the long-term.

Anti-inflammatory and anti-atherogenic effects of the inflammasome NLRP3 inhibitor, arglabin, in ApoE2.Ki mice fed a high fat diet

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BACKGROUND: This study was designed to evaluate the effect of arglabin on inflammasome NLRP3 inhibition and atherosclerotic lesion in ApoE2Ki mice fed a high fat Western-type diet (HFD).

METHODS AND RESULTS: Arglabin was purified and its chemical identity was confirmed by mass spectrometry. It inhibited, in a concentration-dependent manner, IL-1β and IL-18 production, but not IL-6 and IL-12, in LPS and cholesterol crystal-activated cultured mouse peritoneal macrophages with a maximum effect at ~50 nM and EC50 values for both cytokines of ~ 10 nM. LPS and cholesterol crystals did not induce IL-1β and IL-18 production in Nlrp3-/- macrophages. In addition, arglabin activated autophagy as evidenced by the increase of LC3-II protein. Intraperitoneal injection of arglabin (2.5 ng/g of bw, twice daily, 13 weeks) into female ApoE2.Ki mice fed a HFD resulted in a decreased IL-1β plasma level vs vehicle-treated mice (5.2 ± 1.0 pg/mL vs 11.7 ± 1.1 pg/mL). Surprisingly, arglabin also reduced plasma levels of total cholesterol and triglycerides to 41% and 42%, respectively. Moreover, arglabin oriented the proinflammatory M1 macrophages into the anti-inflammatory M2 phenotype in spleen and arterial lesions. Finally, arglabin treatment markedly reduced the median lesion areas in the sinus and whole aorta to 54% (P=0.02) and 41% (P=0.02), respectively.

CONCLUSIONS: Arglabin reduces inflammation, plasma lipids, increases autophagy, and orients tissue macrophages into an anti-inflammatory phenotype in ApoE2.Ki mice fed a HFD. Consequently, a marked reduction of atherosclerotic lesions was observed. Thus, arglabin may represent a new promising drug to treat inflammation and atherosclerosis.

Changes in the amelotin gene structure and expression correlate with the non prismatic-prismatic transition in tetrapods

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Amelotin (AMTN) is an ameloblast-secreted protein thought to be involved in the formation and mineralization of the thin, outer enamel layer in mouse teeth. In rodents, enamel is essentially prismatic with the exception of this outer layer which is prismless. The encoding gene, AMTN, is predominantly expressed in maturation-stage ameloblasts and the protein is found in the basal lamina between the ameloblasts and the enamel surface, as well as in the outer enamel layer. Despite the possible involvement of AMTN in the formation and mineralization of this prismless enamel layer, no data were available in non-mammalian species, in which the whole enamel is prismless.

The aim of this study was to extend the knowledge on AMTN in non-mammalian vertebrate species and to study its evolution in tetrapods (mammals, sauropsids and amphibians).

We found AMTN in the sequenced genomes of many non-mammalian species available in public databases and we obtained additional sequences in jaw transcriptomes and using PCR. Gene structure comparisons showed several independent gain and loss of exons in tetrapods. The predicted amino acid sequences of non-mammalian species displayed two functional motifs that lack in representatives o all mammalian lineages. Moreover, we demonstrated that an intraexonic splice site was recruited in an ancestral mammal then conserved during mammalian evolution.

We studied AMTN expression during enamel formation in a lizard, Anolis carolinensis, an amphibian, the salamander Pleurodeles waltl, and a marsupial, the opossum Monodelphis domestica using in situ hybridization on demineralized jaw sections. Comparison of the AMTN expression pattern in the two non mammalian species with that in the opossum and mice showed drastic differences.

Taken together, these results suggest that (i) the differences in the spatio-temporal expression of AMTN in mammals vs salamander and lizard could be related to its structural modifications (loss of exons and of functional domains in mammals), (ii) these changes have occurred early in the mammalian lineage after its divergence from the sauropsid lineage, and (iii) changes in AMTN structure and expression are correlated to important modifications in the enamel structure that occurred early in mammals, i.e., the transition from non prismatic enamel in non-mammalian tetrapods to prismatic enamel in mammals.

