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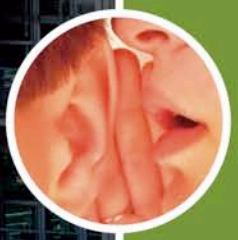
CIG Symposium 2010

SENSING THE ENVIRONMENT

Lausanne | June 16 & 17 | 2010



Detlev Arendt (Germany)
Marie-Christine Broillet (CH)
Martin Chalfie (USA)
George Coupland (Germany)
Caroline Dean (UK)
Consuelo De Moraes (USA)
Claude Desplan (USA)
Russell Foster (UK)
Christine Petit (France)
Steven Reppert (USA)
Ivan Rodriguez (CH)
Leslie Vosshall (USA)

additional speakers will be selected from abstracts

ORGANIZERS
Richard Benton | Christian Fankhauser | Nouria Hernandez

Center for Integrative Genomics (CIG)
University of Lausanne
1015 Lausanne
Switzerland

> Registration by May 15, 2010

UNIL | Université de Lausanne
Centre Intégratif de Génomique

Welcome to the CIG Symposium 2010

The organizing committee warmly welcomes you to the fourth Center for Integrative Genomics (CIG) Symposium at the University of Lausanne!

With the now annual tradition of CIG Symposia, we aim to bring together leading scientists in an emerging field in biology, from Switzerland and abroad, to the CIG to foster dynamic exchange between both local and international researchers and senior and junior scientists. The CIG inaugural symposium, "*Genomics, a new road for science and society*", was held in 2005, followed by "*Metabolism and Cancer*" in 2008 and "*DNA repair and Human Health*" last summer.

In this year's symposium, "*Sensing the Environment*", we have designed a programme that will reveal the many fascinating ways in which animals, plants and bacteria detect and respond to vital visual, chemical and physical stimuli in the external world. By bringing together the best researchers studying important, but diverse, aspects of this topic, we aim for a highly interactive symposium that provokes new reflections on how distinct organisms have evolved similar – or different – solutions to this fundamental biological problem.

We are fortunate to welcome again outstanding speakers to this year's symposium. We thank them for their participation and wish both them and you an exciting and enjoyable meeting, an experience that we hope will persuade you also to join us at next year's symposium on "*Genetics of Behavior*", June 20th-21st 2011!

The organizers,

Nouria Hernandez Richard Benton Christian Fankhauser

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CIG Symposium 2010
Sensing the environment
Lausanne, June 16 and 17

June 16, 2010, Morning ***Chair: Nouria Hernandez***

9:00-9:10	CIG, University of Lausanne, Switzerland **Welcoming remarks – Richard Benton**
9:10-9:50	**Detlev Arendt** EMBL Heidelberg, Germany **Sun, moon and larval settlement: sensory systems controlling the marine life cycle**
9:50-10:30	**George Coupland** Max Planck Institute for Plant Breeding Research, Cologne, Germany **Flowering of Arabidopsis in response to seasonal changes in day length**
10:30-11:00	***Coffee break + Poster installation***
11:00-11:40	**Russell Foster** University of Oxford, UK **The light regulation of rhythmic biology**
11:40-12:00	*Selected talk from the submitted abstracts* **Matthias Heinemann** ETHZ, Zurich, Switzerland **Bacterial adaptation through distributed sensing of metabolic fluxes**
12:00-12:40	**Claude Desplan** New York University, USA **Color vision in Drosophila**
12:40-13:30	***Buffet Lunch***
13:30-14:30	**POSTER SESSION**

June 16, 2010, Afternoon ***Chair: Christian Fankhauser***

14:30-15:10	**Marie-Christine Broillet** University of Lausanne, Switzerland **Danger detection in mice**
15:10-15:30	*Selected talk from the submitted abstracts* **Vincent Croset** CIG, University of Lausanne, Switzerland **Chemosensory iGluRs: an ancient protostome-specific mechanism for tasting and smelling**
15:30-16:10	**Consuelo De Moraes** Penn State University, USA **Chemical ecology of host-parasite interactions**
16:10-16:40	***Coffee break***
16:40-17:20	**Ivan Rodriguez** University of Geneva, Switzerland **Mammalian olfactory chemosensors: from genes to behavior**
17:20-18:00	**Leslie Vosshall** Rockefeller University, USA **Blood lust: the control of mosquito host-seeking behavior**
18:00-19:00	***Apéro* & POSTER SESSION**

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CIG (Centre Intégratif de Génomique)

CIG Symposium 2010
Sensing the environment
Lausanne, June 16 and 17

June 17, 2010 ***Chair: Richard Benton***

9:00-9:40	**Steven Reppert** University of Massachusetts, USA **Navigational mechanisms of migrating Monarch butterflies**
9:40-10:00	*Selected talk from the submitted abstracts* **Friederike Brüssow** DBMV, University of Lausanne, Switzerland **Insect eggs suppress plant defense against chewing herbivores**
10:00-10:40	**Caroline Dean** John Innes Centre, Norwich, UK **Sensing the prolonged cold of winter**
10:40-11:10	***Coffee break + POSTERS***
11:10-11:50	**Christine Petit** Collège de France, Institut Pasteur, Paris, France **From deafness genes to sound processing by the hair bundle**
11:50-12:10	**Presentation of the 2010 Guénin Prize : Nicolas Leuenberger** CIG, University of Lausanne, Switzerland **Sex and Clock to Discover New PPARalpha Functions**
12:10-12:50	**Martin Chalfie** Columbia University, USA **Mechanosensory transduction in *C. elegans***
12:50-13:00	**Closing remarks**

Poster sessions

People presenting posters are requested to put them up as soon as possible, following the poster numbering (see section "posters abstracts"). **Their presence is expected from 13:30 to 14:30 on June 16 (even numbers) and from 18:00 to 19:00 on June 16 (odd numbers).**

General information

Conference venue

Center for Integrative Genomics (level 2 – Auditorium C)
University of Lausanne
Génopode Building
UNIL-Sorge
CH – 1015 Lausanne

Conference contact

Corinne Dentan, conference secretary, in the CIG direction office, Génopode level 2, phone : 021 692 39 00
Nicole Vouilloz, CIG Assistant Director, phone 021 692 39 03, mobile phone : 079 638 57 70

Poster sessions

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Certificates of attendance

Certificates of attendance will be available on request (corinne.dentan@unil.ch) and will be sent by regular mail after the symposium.

Lunch

A standing lunch will be served in the Génopode next to the posters on June 16.

Evening meal/activity

Nothing is formally organized, but we suggest e.g. "Les Brasseurs", Rue Centrale 4, Lausanne, (see : http://www.les-brasseurs.ch/e/lausanne/index.htm)

Internet and telephones

Free WiFi access in the Génopode building : activate Airport and choose 'guest-unil', then enter the password "CIGSymposium".
Free access to internet : you will find in the Génopode hall 4 computers with free access to internet (no possibility to access attachments).
Telephone calls can be made from the pay phone located near the toilets on the same floor of the Auditorium C in the Génopode building. Cards can be purchased at the tobacconist's or newspaper kiosks.

Medical and dental emergencies

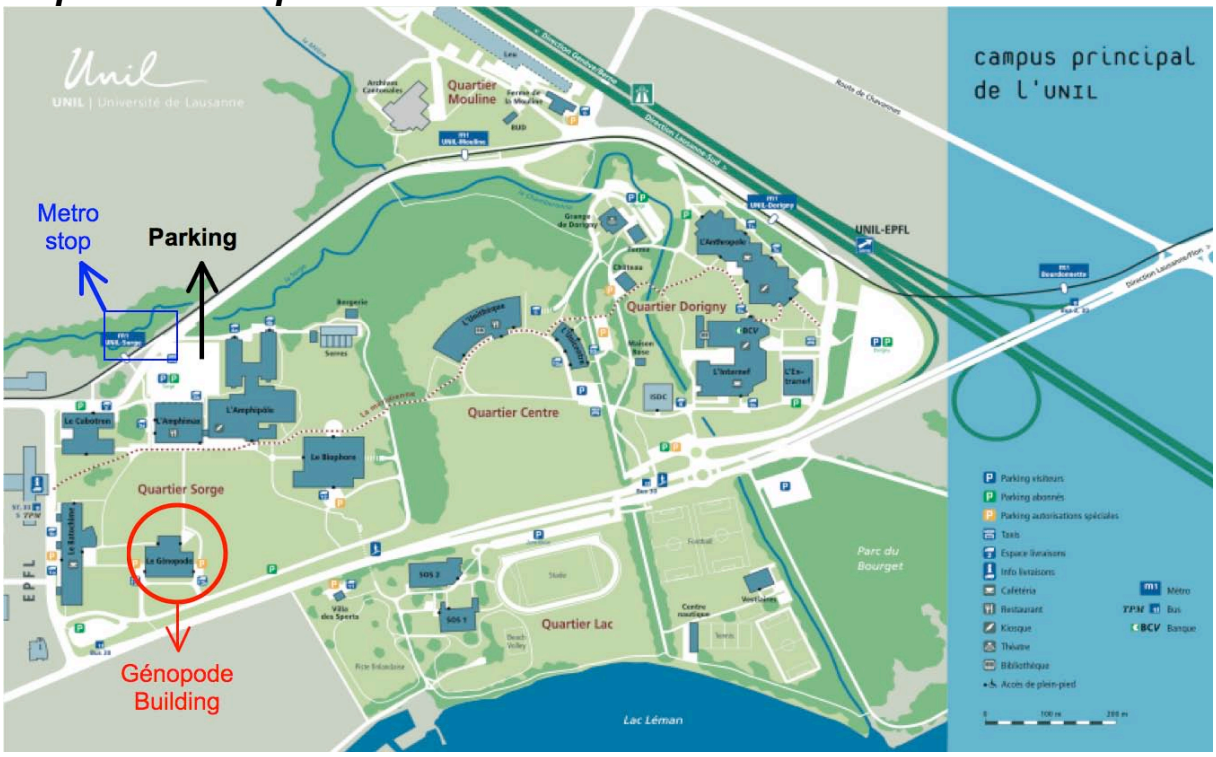
Vidy Med
Route de Chavannes 11
1007 Lausanne
Phone : 021 622 88 88
Open from 07.00 to 23.00
http://www.vidymed.ch/urgences.htm

Adent Clinique médico-dentaire du Croset SA
Chemin du Croset 7
1024 Ecublens
Emergency 7j/7 phone : 0800 101 800
Open from 07.00 to 21.00
http://www.adent.ch/les-cliniques/ecublens-croset

Useful links

Lausanne Public Transport Website	http://www.t-l.ch/
'Lausanne Roule' Free Bike Rental	http://www.suisseroule.ch/index.php?option=com_content&view=article&id=104&Itemid=54&lang=fr
Lausanne-Tourisme Website	http://www.lausanne-tourisme.ch
Lausanne.ch Website	http://www.lausanne.ch

Map of the campus



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Symposia abstracts : oral presentations

Sun, moon and larval settlement: sensory systems controlling the marine life cycle

Detlev Arendt
EMBL Heidelberg, Germany

We are using the marine annelid *Platynereis dumerilii* (Phyllodocida) as a molecular animal model for zooplankton. Our focus is on neurodevelopment, -physiology and behaviour and their control by the marine environment. This way we gain first insight into development, life cycle, physiology and behaviour of marine zooplankton, which is crucial for our understanding of marine life and ocean ecosystems.
As a prerequisite, molecular techniques including wholemount in situ hybridisation, reverse genetics and transgenesis have been established. The system is especially powerful for high-throughput gene expression studies and for single cell expression profiling. Based on this, we are gaining a close-to-complete overview of the *Platynereis* neuron type inventory. Since many of the identified neuron types are conserved between annelids and vertebrates, we use vertebrate pharmacology to interfere with development, transmitter activity or other neuronal processes. By this means, we have studied the phototaxis behaviour of the *Platynereis* zooplankton on cellular and molecular level. We are currently investigating the physiological properties and sensory modalities of the ciliary photoreceptors deeply embedded in the *Platynereis* brain, in order to explore their putative roles in control of larval activity and/or life cycle progression, in response to the daily and lunar life cycle. Also, we explore how the environment impacts on the key developmental transition, larval settlement and, concomitantly, on metamorphosis.
From an evolutionary viewpoint, since we are exploring ancient conditions of marine life, we reason that the study of *Platynereis* will be pivotal also for a deeper understanding of vertebrate development and life cycle and its environmental control.

Flowering of Arabidopsis in response to seasonal changes in day length

George Coupland
Max Planck Institute for Plant Breeding Research, Cologne, Germany

In many plants the transition to flowering is controlled by seasonal cues such as changing day length and temperature. The response to day length is complex involving a combination of time measurement and responsiveness to light. In Arabidopsis we have characterized a circadian-clock regulated pathway that promotes flowering specifically in response to the longer day lengths of spring and early summer. This pathway includes the GIGANTEA (GI), CONSTANS (CO) and FT proteins that act in the vascular tissue of the leaves to promote synthesis of a systemic signal that triggers flower development at the shoot meristem. We describe how day length regulates the activity of different components of the pathway through a combination of transcriptional regulation by the circadian-clock and light-regulated protein stability to ensure that flowering only occurs under long days.

Non-Visual Light Detection by VA and Melanopsin Photopigments

Russel Foster
University of Oxford, UK

Circadian rhythms are endogenous 24h cycles that persist in the absence of external time cues. These rhythms provide an internal representation of a day and optimise physiology and behaviour to the varying demands of night and day. These clocks require daily adjustment to local time, and the primary time cue (zeitgeber) used by most vertebrates is the daily change in the amount of environmental light (irradiance) at dawn and dusk, a process termed photoentrainment. Attempts to understand the photoreceptor mechanisms mediating non-image forming responses to light, such as photoentrainment, have resulted in the discovery of a remarkable array of different photoreceptors and photopigment families, all of which appear to utilise a basic opsin/vitamin A-based photopigment biochemistry. In non-mammalian vertebrates, specialised photoreceptors are located within the pineal complex, deep brain, and dermal melanophores. By contrast, mammals posses only ocular photoreceptors. However, in addition to the rods and cones, there exists a third photoreceptor system based upon a subset of melanopsin-expressing photosensitive retinal ganglion cells (pRGCs). In this presentation the photosensory role of two “irradiance detector” photopigments will be compared – the VA opsin and and melanopsin (Opn4) photopigments.

The discovery of the VA-opsin gene family in fish led to the demonstration that a sub-set of retinal horizontal and ganglion cells are directly photoreceptive and provided the first unambiguous evidence for a non-rod, non-cone photoreceptor in any vertebrate. VA opsins were thought to have a restricted taxonomic distribution, confined to the agnatha and teleost fish. We have now isolated orthologues of VA opsin from all non-mammalian vertebrates and shown that these opsins form functional photopigments. Birds possess photoreceptors located deep within the hypothalamus that regulate seasonal responses to photoperiod. However, the cellular and molecular identity of these photoreceptors has remained unclear. We show in the chicken and quail that VA opsin is expressed within a population of hypothalamic neurones with extensive projections to the median eminence. These results strongly implicate these photoreceptors in daylength detection for the regulation of the avian photoperiodic response.

The mammalian retina contains a small population of photosensitive retinal ganglion cells (pRGCs) which utilize the photopigment melanopsin (*Opn4*). We have shown that two splice variants are transcribed from the mouse *Opn4* locus. Both of these isoforms *(Opn4L and Opn4S)* are expressed in the RGC layer of the adult mouse and form a fully functional photopigment when expressed in Neuro2A cells. Antibodies raised to isoform specific epitopes, have identified discrete populations of retinal ganglion cells. Some ganglion cells express both Opn4L and Opn4S and others only Opn4L. Whilst we have not yet identified the functional significance of the c-terminal splice variants of melanopsin, it seems likely that they are associated with the diversity in pRGC light responses.

In broad terms these two opsin families have highly divergent evolutionary histories and activate very different signaling pathways, yet they appear to perform similar irradiance detection tasks. The presentation will conclude with a discussion relating to the phylogenetic ancestory of the VA and melanopsin photopigments and why two such photoreceptor systems might have evolved in the vertebrates.

Bacterial adaptation through distributed sensing of metabolic fluxes

Matthias Heinemann[1,2]
[1]*ETH Zürich, Institute of Molecular Systems Biology, Switzerland*
[2]*University of Groningen, Biomolecular Sciences and Biotechnology Institute, NL*

The recognition of carbon sources and the adaptation to recognized changes are of particular importance for bacterial survival in fluctuating environments. Despite a thorough knowledge base of *E. coli*’s central metabolism and its regulation, fundamental aspects of the employed sensing and regulation mechanisms remain unclear.

Towards attaining a system-level understanding of how *E. coli* adapts between different carbon sources, we will present a large-scale differential equation model that describes the organism’s central metabolism and its enzymatic, transcriptional and posttranscriptional regulation. To generate this model, we devised a novel approach for parameter estimation that draws on steady state -omics measurement data and exploits a decomposition of the global estimation problem into independent small subproblems.

As revealed by analysis of the developed model, we will show that the interplay of known interactions explains in molecular-level detail the system-wide adaptations of metabolic operation between glycolytic and gluconeogenic carbon sources. Further, we will demonstrate that these adaptations are enabled by an indirect recognition of carbon sources through a mechanism we termed distributed sensing of intracellular metabolic fluxes. This mechanism uses two general motifs to establish flux-signalling metabolites, whose bindings to transcription factors form flux sensors. These sensors are embedded in global feedback loop architectures that orchestrate the regulatory adjustments to recognized changes in carbon source availability. We will present experimental data of a detailed, molecular level follow-up analysis that provides evidence for the generated model predictions.

Overall, in this work we demonstrate a successful execution of a full systems biology cycle: starting from omics data and using a new method for parameter estimation, we developed a large scale kinetic model. Through analysis of the model we identified novel emerging principles that we could validate in detailed follow-up experimental analyses. The insights obtained significantly improve our understanding of bacterial metabolic operation with fluctuating carbon sources.

Color vision in Drosophila

Claude Desplan
New York University, USA

The *Drosophila* compound eye is made of 800 unit eyes (ommatidia) that each contains eight photoreceptors: Six are involved in motion detection while two (R7 and R8) play a major role in color vision. These ommatidia can be grouped into four categories: **p** ommatidia contain UV-sensitive Rh3 in photoreceptors R7 and Blue-Rh5 in R8 while **y** ommatidia express another UV-Rh4 in R7 and green-Rh6 in R8. The **p** and **y** subsets are distributed stochastically throughout the retina in a 30:70 ratio. Comparison between the inputs of R7 and R8, and between **p** and **y** ommatidia allows flies to discriminate between colors, with **p** ommatidia involved in the detection of short wavelengths and **y** ommatidia for longer wavelengths. Dorsal Rim Area **(DRA)** ommatidia express UV-Rh3 in both R7 and R8. They function as polarizing filters that allow the fly to measure the vector of light polarization for navigation on cloudy days. A fourth subset located in the dorsal third of the eye co-expresses UV-Rh3 and -Rh4 in **y**R7 and serves to detect solar vs. anti-solar orientations, also for navigation on sunny days.

I will describe the cascade of genes that specify the different subsets of photoreceptors through a series of fate restrictions and how this cascade is modified to define the various regions of the retina in *Drosophila* and how this spatial organization is used in other insect species: *homothorax* is required for the formation of the **DRA**. *spineless* is expressed in a stochastic manner in R7 cells that express Rh4 (**y**R7). It allows the specification of the whole retina by specifying the y choice in R7 and allowing R7 to instruct R8 of its choice. Finally, *IroC* genes determine the region where yR7 co-express Rh3 and Rh4.

Processing of color information occurs in the medulla that receives input from R7 and R8. The medulla is formed by ~40,000 neurons surrounding a neuropil where photoreceptors and medulla neurons interconnect. Associated with each set of R7/R8 projections, there are ~800 'columns', the functional units in the medulla. We are addressing how medulla cells process color information coming from R7 (sensitive to UV) and R8 (sensitive to blue or green) and send it to higher processing centers in the lobula complex and central brain to mediate color behavior.

We are silencing subsets of medulla neurons using specific Gal4 lines and testing the consequence for color discrimination. We have adapted to color vision the flight simulator originally designed by the Dickinson/Frye labs. In an operant paradigm, the fly is trained to associate color with a reward or punishment before being tested in the absence of the reward.

Danger detection in mice

Marie-Christine Broillet
University of Lausanne, Switzerland

In most mammals, olfaction has evolved in multiple olfactory subsystems to detect general odors and pheromonal social cues. In rodents, for example, the nasal cavity comprises three well described chemosensory organs, the main olfactory epithelium, the vomeronasal organ and the septal organ of Masera. Recently, a new olfactory subsystem has been re-discovered, the so-called Grueneberg ganglion (GG). It has been first described by Hans Grueneberg in 1973, as a "ganglion" of unknown function. The GG is present at the tip of the nose, close to the opening of the naris.