Role of Nicotinamide Riboside Kinase 2 in Dilated Cardiomyopathy and cardiac fibrosis

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Background: Dilated cardiomyopathy (DCM) is a severe heart disease characterized by reduced systolic function and metabolic defects. In a mouse model of DCM, we found an alteration in the nicotinamide adenine dinucleotide (NAD) homeostasis in the heart and a strong induction of the nicotinamide riboside kinase 2. Nmrk2 implicated in the synthesis of NAD, a major coenzyme in energy metabolism and a signaling molecule used by sirtuins. Nmrk2 is also known as the muscle integrin binding protein (MIBP).

Aims: We want to understand the role of Nmrk2 in: i) maintenance of cardiac functions and structure, ii) pathways regulating NAD homeostasis, iii) response to the hypertrophic agonist Angiotensin II; reported to alter cardiac NAD levels.

Methods and results: We generated Nmrk2 KO mice that were viable. Echocardiography at 5, 8, 12 and 24 months revealed a decrease in the ejection fraction (EF) and the development of mild DCM phenotype stabilized after 12 months. Effort tests indicate a strong reduction of endurance. At the histological level, red sirius staining of collagen fibers showed the presence of cardiac fibrosis in the KO. Electron microscopy confirmed the presence of collagen deposits. We observed an accumulation of lysosomes in Nmrk2 KO cardiomyocytes suggesting an alteration of the autophagy.

Echocardiography of control and KO mice treated with Ang II for 15 days, showed a similar increase in the LV mass index. RTQPCR analysis showed an increase in BNP stress marker and decrease in genes regulating NAD homeostasis and integrin signaling in both genotypes.

Conclusion: Nmrk2 enzyme is required to preserve cardiac function and structure. Molecular characterization of compounds modulating this pathway could give future therapeutic prospects for DCM.

Tri- methylation on lysine 3 confers a dual role to Ribosomal Protein L12

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Although histone methylation has been well studied, the functions of non-histone lysine methylation and its regulatory enzymes are poorly defined. In Drosophila, the ribosomal protein RPL12 tri-methylated on lysine 3 (RPL12K3me3), interacts with the chromodomain of Corto, an Enhancer of Trithorax and Polycomb (ETP) involved in both silencing and activation of gene expression. RPL12 and Corto bind chromatin at common sites and regulate a subset of genes implicated in ribosome biogenesis1.

Hence, in addition to its bona fide role in ribosome biogenesis and translation, RPL12 participates in transcriptional regulation of ribosomal protein genes and could be involved in dynamic coordination of ribosome biogenesis. To specifically address the role of RPL12K3me3, we have generated an RPL12 variant protein whose lysine 3 has been replaced by an alanine, RPL12K3A. We are currently analysing its ability to participate in translation and transcription. To further understand the physiological role of this tri-methylation, we aim to identify the RPL12 methyl-transferase. In S. pombe, Set11 specifically trimethylates RPL12 on lysine 3 and has no other substrate2. As tri-methylation of RPL12 on lysine 3 is highly conserved throughout evolution, we are investigating the Drosophila homolog of Set11, CG33230. Its inactivation induces larval lethality and severe growth defects. We are currently producing recombinant RPL12, RPL12K3A and CG33230 in bacteria to perform in vitro methylation assays.

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SourisCity, a new approach to understand inter-individual variability within a group of mice.

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In laboratory conditions, mouse studies usually focus on very specific behaviors, reducing inter-individual variability to a minimum. In contrast, in more natural conditions, mice express a large behavioral repertoire, with spontaneous inter-individual differences emerging within a group. The project « SourisCity » aims at understanding this behavioral variability. We examined the distribution of circadian activity and subgroup formation within a large group of mice. We correlated these aspects to the hierarchical position of each mouse. We used an ethological set up, consisting of a large and enriched enclosure divided in several compartments where up to twenty adult male mice lived together for several months. We followed mice individually throughout the recording period using radio frequency identification (RFID) chips. Movements between compartments were possible through tubes, in which crossing of each mice were monitored with RFID antennas. We observed that the activity of mice was not only based on the circadian cycle, but also on shorter time periods. We also highlighted that mice formed subgroups within the large enclosure. The stability of these subgroups remains to be examined. Overall, this study sets up the basement for an integrated approach to understand mouse inter-individual variability at the behavioral level. Such a setup will be used to unravel decision-making processes within groups.