We morphologically characterized the mouse Grueneberg ganglion and identified it as the olfactory subsystem mediating alarm pheromone detection in neonate and adult mice. To perform this primordial function, the GG has a unique and basic morphology; a ganglion protected from the external world by water-permeant keratin. It is composed of two different cell populations: neurons of olfactory origin bearing multiple primary cilia, putative sites of chemosensory transduction and glial cells of triangular shape with thin cytoplasmic extensions individually enveloping GG neurons. The GG acts as a warning system dedicated to the recognition of short-lived molecules encoding danger. These molecules are released by conspecifics and they require immediate attention. The unusual location of the GG at the tip of the nose, far from the main olfactory system, allows the stimuli to be rapidly detected. Alarm pheromone sensing is a conserved modality present from primitive organisms such as worms to humans. The presence of a GG has been identified in many mammalian species including human embryos. When produced by conspecifics alarm pheromones play an important role in increasing overall species fitness.

Of the different sensory modalities found in the nose, the Grueneberg ganglion is at this moment the least characterized. Many questions remain open. The chemical nature of mammalian alarm pheromones is not known yet. Their transduction cascade, their intracellular signaling pathways have to be characterized. The brain centers activated by these alarm signals, beyond the olfactory bulb, have to be identified. No doubt this organ plays an important role in intraspecies signaling as can be readily observed from the extreme behavioral reactions that it triggers upon activation in mice and it seems likely that it plays a similar role in other mammalian species. Therefore, an in-depth characterization of this ganglion will certainly lead to important insights into the function of this sensory system, beyond the rodent model, in intraspecies communication in mammals in general.

Chemosensory iGluRs: an ancient protostome-specific mechanism for tasting and smelling

Vincent Croset
University of Lausanne, Switzerland

Ionotropic Glutamate Receptors (iGluRs) are a very ancient and widespread family of proteins. They are present in most multicellular organisms and have been shown to be involved in multiple processes, like fast neuronal communication at synapses in metazoans, cell-cell communication in plants, or chemotaxis in cyanobacteria.
Recently, 61 new iGluR-like receptors, called Ionotropic Receptors (IRs), have been discovered in the fruit fly *Drosophila melanogaster*, revealing additional functions for iGluR-related proteins. Some of these proteins have been shown to be responsible for chemical detection in sensory neurons from the third antennal segment, which is the main olfactory organ in insects. Furthermore, several non-antennal IRs are expressed in several larval and adult gustatory organs, suggesting that IRs are involved in chemosensory perception, both at the olfactory and gustatory levels. It is remarkable that a spectacular spatial and functional transition occured in order to enable the emergence of chemosensory IRs expressed in the dendrites of reduced subsets of neurons from synaptic iGluRs broadly expressed troughout the brain. In addition, IRs underwent spectacular expansion and diversification in order to acquire new chemosensory functions. This opens many questions about the origin and diversification of the IR repertoire: which species have IRs? What was the first IR? What are the mechanisms that allowed IR expansion? Here, I present a structural, phylogenetic and expression analysis of IR evolution. A broad genetic screen was performed and demonstrates that the first IR (IR25a) emerged from an ancestral iGluR in a primitive protostome in the early Cambrian (~540 MYA). Moreover, expression data in molluscs and nematodes shows that it may have acquired its chemosensory function very early. In contrary, most of the olfactory IRs are only present in insects, and their expansion was initiated by the duplication of IR25a into IR8a, which has acquired a specific olfactory function and has been shown to be acting as a co-receptor. Finally, the analysis of the mechanisms of IR evolution shows that one retroposition event might have been a key factor in the rapid emergence of new IR genes.
Altogether, these data provide a broad view on how the IRs evolved, and bring many additional informations about how big families of chemosensory genes can evolve, diverge, and acquire a high level of species-specificity in order to respond to a wide range of environmental stimuli. In addition, this work suggests that the development of a powerful sense of smell is a predominant condition for the orientation in a tridimensional environment and may thus have been a key factor of the development of flight in insects.

Chemical Ecology of Host-Parasite Interactions

Consuelo De Moraes
Penn State University, USA

Research in the field of chemical ecology has focused primarily on the role of chemical signals and defense compounds in mediating plant-insect interactions, particularly in agricultural ecosystems. In recent years increased attention has been paid to natural systems and to different classes of chemically mediated ecological interactions, including disease ecology and plant-plant communication. My research program focuses primarily on the signaling functions of volatile (airborne) compounds emitted by plants and other organisms. In this presentation, I discuss some of our recent work on host-parasite interactions, including the role of volatiles in host location by parasitic plants and the the induction of changes in host volatiles by vector-borne pathogens. This research has implications both for our growing understanding of the ecological significance of plant parasite interactions and as well as for epidemiology and and disease diagnosis.

Mammalian olfactory chemosensors: from genes to behavior

Ivan Rodriguez
University of Geneva, Switzerland

Mammalian species rely on their olfactory system to adequately interact between individuals and with their surroundings. At the core of this complex sensory system are large superfamilies of specialized G-coupled receptors, which are present at the interface between the outside and the inside worlds, on dendrites of olfactory sensory neurons of the main olfactory or vomeronasal epithelia. Surprisingly, these receptors play multiple roles. They first define the agonist profile of a given sensory neuron. But they also regulate chemoreceptor gene expression, in the sense that they are involved in the maintenance of the monogenic and monoallelic transcription that characterizes olfactory receptor gene expression. This limited transcription defines how narrowly tuned a given sensory neuron is. Third, olfactory chemoreceptors are involved in the precise convergence of like-axons in the olfactory bulb, a confluence that represents the first step of olfactory coding. Chemoreceptors thus not only define olfactory neural circuits, but are directly implicated in their establishment and functioning. Some of these circuits, due to the nature of the chemoreceptors they express, appear highly specialized. This seems to be the case of a group of vomeronasal sensory neurons that transcribe members of a small family of formyl peptide receptor genes. These genes are, like most olfactory chemoreceptor genes, characterized by monogenic transcription and a punctate expression pattern in the sensory neuroepithelium. In vitro expression of the corresponding receptors provides sensitivity to disease/inflammation-related ligands. The same molecules activate vomeronasal neurons in vivo. Taken together, these observations suggest that the neural circuit expressing formyl receptor proteins may play a function associated with the identification of pathogenic states, or with the discrimination of pathogens.

Blood lust: the control of mosquito host-seeking behavior

Leslie Vosshall
Rockefeller University, USA

Mosquitoes display an amazing and important sexual dimorphism in behavior. While male mosquitoes feed entirely on plants, gravid females require a blood meal to sustain egg maturation. In Aedes aegypti females, the blood meal triggers a period of host avoidance that lasts several days. Certain mosquito species have evolved an intense attraction to humans and in doing so serve as deadly vectors of infectious disease that plague most of the developing world. We are embarking on a new research direction to use molecular genetics in mosquitoes to understand the sensory cues and internal signals that regulate host-seeking behavior. I will present new data on modulation of host-seeking behavior and how this varies in different wild strains of mosquitoes.

Navigational mechanisms of migrating monarch butterflies

Steven Reppert
University of Massachusetts Medical School, USA

Recent studies of the iconic fall migration of monarch butterflies have illuminated the mechanisms behind the navigation south while using a time-compensated sun compass. Skylight cues, such as the sun itself and polarized light, are processed through both eyes and are likely integrated in the brain's central complex, the presumed site of the sun compass. Time compensation is provided by circadian clocks that have a distinctive molecular mechanism and that reside in the antennae. Monarchs might also use a magnetic compass, because they possess two cryptochromes that have the molecular capability for light-dependent magnetoreception. Multiple genomic approaches are now being used with the aim of identifying navigation genes. Monarch butterflies are thus emerging as an excellent model organism in which to study the molecular and neural basis of long-distance migration.

Insect eggs suppress plant defense against chewing herbivores

Friederike Brüssow
University of Lausanne, Switzerland

Plants activate direct and indirect defenses in response to insect egg deposition. However, whether eggs can manipulate plante defense is unknown. In *Arabidopsis thaliana*, oviposition by the butterfly *Pieris brassicae* triggers cellular and molecular changes that bear a strong similarity with the changes caused by bacterial pathogens. In the present study, we found that the plant defense signal salicylic acid (SA) accumulates at the site of oviposition. This is unexpected since the SA pathway is involved in the defense against fungal and bacterial pathogens whereas it negatively interacts with the jasmonic acid (JA) pathway, which is crucial for the defense against herbivores. In addition, application of *P. brassicae* egg extract onto leaves resulted in a reduced induction of insect-responsive genes after challenge with caterpillars, suggesting that egg-derived elicitors suppress plant defense. Accordingly, larval growth of the generalist herbivore *Spodoptera littoralis* was significantly higher on plants treated with egg extract than on control plants. In contrast, suppression of gene induction and enhanced insect performance were not found in the SA-deficient mutant *sid2-1*, indicating that SA mediates this phenomenon. Our findings reveal a novel facet of the cross talk between SA- and JA-signaling pathways and suggest that insects have evolved a way to suppress the induction of defense genes by laying eggs that release elicitors. We propose that egg-induced SA accumulation negatively interferes with the JA pathway and thus provides an advantage to the hatching larvae.

Sensing the prolonged cold of winter

Caroline Dean
John Innes Centre, Norwich, UK

At a certain stage in their life-cycle plants flower, that is they undergo the transition from vegetative to reproductive development. The correct timing of this transition is crucial for reproductive success, so the plant integrates multiple environmental and endogenous signals to judge when to flower. The Dean laboratory is studying the importance of prolonged cold for flowering, a process known as vernalization.
Our current view of the vernalization pathway has been built up though identification of Arabidopsis mutants and analysis of the corresponding genes, complemented by chromatin biochemistry. The vernalization pathway in Arabidopsis mediates the silencing of a target – *FLC,* by a conserved Polycomb mechanism. The talk will describe our understanding of the triggering of *FLC* repression by prolonged cold; the nucleation of chromatin silencing at a specific site in *FLC;* and the spreading of the silencing yet spatial restriction to *FLC.* Our aim is to describe this epigenetic silencing in a quantitative mathematical model.
Arabidopsis accessions have adapted to a wide range of latitudes and climates. We are studying whether variation in vernalization has contributed to this adaptation and have found that molecular variation at *FLC* is an important component. Our current understanding of this variation, its evolutionary origins and ecological significance will be discussed.

From deafness genes to sound processing by the hair bundle

Christine Petit
Collège de France, Institut Pasteur, France

The hair bundle is a mechanosensitive antenna protruding at the apical surface of the sensory hair cells. It detects sound wave pressure, acceleration and external fluid movements in the auditory sensory organ, the vestibular organs and the neuromasts of the lateral line system, respectively. All operate mechanoelectrical transduction, i.e. they convert mechanical energy into changes in hair cell membrane potential.
In the mammalian auditory organ, the cochlea, hair bundles ensure elaborated sound processing. They act as frequency filters, as their response is sharply tuned to specific sound frequencies, a characteristic that depends on the hair bundle geometry and stiffness. Hair bundles also participate in the amplification of sound stimulation, a property mediated by their apical anchoring in an acellular gel called the tectorial membrane.
The basic principles underlying the function of the ear, and especially of the cochlea, were mostly defined by physicists, with some of the earliest studies being initiated in the middle of the 19th century. In contrast, the molecules involved in the development and function of the cochlea eluded characterization until the beginning of the 1990s, mainly due to the paucity of the various cell types present in this organ. The study of inherited deafness in humans has allowed this issue to be resolved and has launched the molecular physiology of hearing. Mouse models, with only a few exceptions, faithfully mimic human auditory impairment. In the early-onset forms of sensorineural deafness, mouse models have shown that the hair cells are the most frequently affected cells and their hair bundle often is the primary target of the genetic defect. These models, when analysed by multidisciplinary approaches, enable to decipher molecular mechanisms underlying the development and functioning of the hair bundle. In addition, some mouse models provide unique experimental conditions whereby specific cochlear structures are lacking, thus allowing the discovery of new cochlear and especially new hair bundle physiological properties.
The presentation will focus on the advances regarding the molecular bases of the auditory mechanoelectrical transduction. So far, these are exclusively based on the study of mouse models for the Usher syndrome (sensorineural deafness associated to retinitis pigmentosa). The proteins encoded by the Usher type-I genes (myosin VIIa, harmonin -a PDZ domain–containing protein, cadherin-23, protocadherin-15, and sans -a putative scaffolding protein) directly interact and form fibrous links that interconnect the stereocilia together as well as with the kinocilium in the growing hair bundle. They compose transient embryonic hair bundle links and the tip-link (cadherin-23 and protocadherin-15), and anchor them to the stereocilia actin filaments (sans, harmonin and myosin VIIa). The former links are required for the hair bundle cohesion at its earliest developmental stage and the latter controls the gating to the mechanotransduction channel.
New properties of the hair bundle that emerged from the genetic approach will also be discussed. Sound waveform distortions are generated in the cochlea which create sounds absent from the acoustic stimulus and that we perceive. In addition, the organ achieves a suppressive masking that is essential for speech intelligibility. The study of a mouse model of human deafness has shown that both properties stem from the same origin, i.e. the presence of a subset of hair bundle links, the top connectors, that ensure the connection of the stereocilia tips. These non-linear responses of the hair bundle result from either the constraint exerted by the top connectors on the hair bundle displacement or a property gained from the collective work of the mechanotransduction channels, as a consequence of the coupling of the stereocilia tips by the top connectors.

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Mechanosensory Transduction in *C. elegans*

Martin Chalfie
Columbia University, USA

The senses that allow us to touch, hear, detect acceleration, and determine body position all respond to mechanical signals. In contrast to senses such as vision, taste, and smell where the molecular components that detect (transduce) the sensory signals are known, the molecular mechanisms underlying the mechanical senses are not. My lab has used traditional and molecular genetics to identify genes needed for touch sensitivity in the nematode Caenorhabditis elegans. Several of these genes are needed for the development of the touch-sensing cells; others are needed for their function. Electrophysiological studies demonstrate that several of the latter genes encode proteins that form a channel complex that transduces touch. Recent investigations have implicated membrane lipids and the integrin-signaling pathway in the action of this complex.

Posters abstracts

1

Molecular, physiological and behavioural analysis of novel sensory circuits in *Drosophila melanogaster*

Rati Bell and Richard Benton
Center for Integrative Genomics, University of Lausanne, Switzerland

Determining how animals detect and respond to environmental stimuli, such as chemicals, light or temperature, has long been an important goal towards understanding how neural circuits represent and process information in the brain. An attractive system to dissect the molecular and neural basis of sensory detection is the fruit fly, *Drosophila melanogaster*. Many sensory circuits in *Drosophila*, such as those of the olfactory and gustatory systems, display a similar organisational logic to those of mammals, but with vastly reduced numerical complexity. Moreover, *Drosophila* offers powerful genetic tools to manipulate the function of individual proteins or neurons within these circuits, and is readily accessible to both physiological and behavioural analysis.
My project aims to define the role of uncharacterised sensory structures called the arista and sacculus, which are located on the *Drosophila* antenna, a major head sensory organ. Previous morphological and surgical studies of aristal and sacculus neurons have implicated them in chemosensory, hygrosensory and/or thermosensory detection, indicating they are likely to have a unique and critical role as multi-modal sensory detectors for this animal. However, inaccessibility of these neurons to peripheral electrophysiological recordings and the lack of molecular markers of these neurons have prevented investigation of their precise function.
Recently, we identified members of the Ionotropic Receptor (IR) family of sensory receptors that are expressed in the arista and sacculus. IRs represent a divergent class of ionotropic glutamate receptors (iGluRs), a highly-conserved family of ligand-gated ion channels present in prokaryotes, plants and animals. While the ion channel pore is well conserved between IRs and iGluRs, the IR ligand binding domains are highly divergent and lack known glutamate-binding residues. This suggests that the IRs could recognize novel, diverse ligands. These IR genes provide the essential genetic entry-points to permit detailed investigation of these mysterious sensory circuits, through calcium imaging. Here I present preliminary results that show activation of IRs expressed in the sacculus by acidic ligands amongst others.

2

Actin cables and the exocyst form two independent morphogenesis pathways in the fission yeast

Felipe O. Bendezu and Sophie G. Martin
Center for Integrative Genomics, University of Lausanne, Switzerland

Cell morphogenesis depends on polarized exocytosis. One widespread model posits that sequential vesicle transport by motors along cytoskeletal elements and exocytosis drive this process. Unexpectedly, we discovered that complete disruption of actin cables or type V myosin motors and microtubules did not abolish polarized growth in the fission yeast. Similarly, mutations in the exocyst, a complex that tethers vesicles for exocytosis, do not abrogate polarized growth. However, disruption of both actin cables and exocyst led to isotropic growth. Exocytic vesicles, marked with the v-SNARE Syb1 or the cargoes Bgs1 and Bgs4, localized to cell tips in either single mutant, but were dispersed in the double mutant. In contrast, CRIB-GFP, a reporter of Cdc42 activity, localized to discreet cortical sites even in the double mutant. The localization of exocyst components Sec6 and Sec8 depended on *cdc42* and on the phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2). Conversely, localization of the exocyst and the formin For3 responsible for cable assembly were independent of each other, suggesting they represent independent morphogenesis pathways downstream of Cdc42. Thus, transport and tethering of vesicles do not function as linear processes but play independent, additive roles for cell morphogenesis.

3

The relative contribution of ASICs and TRPV1 to pH sensing in dorsal root ganglion neurons is temperature-dependent

Blanchard M., Kellenberger S.
Dep. of Pharmacology and Toxicology, University of Lausanne, Switzerland

Acid-sensing ion channels (ASICs) and the Transient Receptor Potential Vanilloid 1 channel (TRPV1) are acid-activated cation channels in sensory neurons. The contribution of ASICs and TRPV1 to acid-induced currents in sensory neurons has so far been compared at room temperature. Due to its inherent temperature dependence, TRPV1 may have an increased pH sensitivity at physiological temperature. We have analyzed ASIC and TRPV1 function in a recombinant expression system and in dorsal root ganglion (DRG) neurons at room and at physiological temperature. An increase in temperature from 25° to 35°C had only minor effects on ASIC and TRPV1 gating pH dependence, decreased ASIC current amplitudes and accelerated ASIC open-channel inactivation kinetics. As a consequence, the current amplitude of TRPV1 in small diameter DRG neurons induced by a 10-s acidification to pH 6 increased relative to ASICs at 35°C and was at ~30% of that of ASICs. Under the same conditions, the number of transported charges was 3-fold higher for TRPV1 than for ASICs. Current-clamp experiments showed a decrease in ASIC-mediated depolarization at the higher temperature in a subpopulation of neurons. In conclusion, ASICs and TRPV1 contribute differently to pH sensing in small diameter DRG neurons at physiological temperature. While ASICs are the main pH sensor at pH ≥ 6, TRPV1 becomes more important at pH ≤ 6 and during sustained acidification.

4 selected talk

Insect eggs suppress plant defense against chewing herbivores

Friederike Brüssow, Caroline Gouhier-Darimont, Antony Buchala, Jean-Pierre Métraux, and Philippe Reymond
Department of Plant Molecular Biology, University of Lausanne, Switzerland

Plants activate direct and indirect defenses in response to insect egg deposition. However, whether eggs can manipulate plante defense is unknown. In *Arabidopsis thaliana*, oviposition by the butterfly *Pieris brassicae* triggers cellular and molecular changes that bear a strong similarity with the changes caused by bacterial pathogens. In the present study, we found that the plant defense signal salicylic acid (SA) accumulates at the site of oviposition. This is unexpected since the SA pathway is involved in the defense against fungal and bacterial pathogens whereas it negatively interacts with the jasmonic acid (JA) pathway, which is crucial for the defense against herbivores. In addition, application of *P. brassicae* egg extract onto leaves resulted in a reduced induction of insect-responsive genes after challenge with caterpillars, suggesting that egg-derived elicitors suppress plant defense. Accordingly, larval growth of the generalist herbivore *Spodoptera littoralis* was significantly higher on plants treated with egg extract than on control plants. In contrast, suppression of gene induction and enhanced insect performance were not found in the SA-deficient mutant *sid2-1*, indicating that SA mediates this phenomenon. Our findings reveal a novel facet of the cross talk between SA- and JA-signaling pathways and suggest that insects have evolved a way to suppress the induction of defense genes by laying eggs that release elicitors. We propose that egg-induced SA accumulation negatively interferes with the JA pathway and thus provides an advantage to the hatching larvae.