Prostaglandin E2 produced by pyramidal neurons contributes to neurovascular coupling in the rodent cerebral cortex

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Vasodilatory prostaglandins play a key role in neurovascular coupling (NVC), the tight link between neuronal activity and local cerebral blood flow, but their precise identity, cellular origin and the receptors involved remain unclear. Here we show that N-methyl-D-aspartate (NMDA)-induced vasodilation and hemodynamic responses evoked by whisker stimulation involve cyclooxygenase-2 (COX-2) activity and activation of the prostaglandin E2 (PgE2) receptors EP2 and EP4. Using liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) we demonstrate that PgE2 is released by NMDA in cortical slices. The characterization of PgE2 producing cells by immunohistochemistry and single-cell reverse transcriptase-PCR (scRT-PCR) revealed that pyramidal cells and not astrocytes are the main cell type equipped for PgE2 synthesis, one third expressing COX-2 systematically associated with a PgE2 synthase (PGES). Consistent with their central role in NVC, in vivo optogenetic stimulation of pyramidal cells evoked COX-2 dependent hyperemic responses.

These observations identify PgE2 as the main prostaglandin mediating sensory-evoked NVC, pyramidal cells as their principal source and vasodilatory EP2 and EP4 receptors as their targets.

Role of neural estrogen receptor alpha in sexual bevaior of mice

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Sexual reproduction in mammals is based on anatomical and behavioral sex differences, which allow sexual attraction and mating between male and female partners. Gonadal hormones play a key role in the sexual differentiation of the brain and behavior during development and in their activation in adulthood. It is well established that testosterone secreted perinatally by the male's testes is aromatized in estradiol in the brain and then organizes the neural circuitry controlling male sexual behavior in adulthood. In females, it has been admitted for decades that no active perinatal sex hormone signaling was required for differentiation. However, the aromatase knockout mice provide new evidence showing that estradiol is also a key player in the differentiation and the activation of the female brain and behavior. Although this finding reopens the question of brain feminization, the molecular machinery underlying the effects of estradiol in development and activation in adulthood are still poorly understood. We therefore generated a novel transgenic mouse model lacking the alpha isoform of estradiol receptor (ERα) specifically in the nervous system to determine the mechanisms of action of this hormone. Both males and females of this mouse line were characterized at physiological and behavioral levels. Behavioral tests included sexual behavior, mate preference, and general behavior assessment. Interestingly, whereas females don't display lordosis behavior (the female typical sexual behavior), their male littermates still exhibit mounting behavior (the male typical sexual behavior) and ejaculate, but with increased latencies. These results suggest that ERα is critical in the development and activation of sexual behavior. Immunohistochemical analyses of sexually dimorphic neuronal populations are in progress to determine more precisely the impact of ERα in the organization of the neural pathway underlying sexual behavior.

Neuro-protective effects of NAD+ and NR on axonal degeneration.

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Synaptic and axonal degeneration (AD) are major events preceding neuronal death in neurodegenerative diseases. Furthermore, levels of nicotinamide adenine dinucleotide (NAD+) are strongly reduced in different degeneration models and has been described as an important coenzyme for axonal integrity. Enhancing cellular NAD+ synthesis by addition of biosynthesis precursors is one of the numerous therapeutic strategies investigated against neuronal pathologies. Among these precursors, nicotinamide riboside (NR) is a good candidate as it has already been shown to delay AD in peripheral nervous system and to prevent cognitive impairment in a mouse model of Alzheimer's disease. However, the role of NR metabolism in degeneration processes of the central nervous system has not been studied yet. We used a NMDA-induced excitotoxicity model in primary cortical neurons to explore NAD+ and NR effects on neuronal death and AD. For the first time, we showed that both NAD+ and NR reduce NMDA-induced AD with a more pronounced effect with NR. It was previously described in different cell lines that NAD+ is metabolized to NR via an extracellular pathway before entering into the cell. This pathway could be incomplete in cortical neurons and could explain the weaker effect of NAD+ as compared to NR. Using different pharmacological inhibitors, we found that the extracellular pathway is not present in these neurons and that an extracellular conversion of NAD+ to NR cannot explain the weak effect of NAD+. Surprisingly, neither NAD+ nor NR, prevented somatic cell death suggesting that the NAD+-dependent self-destruction program is exclusively axonal. Finally, using microfluidic devices to compartimentalize soma and axons, we found that the NR protective effect is mainly restricted to the axonal compartment, and that somatic NR treatments are needed for a maximal axonal protection.