5 selected talk

Chemosensory iGluRs: an ancient protostome-specific mechanism for tasting and smelling

Vincent Croset and Richard Benton
Center for Integrative Genomics, University of Lausanne, Switzerland

Ionotropic Glutamate Receptors (iGluRs) are a very ancient and widespread family of proteins. They are present in most multicellular organisms and have been shown to be involved in multiple processes, like fast neuronal communication at synapses in metazoans, cell-cell communication in plants, or chemotaxis in cyanobacteria.
Recently, 61 new iGluR-like receptors, called Ionotropic Receptors (IRs), have been discovered in the fruit fly *Drosophila melanogaster*, revealing additional functions for iGluR-related proteins. Some of these proteins have been shown to be responsible for chemical detection in sensory neurons from the third antennal segment, which is the main olfactory organ in insects. Furthermore, several non-antennal IRs are expressed in several larval and adult gustatory organs, suggesting that IRs are involved in chemosensory perception, both at the olfactory and gustatory levels. It is remarkable that a spectacular spatial and functional transition occured in order to enable the emergence of chemosensory IRs expressed in the dendrites of reduced subsets of neurons from synaptic iGluRs broadly expressed troughout the brain. In addition, IRs underwent spectacular expansion and diversification in order to acquire new chemosensory functions. This opens many questions about the origin and diversification of the IR repertoire: which species have IRs? What was the first IR? What are the mechanisms that allowed IR expansion? Here, I present a structural, phylogenetic and expression analysis of IR evolution. A broad genetic screen was performed and demonstrates that the first IR (IR25a) emerged from an ancestral iGluR in a primitive protostome in the early Cambrian (~540 MYA). Moreover, expression data in molluscs and nematodes shows that it may have acquired its chemosensory function very early. In contrary, most of the olfactory IRs are only present in insects, and their expansion was initiated by the duplication of IR25a into IR8a, which has acquired a specific olfactory function and has been shown to be acting as a co-receptor. Finally, the analysis of the mechanisms of IR evolution shows that one retroposition event might have been a key factor in the rapid emergence of new IR genes.
Altogether, these data provide a broad view on how the IRs evolved, and bring many additional informations about how big families of chemosensory genes can evolve, diverge, and acquire a high level of species-specificity in order to respond to a wide range of environmental stimuli. In addition, this work suggests that the development of a powerful sense of smell is a predominant condition for the orientation in a tridimensional environment and may thus have been a key factor of the development of flight in insects.

6

PKS4 can regulate auxin transport to modulate hypocotyl growth orientation

Emilie Demarsy, Isabelle Schepens, Christian Fankhauser
Center for Integrative Genomics, University of Lausanne, Switzerland

Light is a crucial environmental factor that elicits adaptative behaviors in many species, especially in plants. Being sessile and photoautotrophic plants possess sophisticated light-sensing systems. Upon light perception, several photoreceptors (phototropins, cryptochromes, phytochromes) are activated and act in concert to control plant growth direction. The plant growth hormon auxin act downstream of these two pathways to trigger the differential growth of the plant. However the signaling cascade linking the photoreceptors activity to the regulation of auxin response is still poorly understood.

PKS4 protein (Phytochrome Kinase Substrate) has been shown to act in both phytochrome and phototropin signaling pathways to regulate assymetric growth of hypocotyl in response to phototropic and gravitropic stimuli (Lariguet et al., 2006 ; Schepens et al., 2008). Upon light perception PKS4 is phosphorylated and this phosphorylation depends on phot1 specifically. Here we present evidence that PKS4 acts upstream of auxin signaling. PKS4 light-dependent phosphorylation is not affected by exogeneous auxin application or inhibition of auxin transport. On the other hand characterization of PKS4 overexpressing lines and null mutant suggest that PKS4 can regulate auxin transport.

7

The role of transcription factories in the organization of nuclear architecture

Dorier J., Stasiak A.
Center for Integrative Genomics, University of Lausanne, Switzerland

Using numerical simulations, we investigate the underlying physical effects responsible for the overall organization of chromosomal territories in interphase nuclei. In particular, we address the following three questions: 1. Why are chromosomal territories with relatively high transcriptional activity on average, closer to the centre of cell's nucleus than those with the lower activity? 2. Why are actively transcribed genes usually located at the periphery of their chromosomal territories? 3. Why are pair-wise contacts between transcriptionally active and inactive loci less frequent than those involving only active or only inactive loci? We show that transcription factories-mediated contacts between active genes belonging to different chromosomal territories are instrumental for all these features of nuclear organization to emerge spontaneously due to entropic effects arising when chromatin fibres are highly crowded.

8

Genome-wide association studies for chemosensory research: The PROP-T2R38 association as a benchmark

Ulrich K. Genick*[1], Zoltan Kutalik[2,3], Mirko Ledda[1], Edgard Morya[4], Nicholas Godinot[1], Nathalie Martin[1], Koichi Sameshima[3], Sven Bergmann[2,3] and Johannes le Coutre[1].
[1] *Department of Food-Consumer Interaction, Nestlé Research Center, Lausanne, Switzerland*
[2] *Department of Medical Genetics, University of Lausanne, Switzerland*
[3] *Swiss Institute of Bioinformatics, University of Lausanne, Switzerland*
[4] *Associação Alberto Santos Dumont para Apoio à Pesquisa (AASDAP), Sao Paulo, Brazil*
* *to whom correspondence should be addressed (ulrich.genick@rdls.nestle.com)*

The acuity of the chemical senses varies substantially from one person to the next. Part of this variation is expected to be driven by genetics. Identification of the specific genetic factors driving this variation will provide new insights into the molecular mechanisms of taste perception and will allow a better understanding of how taste sensitivity varies across different ethnic populations.
In the present study we have evaluated the usefulness of Genome Wide Association Studies (GWAS) as a tool for the identification of the genetic factors that shape taste sensitivity. Using the well-documented association between variations in the perception of the bitter compound PROP and variations in the T2R38 taste receptor gene as an example we evaluated i) which sensory parameters are best suited as phenotypic input for a GWAS ii) how these parameters are best analyzed and iii) how many subjects are required for the successful identification of genetic markers that drive taste sensitivity.
Our results show that detection thresholds measured via the staircase method are particularly powerful phenotype parameters for GWAS analysis. With this phenotype parameter less than 100 subjects were sufficient to pinpoint the responsible genetic variants in the T2R38 receptor in an unbiased, genome-wide search.
These results indicate that the GWAS approach can be a powerful tool for identifying genetic factors underlying variation in chemosensory perception.

9

Molecular and cellular analysis of SNMP, a CD36-related receptor essential for pheromone detection in *Drosophila*

Carolina Gomez-Diaz, Jaime Humberto Reina, Marion Graf and Richard Benton
Center for Integrative Genomics, University of Lausanne, Switzerland

CD36 transmembrane proteins are involved in diverse fundamental cellular processes in many organisms such as ligand uptake, cell adhesion and innate immune detection. Despite its conserved and widespread roles, the molecular mechanisms by which these proteins act are unclear. We recently characterised a CD36-related receptor in the fruit fly, *Drosophila melanogaster*, named Sensory Neuron Membrane Protein (SNMP). SNMP is found in the sensory cilia of olfactory sensory neurons that have been implicated in pheromone detection and acts as a co-factor for the receptor OR67d in recognition of the sex and aggregation pheromone cis-vaccenyl acetate (cVA). SNMP thus defines a new *in vivo* model system to understand the mechanism of CD36 protein action, as we know the identity of both upstream ligands (pheromones) and downstream physiological effects (odorant receptor-evoked neuronal activity).

We have initiated a large-scale structure function analysis of SNMP, comprising a full-protein deletion scan and point mutations of predicted post-translational modification sites. Analysis of these mutant proteins in transgenic flies will allow us to define protein domains that are essential for the localisation and pheromone recognition properties of SNMP. In parallel, we are reconstituting SNMP function in heterologous cells to allow us to investigate the existence of biochemical interactions of SNMP with pheromone ligands and/or odorant receptors. Together these experiments will provide insights into both the molecular basis of pheromone detection in insects and the molecular mechanisms of CD36 protein function.

10

PPARbeta in astrocytes maturation and functions

Matthew Hall, Béatrice Desvergne
Center for Integrative Genomics, University of Lausanne, Switzerland

PPARβ is highly expressed in the embryonic and adult brain, where it is expressed in astrocytes and neurons. Whereas the role of PPARβ in metabolic regulations has been extensively explored, very little is yet known on its activity in the brain. To tackle this question we prepared primary astrocyte cultures from PPARβ WT and from PPARβ null animals. We first observed an impaired stellation of PPARβ -/- astrocytes when challenged either through exposure to MnCl2 or in neuron/astrocyte cocultures. This was accompanied by the aspect of strong stress fibers and anchoring foci in PPARβ -/- cells, not seen in WT cells. We further explored the main astrocyte functions that include metabolism, proliferation, migration and glutamate uptake. We show that PPARβ -/- astrocytes have an impaired glutamate uptake, with a 2.5 fold reduced rate in the initial phase of uptake compared to WT control. In parallel, glucose uptake is impaired whereas lactate release is even lower, resulting in an unbalanced glucose uptake / lactate release ratio. We are now defining the molecular mechanisms involved, analysing energy status of the cells, the glycolysis pathway, and gene expression in PPARβ -/- vs. WT astrocytes.

11

Reduction of plant growth in response to MAMPs: how and why?

Dagmar Hann, Lea Steinle and Thomas Boller
Institute of Plant Physiology, University of Basel, Switzerland

Plant growth is tightly connected to changes in the environment. In response to microbial attack, plants often reduce their growth rate. It is widely believed that this is due to a shift in resource allocation and an enhanced investment into defense. Reduction of growth is also part of the plant's response to microbe-associated molecular patterns (MAMPs), its first line of defense (1). For example, a strong growth inhibition is observed in Arabidopsis seedlings upon recognition of the bacterial MAMPs, flagellin or elongation factor Tu, through their cognate receptors FLS2 and EFR1. At the same time, approximately 1000 genes (mainly related to defense) are induced, and 200 genes (a subset related to growth) are repressed. Interestingly, growth inhibition imposed by the MAMPs is reversible. Both MAMP receptors interact with another receptor kinase, known as BAK1 for BRI1-associated kinase 1, upon ligand perception (2, 3). BRI1 itself is the receptor of the growth hormone brassinolide and requires BAK1 for full signaling similar to FLS2 and EFR. Therefore, it is a plausible hypothesis for growth reduction in response to MAMPs that BAK1 is detracted from BRI1 to fulfill its role in immune signaling. However, this is probably not sufficient to provoke growth inhibition, because brassinolide synthesis mutants are still inhibited by flg22, and brassinolide treatment does not counteract growth inhibition (3). However, other hormone pathways, such as auxin signaling, are affected by MAMP perception as well. Therefore we investigated several mutants related to diverse hormone signaling pathways for their ability to respond to MAMPs by seedling growth inhibition. In addition, we tried to counteract growth inhibition by addition of plant growth promoting hormones.

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12 selected talk

Bacterial adaptation through distributed sensing of metabolic fluxes

Oliver Kotte[1], Judith Zaugg[1], Karl Kochanowski[1], Matthias Heinemann[1,2]
[1]*ETH Zürich, Institute of Molecular Systems Biology, Switzerland*
[2]*University of Groningen, Biomolecular Sciences and Biotechnology Institute, NL*

The recognition of carbon sources and the adaptation to recognized changes are of particular importance for bacterial survival in fluctuating environments. Despite a thorough knowledge base of *E. coli*'s central metabolism and its regulation, fundamental aspects of the employed sensing and regulation mechanisms remain unclear.
Towards attaining a system-level understanding of how *E. coli* adapts between different carbon sources, we will present a large-scale differential equation model that describes the organism's central metabolism and its enzymatic, transcriptional and posttranscriptional regulation. To generate this model, we devised a novel approach for parameter estimation that draws on steady state -omics measurement data and exploits a decomposition of the global estimation problem into independent small subproblems.
As revealed by analysis of the developed model, we will show that the interplay of known interactions explains in molecular-level detail the system-wide adaptations of metabolic operation between glycolytic and gluconeogenic carbon sources. Further, we will demonstrate that these adaptations are enabled by an indirect recognition of carbon sources through a mechanism we termed distributed sensing of intracellular metabolic fluxes. This mechanism uses two general motifs to establish flux-signalling metabolites, whose bindings to transcription factors form flux sensors. These sensors are embedded in global feedback loop architectures that orchestrate the regulatory adjustments to recognized changes in carbon source availability. We will present experimental data of a detailed, molecular level follow-up analysis that provides evidence for the generated model predictions.
Overall, in this work we demonstrate a successful execution of a full systems biology cycle: starting from omics data and using a new method for parameter estimation, we developed a large scale kinetic model. Through analysis of the model we identified novel emerging principles that we could validate in detailed follow-up experimental analyses. The insights obtained significantly improve our understanding of bacterial metabolic operation with fluctuating carbon sources.

13

Nuclear phyA signaling promotes phototropism

Chitose Kami, Martine Trevisan, Andreas Hiltbrunner and Christian Fankhauser
Center for Integrative Genomics, University of Lausanne, Switzerland

The phytochromes (phy) are important photoreceptors in higher plants (phyA-phyE in *Arabidopsis*). phyA has a number of specific features such as its light labile nature and its ability to enter the nucleus in response to far-red light (a light quality encountered under a canopy). phyA promotes not only red and far-red light responses but also activity of the blue light sensors phototropins but the underlying mechanism has remained unclear. Nuclear accumulation of phyA is dependent on two related proteins called FHY1 (Far-red elongated HYpocotyl 1) and FHL (FHY1 Like), which mediate nuclear import of light-activated phyA (Rösler et al. 2007; Genoud et al. 2008). The characterization of the *fhy1fhl* double mutant in which phyA remains in the cytoplasm suggests that phyA needs to get into the nucleus to trigger most responses (Rösler et al. 2007; Genoud et al. 2008). However one study has suggested that phyA in the cytoplasm is required to promote phototropism (Rösler et al. 2007).
In this study, we compared the ability of nuclear and cytosolic phyA to promote phototropism to get further insight in the mechanism of phyA enhancement of phototropin signaling. phyA-NLS-GFP plants have a constitutively nuclear phyA and they were compared to the WT in which phyA enters the nucleus in response to light and with *fhy1fhl* in which phyA remains in the cytoplasm. Our results suggest that nuclear phyA and not cytosolic phyA is most efficient to promote phototropism. Our data suggest a rather distinct mechanism of photochrome-mediated promotion of phototropin response than previously proposed.
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14

Control of Cell Polarity by the Microtubule-associated Protein Tea4

Kokkoris Kyriakos, Hachet Olivier, Martin Sophie
Center for Integrative Genomics, University of Lausanne, Switzerland

Cell polarity is an essential property of most cell types and relies on a dynamic cytoskeleton of actin filaments and microtubules. In rod-shaped *S. pombe* cells microtubules (MTs) are organised along the length of the cell and transport polarity factors to cell tips to regulate cell polarity. An important cell polarity factor is the protein Tea4, which is responsible for correct cell morphogenesis and bipolar growth.
Tea4 contains a conserved SH3 domain (Src Homology domain 3), the function of which remains unknown. Here we show that the SH3 domain of Tea4 is essential for Tea4 function *in vivo* and present a characterisation of its function and binding partners. First, we investigated the role of this SH3 domain by generating point mutations in its ligand-binding interface (SH3*) and showed that this domain is essential for Tea4 function *in vivo*. Cells with *tea4SH3** mutations show aberrant cell shapes and monopolar growth patterns similar to *tea4*Δ. In addition, Tea4 SH3 domain is important for proper localization of multiple cell polarity proteins. Second, using tandem affinity purification we identified Tea4 partners. Comparison of Tea4 and Tea4SH3* complexes demonstrates that point mutations in the SH3 domain abolish the association with type 1 phosphatases (Dis2 and Sds21). Interestingly, preliminary results indicate that Tea4 also binds Pom1, a kinase that couples cell length with cell cycle. Our results bring together missing pieces of the yet unsolved puzzle of regulation of cell polarity and morphogenesis.

15

The Anopheles gambiae Odorant Binding Protein 1 (AgamOBP1) Mediates Indole Recognition in the Antennae of Female Mosquitoes

Thomas Kröber and Patrick M. Guerin
Institute of Biology, University of Neuchâtel, Switzerland

The mosquito *Anopheles gambiae* is the major vector of malaria in sub-Saharan Africa and responsible for thousands of deaths daily. The genome of the malaria mosquito *Anopheles gambiae* has been sequenced and annotated 8 years ago. This opened the possibility to investigate physiological processes at the molecular level. Host finding is crucial to *A. gambiae* survival and implicates the mosquito olfactory system. Little is known about the combinations of ligands and odorant binding proteins (OBPs) that can produce specific odour-related responses *in vivo*. We identified a ligand, indole, for an odorant binding protein, AgamOBP1, modelled the interaction in silico, and confirmed the interaction using biochemical assays. RNAi-mediated gene silencing coupled with electrophysiological analyses confirmed that AgamOBP1 binds indole in *A. gambiae* since the antennal receptor cells do not respond to indole in the absence of expression of AgamOBP1*. This demonstrates the significance of OBPs in odour recognition. Purified recombinant AgamOBPs are being used in high-throughput screening assays to identify new ligands from libraries of synthetic and natural compounds that may serve to block host perception by *A. gambiae*. Furthermore, the research can be expanded to ligands for OBPs of other medically important insects.

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16

Phytochrome Interacting Factors 4 and 5 redundantly limit seedling de-etiolation in continuous far-red light

Séverine Lorrain[1], Martine Trevisan[1], Sylvain Pradervand[2], Christian Fankhauser[1,3].
[1]*Center for Integrative Genomics, University of Lausanne, Switzerland*
[2]*Lausanne Genomic Technologies Facility (GTF), Center for Integrative Genomics, University of Lausanne, Switzerland*

Phytochromes are red/far red photosensors regulating numerous developmental programs in plants. Among them phytochrome A (phyA) is essential to enable seedling de-etiolation in continuous far-red (FR) light a condition mimicking the environment under a dense canopy. The ecological relevance of this response is demonstrated by the high mortality rate of *phyA* mutants germinating in deep vegetational shade. phyA signaling involves a direct interaction of the photoreceptor with members of the bHLH transcription factor family, PIF1 and PIF3 (Phytochrome Interacting Factor). We investigated the involvement of 2 other PIFs, PIF4 and PIF5, in phyA signaling and found that they redundantly control de-etiolation in FR light. The *pif4pif5* double mutant is hypersensitive to low fluence rates of FR light. This phenotype is dependent on FR light perception by phyA but does not rely on alterations of the phyA level. Our microarrays analysis shows that PIF4 and PIF5 are part of an inhibitory mechanism repressing the expression of some light-responsive genes in the dark and are also needed for full expression of several growth-related genes in the light. Unlike PIF1 and PIF3, PIF4 and PIF5 are not degraded in response to FR light indicating that they are light-regulated by a different mechanism. Our genetic analysis suggests that this is achieved through the sequestration of these PIFs by the closely related bHLH transcription factor HFR1 (long Hypocotyl in FR light). This parallels what we described in response to shade-mimicking conditions.

17

How does brain sense glucose ? Study of brain-specific glut2 knock-out mice

Lourdes Mounien[1], Pascal Seyer[1], Salima Metref[1], Anabella Da Costa[1], David Tarussio[1], Frédéric Preitner[1], Marc Foretz[2], Bernard Thorens[1]
[1]Department of Physiology and Center for Integrative Genomics, University of Lausanne, Switzerland; Present address: [2]Institut Cochin - INSERM U567 - CNRS UMR8104 - Université René Descartes Paris 5 Dpt Endocrinologie, Métabolisme et Cancer; Paris, France

Many proteins, including ion channels, glucose transporters, or enzymes have been associated with glucose sensing in different tissues. A role for the glucose transporter Glut2 in glucose-sensing and the control of glucose and energy homeostasis has been established in mice with a disruption of the *Glut2* gene which express a transgenic glucose transporter in their pancreatic β-cells to restore normal glucose-stimulated insulin secretion (*ripglut1;glut2*$^{-/-}$). However, Glut2 is also expressed in many other tissues, including liver, intestine and kidney and its absence from these tissues may impact on glucose and energy homeostasis. To directly assess the role of central Glut2 in metabolic regulation, we thus generated *Glut2*$^{lox/lox}$ mice and crossed them with Nestin-Cre mice to generate brain-specific *Glut2* gene inactivation.
Brain-specific *glut2* knock-out mice exhibited significant intolerance to intraperitoneal glucose injection. This was caused by impaired glucose-stimulated insulin secretion and not by insulin resistance. The insulin secretion defect was worsened upon high fat diet (HFD) feeding of the mice, and this also led to impaired plasma glucagon levels. Morphometric analysis of the endocrine pancreas revealed reduced β-cell mass in both normal chow and HFD fed mice and there was a relative increase in the a-to-β cell mass ratio.
These results indicate that absence of Glut2 from the brain leads to impaired endocrine pancreas structure and function. We hypothesize that central Glut2 is required for glucose-dependent control of the autonomic nervous system, in particular for activation of the parasympathetic branch, which is known to control of beta-cell mass.