Our results demonstrate for the first time that NR has a strong and local neuro-protective effect in NMDA-induced AD. These findings open new therapeutic strategies to prevent neurodegenerative diseases.

Structuring genetic and taxonomic diversity in gut microbes of lizards affected by a quick dietary change.

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Podarcis sicula is a species of insectivorous lizards, present in different countries, including Croatia. At the end of the sixties, Nevo & al. (1972) wanted to sudy the competition between these species on islands. They introduced 10 Podarcis sicula from Pod Kopiste on Pod Mrcaru, and 10 Podarcis melisellensis from Pod Mrcaru, on Pod Kopiste.

Scientists came back 35 years later, and observed that Podarcis melisellensis had disappeared, and Podarcis sicula on Pod Mrcaru had became omnivorous (80 % herbivorous). Many morphological changes correlated with this dietary shift, but changes at the level of the gut microbiome and microbiota were not investigated.

Here, we have sequenced 16 samples from gut of insectivorous and omnivorous lizards by Illumina Miseq. We obtained between 3,544,700 and 7,397,327 of paired ends reads (about 300bp) by sample.

We tested two hypotheses, about evolutions of genes content and taxonomic composition associated with the dietary shift: Can we notice the acquisition or loss of gene families ? Did taxa appear or disappear in the gut microbial populations of omnivorous lizards ?

We used different approaches (pca and clustered heatmap on present taxa, abundance analysis of taxa and gene content using reads annotation results, networks based on reads similarities...) to study the diversity of these lizards gut microbiomes and microbiota, and to find some structures correlated with their diet. Preliminary analyses suggest that abundances of taxa and functions changed, without functional or taxonomic gains or losses.

GSK3-mediated MAP1B phosphorylation regulates neurite branching and microtubule dynamics

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The microtubule-associated protein MAP1B plays a key role in axon regeneration. We investigated the role of GSK3-mediated MAP1B phosphorylation in local fine-tuning of neurite branching and the underlying microtubule (MT) dynamics.

In wildtype adult dorsal root ganglia (DRG) neurons, MAP1B phosphorylation is locally reduced at branching points, and branching dynamics from growth cones and distal neurite shafts is increased upon GSK3 inhibition. While map1b-/- neurites, that display increased branching, are not affected by GSK3 inhibition, transfection of map1b-/- neurons with full-length map1b-cDNA restores the wildtype branching phenotype, demonstrating that MAP1B is a key effector downstream of GSK3. Experiments in mutant mice lacking tyrosinated MTs indicate a preferential association of phospho-MAP1B with labile tyrosinated MTs. Interestingly, inhibition of GSK3-mediated MAP1B phosphorylation in map1b-cDNA-transfected fibroblasts protects both tyrosinated labile, and acetylated stable MTs from nocodazole-induced depolymerization, while detyrosinated MTs are less abundant in presence of MAP1B.

Our data thus provide new insight into the molecular link between GSK3, MAP1B, neurite branching and MT stability regulation. We suggest that, at branching points, MAP1B undergoes a fine regulation of both its phosphorylation and expression levels, in order to modulate the local balance between acetylated/detyrosinated stable, and labile tyrosinated MTs.

How to maintain the correct number of chromosomes during meiosis in mammalian oocytes?