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Impact of transposable elements in organization and functioning of allopolyploid genomes

Christian Parisod[1,2,¶], Karine Alix[3], Boulos Chalhoub[4] and Marie-Angèle Grandbastien[1]
[1]Institut Jean-Pierre Bourgin, Laboratoire de Biologie Cellulaire, INRA, Versailles, France
[2]National Centre for Biosystematics, Natural History Museum, University of Oslo, Norway
[3] AgroParisTech, UMR de Génétique Végétale, INRA – Université Paris-Sud – CNRS – AgroParis Tech, Ferme du Moulon, Gif-sur-Yvette, France
[4] Unité de Recherches en Génomique Végétale, URGV-INRA, Évry, France
¶Present address: Laboratoire de Botanique Evolutive, Université de Neuchâtel, Switzerland

Transposable elements (TEs) represent an important fraction of plant genomes and are likely candidate sequences playing a pivotal role in fuelling genome reorganization and functional changes following allopolyploidization. Different processes associated with allopolyploidy (i.e. genetic redundancy, bottleneck during the formation of allopolyploids or genome shock following genome merging) may allow accumulation of TE insertions. By surveying the literature as well as by comparative analysis across different allopolyploid systems, our objective is to shed light on the structural, epigenetic and functional modifications driven by TEs during allopolyploidization and subsequent diploidization. Available evidence indicate that TE proliferation in the short- or the long-term after allopolyploidization might be restricted to few TEs, in specific polyploid systems. In contrast, data indicate major structural changes in the TE genome fraction immediately after allopolyploidization, mainly through losses in TE sequences due to recombination. Emerging evidence also suggest that TEs are targeted by considerable epigenetic changes, which might impact gene expression and genome stability. Furthermore, TEs might directly or indirectly support the evolution of new functionalities in allopolyploids during diploidization. All data stress allopolyploidization as a shock associated with drastic genome reorganization. Mechanisms controlling TEs during allopolyploidization as well as their impact on diploidization are discussed.

Keywords
allopolyploidy, diploidization, genome evolution, stress, transposable element

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Getting to the site of action: Where do phototropins act in Arabidopsis?

Preuten T.
Center for Integrative Genomics, University of Lausanne, Switzerland

Phototropin blue-light receptors (phot1 and phot2) in Arabidopsis activate a range of light responses, including phototropism, leaf movement, stomata opening, leaf expansion and chloroplast movement. Those responses generally serve to optimize photosynthesis and allow the plant to adapt to changing light environments. To this end, phototropins act in different cell types and parts of the plant, e.g. in guard cells, mesophyll cells or the hypocotyl elongation zone. Phototropins are light regulated protein kinases that are located at the plasma membrane in the dark. Upon irradiation with blue light their kinase function is activated and a fraction is internalized to the cytoplasm (phot1) or Golgi-vesicles (phot2).
To date it has not been shown if the phototropins generally act cell autonomously, as is the case for chloroplast movements or if phototropic growth responses involve transportation of a signal from the leaves to the site of the reaction, as is suggested by classic experiments. Furthermore, it is not known if kinase activity depends on delocalization from the plasma membrane or if the withdrawal from the membrane is a mechanism of desensitization.
To address these questions, transgenic Arabidopsis lines containing constructs that allow expression of phototropins under the control of tissue-specific promoters were established to check for complementation of phot1phot2 double-knockout plants. Additionally, myristoylation is used to constitutively tether the phototropins to the plasma membrane and prevent internalization. Complementation of phot1phot2 lines will be checked. Further phenotypical, microscopical, genetical and biochemical analyses will allow us to better understand how and where the phototropin blue-light receptors help to translate light signals into cellular and subcellular responses. Their interaction partners in different responses and distinct tissues will as well be studied in more detail. This will lead to a better understanding as to how plants manage to accumulate maximum amounts of biomass through optimal rates of photosynthesis under changing environmental conditions.

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PPARα orchestrates sexual dimorphism in hepatic functions

Gianpaolo Rando[1], Nicolas Leuenberger[1], Vincent Zoete[2], Walter Wahli[1]
[1]*Center for Integrative Genomics, National Research Center Frontiers in Genetics, University of Lausanne, Switzerland*
[2]*Molecular Modelling group, Swiss Institute of Bioinformatics, Lausanne, Switzerland*

Peroxisome proliferator-activated receptors form a small family of three nuclear receptors (PPARα, PPARβ/δ,, and PPARγ), which act as lipid sensors to modulate gene expression. As most metabolic studies are conducted in male animals, understanding the sex specificity of the underlying molecular pathways has been neglected. For instance, PPARα has been considered as having low activity in female liver, because of the lack of peroxisome proliferation when females are exposed to peroxisome proliferators.
This point of view is now challenged by the observation that there is a sexual dimorphism in PPARα post-translational modification, which plays an active role in gene repression. In female mice, PPARα has broad repressive actions on hepatic genes involved in steroid metabolism and immunity. Using the steroid oxysterol 7α-hydroxylase cytochrome P4507b1 (Cyp7b1) gene as a model, we elucidated the molecular mechanism of this sex-specific PPARα-dependent repression. Initial sumoylation of the ligand-binding domain of PPARα triggered the interaction of PPARα with GA-binding protein alpha (GABPα) bound to the target Cyp7b1 promoter. DNA and histone methyltransferases were then recruited, and the adjacent Sp1-binding site and histones were methylated. These events resulted in loss of Sp1-stimulated expression and thus downregulation of Cyp7b1. Physiologically, this repression conferred on female mice protection against experimetally estrogen-induced intrahepatic cholestasis.
Coregulator recruitment causes tissue-specific actions of nuclear receptors. To explore whether sexual dimorphism affects coregulators also, we analyzed hepatic PPARα protein complexes in both sexes. We found three proteins that interact preferentially with PPARα in female liver. We identified the interaction motif of one of them and explored its coregulator abilities, which required NADP+, suggesting that PPARα trans-repression is redox-sensitive. One of the processes, which are repressed in females, is isoprenoid synthesis. Co-treatment of hepatoma cells with 17β-estradiol and PPARα ligands diminished isoprenoid synthesis, which was associated with reduced cell proliferation.
Collectively, our data identify PPARα as a key actor of hepatic sexual dimorphism. The ongoing characterization of this function aims to unveil why the female liver is more resistant to inflammation and cancer.

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Two distinct mechanisms determine photoperiod-dependent differences between the circadian Dbp and Rev-Erb alpha genes

[1]Ripperger J., [2]Stratmann M., [1]Stadler F., [3]Tamanini F., [3]Vanderhorst G.
Unit of Biochemistry, University of Fribourg, Switzerland[1], University of Geneva, Switzerland[2], Erasmus Medical Center, Rotterdam, The Netherlands[3]

Mammals can anticipate daily recurring events even under steadily changing photoperiods. This necessitates continuous adaptation of their endogenous circadian ("= about a day") clocks. To create robust circadian rhythms the PERIOD (PER) and CRYPTOCHROME (CRY) proteins temporarily restrict the transcriptional activity of BMAL1 and CLOCK. BMAL1 and CLOCK also govern rhythmic output in different phases over the circadian cycle. Consequently, mechanisms must exist that gate their regulatory potential. Here we describe two mechanisms that determine the phases of *albumin D-site binding protein (Dbp)* and *Rev-Erba* gene expression in the liver. Although genuine targets for regulation by BMAL1 and CLOCK they are not expressed in the same phase. A regulatory element in the promoter region of *Dbp* was identified which bound CRY1 to delay BMAL1 and CLOCK dependent transcription. In contrast, circadian transcription of the *Rev-Erba* gene was prematurely suppressed by auto-repression. These mechanisms together set the relative phase difference of both genes not only in accordance with the circadian cycle, but also with the photoperiod. Thus, sophisticated regulatory mechanisms maintain anticipation independent of the photoperiod.

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Glycemia sensing by Glut2 expressing GABAergic neurons in brainstem

[1]Sanno H.*, [2]Lamy C.*, [2]Chatton J.-Y., [1]Thorens B.
Center for Integrative Genomics and Department of Physiology[1], University of Lausanne, Switzerland
Department of Cell Biology and Morphology[2], University of Lausanne, Switzerland
*These authors are equally contributed.

Hypothalamic arcuate nucleus (ARC) neurons play an important role in glucose and energy homeostasis. On the one hand, NPY and AgRP neurons, which are inhibited by leptin and insulin, stimulate food intake and decrease energy expenditure whereas POMC neurons, which are stimulated by leptin, inhibit food intake and increases weight loss. Neurons from the ARC are also regulated by low or high glucose concentrations by incompletely understood mechanisms. It has however been suggested that glucose sensitive catecholaminergic neurons of the basolateral medulla (BLM) may indirectly control ARC neurons. Here, we studied the role of Glut2, an essential component of glucose sensing in pancreatic beta-cells, in central glucose sensing. We previously showed that Glut2-null mice (ripGlut1;Glut2-/-) have an increase in daily food intake associated with a deregulation of the NPY and POMC neurons activity. The site of Glut2 expression in the central nervous system using Glut2Cre/eYFP flox mice was identified. Glut2/eYFP neurons were found in the lateral, dorsomedial, ventromedial, and paraventricular hypothalamic nuclei as well as many areas of the brainstem, including the nucleus of the tractus solitarius (NTS), the dorsal motor nucleus of the vagus (DMNX), and the BLM.
Increase in activation of glucoprivation sensitive neurons in the NTS and DMNX and glucose excited in the BLM was shown. Approximately 80% of Glut2/eYFP neurons in brainstem co-express GABAergic marker GAD67 and are also positive for the interneuron markers, parvalbumin and calbindin. To further characterize glucose responsive population in brainstem, we employed whole-cell recordings with successive extracellular glucose changes on acute brain slices followed by single cell RT-PCR analysis.
Our data suggest that Glut2 expressing neurons in the brainstem are interneurons that release the inhibitory neurotransmitter GABA by detecting the level of glucose in the brain. Together with other data showing direct connections between neurons of the brainstem and several hypothalamic nuclei, we propose that Glut2-expressing neurons in the brainstem play a role in glycemia sensing and the control of POMC or NPY neurons in ARC, thereby contributing to glucose and energy homeostasis.