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Meiosis is composed of two successive cell divisions that generate haploid gametes from a diploid precursor cell. The first division, meiosis I, leads to the separation of homologous chromosomes and the second division, meiosis II, leads to the separation of sister chromatids. Segregation errors in meiosis can cause the generation of aneuploid gametes (with a wrong number of chromosomes) and after fertilization, to the development of trisomies, such as trisomy 21, or spontaneous abortions. In order to understand how correct ploidy is maintained during meiosis we study the molecular mechanisms that control chromosome segregation in mammalian oocytes by using live imaging and classical cell biology approaches.

Correct chromosome segregation in meiosis I depends on the Spindle Assembly Checkpoint or SAC. The SAC verifies the correct attachment of chromosomes to the bipolar spindle and prevents anaphase onset in presence of attachment defects. Although the SAC has been well studied in mitosis, some aspects of this mechanism are still unclear in meiosis, in particular: Do the actors of the SAC have the same role in mitosis and in meiosis? Is the SAC sensitive to the absence of tension generated by microtubule pulling forces in meiosis?

Moreover in meiosis, to induce the separation of homologous chromosomes during the first division and of sister chromatids during the second division, the cohesin Rec8 (which maintains the sister chromatids together) is removed in a two-step process. Removal of Rec8 from arms allows the separation of chromosomes in meiosis I, and removal of rec8 from centromeres in meiosis II allows separation of sister chromatids. In meiosis I, centromeric Rec8 is protected from cleavage. The protection of centromeric Rec8 in meiosis I is controlled by a mechanism involving Shugoshin, PP2A and I2PP2A. One axis of our research is to better understand how this mechanism is regulated, in particular: How is the centromeric localisation of Shugoshin controlled? How is I2PP2A regulated? Are some SAC proteins involved in this mechanism? And finally, how is Rec8 removal regulated?

Towards unravelling P-body assembly

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In eukaryotic cells, untranslated mRNA that are repressed, stored or targeted to degradation are found in cytoplasmic RNP granules such as P-bodies, neuronal granules, germ granules and stress granules. P-bodies are dynamic structures whose size and number vary in response to cell environment and depending on cell cycle stages. These granules consist of mRNP macroaggregates that contain factors belonging to decay and repression pathways. However, the role of these macroaggregates and the mechanism of their assembly remain elusive.

We previously showed that DDX6, a DEAD-box helicase, is highly concentrated in P-bodies and that it is essential for P-body assembly (Ernoult-Lange et al, RNA 2012). We undertook TAP-tag experiments coupled to mass spectrometry to identify DDX6 partners. We found 3 major complexes including the decapping complex, a CPEB-like complex and an ataxin2/2L complex. In spite of its strong enrichment in P-bodies, a large fraction of DDX6 has a diffuse localization in the cytoplasm. Among the three complexes, only the decapping complex and the CPEB-like complex were recruited into P- bodies. Next, we used a RNA interference strategy to test the importance of each complex for de novo P-body assembly in different conditions. Overall, repressive complexes, rather than decay and Ataxin2/2L complexes were required for proper P-body assembly. While some factors were only required in specific conditions three proteins were essential in all tested conditions: DDX6, 4E-T and LSM14A.

Ayache, J. et al. P-body assembly requires DDX6 repression complexes rather than decay or Ataxin2/2L complexes. Molecular Biology of the Cell, May 20 2015.

Theoretical Analysis on Stochastic Kinetics of Eukaryotic Genome Replication

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Despite of the wealth of information on molecular regulation of chromosome replication, and of the quantitative knowledge of some stochastic aspects of this process, the current understanding of the dynamic properties of genome replication mostly relies on researches on population-averaged cellular properties. Comparatively little is known on the heterogeneous effects of different replication timing patterns across cells, which however, constitute a classic question of biology. We study cell-to-cell variability of the duration of S phase and its dependence on the location and the strength of origins, employing a stochastic model for genome replication assuming that origins fire stochastically and replication forks move at constant speed. Our stochastic simulation and theoretical estimates based on this model characterize the influence of spatial distribution and strength of the origins on the duration of S-phase and chromosome replication, and its cell-to-cell variability. The estimate, calibrated with the simulation can be used for efficient predictions of S-phase duration in real chromosomes.

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