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The mammalian clock component PERIOD2 coordinates circadian output by interaction with nuclear receptors

Schmutz I., Ripperger J., Albrecht U.
Unit of Biochemistry, University of Fribourg, Switzerland

Life on Earth is challenged by daily light-dark changes in the environment. Many organisms developed endogenous clocks that allow them to track time and to anticipate such recurring changes. In mammals, many behavioral, physiological and metabolic parameters show daily oscillations, even in the absence of external timing cues. To generate robust rhythms with a period length of about 24 hours, cellular clocks make use of molecular oscillators consisting of transcriptional-posttranslational feedback loops. The core loop of the molecular oscillator establishes circadian rhythms by the transcriptional repressors PERIOD (PER) and CRYPTOCHROME (CRY) that counteract the positive factors BMAL1 and CLOCK. Furthermore, nuclear receptors mediate circadian transcriptional control of *Bmal1* and a number of metabolic target genes. However, the coordination between the circadian oscillator and the output via nuclear receptors remains to be elucidated in detail.
Here we identified new molecular functions of the clock component PER2. PER2 interacts with several nuclear receptors, including PPARα and REV-ERBα. *In vivo*, PER2 is bound at the promoters of nuclear receptor target genes like the clock component *Bmal1*, and the metabolic genes *Hnf1*α and *Glucose-6-phosphatase*. In this manner, PER2 can serve as co-regulator of nuclear receptor-mediated transcription and can propagate clock information to metabolic and physiologic pathways via nuclear receptors. Hence, PER2 may be key factor for the temporal organization of biological output processes by the circadian clock.

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Functional neuro-architecture of the fly's "second nose": physiological, anatomical and behavioural characterisation of Ionotropic Receptor olfactory

Silbering, AF[1], Grosjean, Y[1,2], Rytz, R[1], Jefferis, GSXE[3] and Benton, R[1]
[1]*Center for Integrative Genomics, University of Lausanne, Switzerland*
[2]*Centre des Sciences du Goût et de l'Alimentation, UMR-6265 CNRS, UMR-1324 INRA, Université de Bourgogne, Dijon, France*
[3]*Division of Neurobiology, MRC Laboratory of Molecular Biology, Cambridge, UK*

The olfactory system of *Drosophila melanogaster* is a powerful model to study the link between the stimuli present in the environment and the behavioural responses they evoke. The recently identified variant subfamily of ionotropic glutamate receptors, the Ionotropic Receptors (IRs), represents a new class of olfactory receptors in the fruit fly, which defines a "second nose" for this animal, together with the evolutionarily unrelated, Odorant Receptors (ORs). A comprehensive view of the organisation and function of the IR olfactory circuitry, and how these properties compare with those of the ORs are outstanding questions, which we have addressed by physiological, anatomical, and behavioural approaches. Peripheral electrophysiological analysis of IR neuron responses to more than 160 chemically diverse odours reveal that IRs are very narrowly tuned to a small number of amines, acids and aldehydes , contrasting with the broader chemical specificity of the OR repertoire towards esters, alcohols and ketones. Using selective IR promoter-driven reporters we reveal segregation of IR and OR sensory input to the primary olfactory centre in the brain, and visualise the spatial map of odour-evoked activity in individual IR glomeruli. Second order projections of IR circuits are, however, overlapping with those of ORs, suggesting integration of IR and OR information in higher brain centres. Behavioural analysis using broadly-expressed co-receptor mutants to selectively eliminate OR or IR-dependent olfactory sensory inputs, reveals that both OR and IR circuits can mediate attractive and aversive behaviours towards odours. Notably, several stimuli produce behavioural responses of opposite valence via these different circuits, suggesting these noses fulfil complementary functions to fine-tune a fly's behaviour towards important environmental odour blends.

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Glucocorticoid-Induced Leucine Zipper (GILZ) and its in vivo role

Suarez P., Hummler E.,
Dep. of Pharmacology and Toxicology, University of Lausanne, Switzerland

The glucocorticoid-induced leucine zipper (Gilz) is an X-linked transcription factor and was originally described as a dexamethasone-induced transcript in murine thymocytes. It is a member of the transforming growth factor b1-stimulated clone 22 domain (TSC22D) family. Gilz (also termed TSC22D3) is widely expressed and an important role in immunity, adipogenesis, renal sodium handling has been proposed. We generated mice constitutively lacking a vital region of the Gilz gene, thus abolishing the function of this gene. The expression of Gilz mRNA transcripts and protein was completely abolished in all tissues tested. Knockout mice are viable. We tested the role of Gilz in peritoneal, splenocyte and bone marrow-derived macrophages inflammation and sepsis models, but mice lacking Gilz only showed minor responses. With age, Gilz-deficient mice contain less fat and are lighter. Following sodium and water deprivation experiments, water and salt homeostasis is conserved. Sterility of knockout males is associated with a severe testis dysplasia. Generally, seminiferous tubules are smaller and the number of Sertoli and germ cells is reduced while increased apoptosis is evidenced by TUNEL staining, but not cell proliferation. The interstitial Leydig cell population is augmented, and higher plasma FSH and testosterone levels are found. Interestingly, the expression of PPARg2 was diminished in the testis and in other tissues suggesting the existence of a regulatory mechanism between these genes. In summary, mice deficient for Gilz reveal functional redundancy amongst members of the TSC22D family. Solely, Gilz does not play the important role attributed according to the in vitro experiments and seem by itself unveil an important role in spermatogenesis.

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Thiamine pyrophosphate (TPP)-responsive riboswitch in A. thaliana: Structure and kinetic of TPP association with its RNA binding element

Guedich S. [1], Gabus C.[3], Ban N.[2], Dumas P. [1], Burnouf D.[1], Thore S.[3]
[1]CNRS-UPR9002, Strasbourg, France, [2]Institute of Molecular Biology and Biophysics, ETH-Zürich, Switzerland and [3]Department of Molecular Biology, University of Geneva, Switzerland

In bacteria and in eukaryote, a new level of gene expression regulation has recently been demonstrated (1). It is based on genetic elements located in the 5' or 3'-untranslated region of several mRNAs encoding proteins used to synthesize essential metabolites such as thiamine pyrophosphate (TPP). These specific sequences, called riboswitches, are composed of two domains, a metabolite-binding domain and a gene expression platform. Metabolite binding to the riboswitch aptamer domain promotes structural rearrangements in the expression platform that influence gene expression through, for example, early transcription termination, decrease of translation, or intron splicing (2).
We present the crystal structure of the eukaryotic *Arabidopsis thaliana* TPP specific riboswitch in complex with its natural ligand (3). The riboswitch specifically recognizes the TPP via conserved residues in the bulges of two highly distorted parallel sensor helices such that its pyrimidine ring stacks with bases of one helix while its pyrophosphate group interacts with the second sensor helix. We also measure the binding constant of TPP for its riboswitch in solution. Analyzing the complex fold of the RNA in light of the biochemical data on several functional mutants suggests a mechanism for the sequence of folding events that turn the riboswitch to its "off" state. In addition, structures of two thiamine analogues bound to the riboswitch suggests leads for the design of new compounds targeting TPP-specific riboswitches and explains the basis for pyrithiamine resistance found in certain fungal and bacterial riboswitches (4). These structures provide an excellent starting point for structure-based *in vivo* and *in vitro* experiments aimed at studying the mechanism of TPP riboswitch based regulation of gene expression in general.

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PPARβ/δ regulates insulin secretion and pancreatic β-cell mass in mice

José Iglesias[1,2], Akadiri Yessoufou[1] , Sebastian Barg[3,4], Sylvain Pradervand[1], Angela McDonald[3], Claire Bonal[5], Marie Debril[1], Daniel Metzger[6], Pierre Chambon[6], Pedro Herrera[5], Guy A. Rutter[4], Bernard Thorens[1] and Walter Wahli[1]

[1]Center for Integrative Genomics, National Research Center Frontiers in Genetics, University of Lausanne, Switzerland;
[2]Montreal Diabetes Research Center, University of Montreal, Canada;
[3]Section of Cell Biology, Division of Medicine, Imperial College London, UK;
[4]Department of Medical Cell Biology, Uppsala University, Sweden;
[5]Department of Genetic Medicine and Development, University of Geneva Medical School, Switzerland;
[6]Institut de Génétique et de Biologie Moléculaire et Cellulaire, Illkirch, France.

Peroxisome proliferatior-activated receptor β /δ is a ligand-activated transcription factor that belongs to the nuclear receptor superfamily. PPARβ/δ is expressed very early during embryogenesis and in adults; it has a broad expression pattern. It has been demonstrated that PPARβ/δ agonists decrease islet hyperplasia in leptin-deficient ob/ob mice. Moreover, evidence is increasing that PPARβ/δ protects against obesity and improves dyslipidemia and insulin resistance via effects in metabolic organs. However, its function in pancreas remains unclear. To address this point, we specifically deleted PPARβ/δ in the whole epithelial compartment of the mouse pancreas. This mutation induced an increased number of islets, which was associated with hyperinsulinemia. Isolated PPARβ/δ-null islets exhibited an accelerated second phase of glucose-stimulated insulin secretion. Higher levels of PKD and cofilin activity in PPARβ/δ-null islets correlated with altered Golgi organization and enhanced F-actin depolymerisation, causing stimulated insulin secretion and associated systemic effects. Taken together, these results provide evidence that PPARβ/δ acts as a repressive regulator of β-cell mass and insulin exocytosis, and novel information on its metabolic action.

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Analysis of the peripheral neuropathy, including small sensory neuropathy, in diabetic conditions

Jennifer Zenker, Olivier Poirot, Anne-Sophie De Preux-Charles, Estelle Arnaud, Jean-Jacques Medard, Roman Chrast
Department of Medical Genetics, University of Lausanne, Switzerland

Diabetes mellitus (DM) is a major cause of peripheral neuropathy. However, the underlying pathophysiological mechanisms of diabetic peripheral neuropathy (DPN) are still poorly understood. The most typical symptoms are pain, burning, tingling and numbness indicating a severe small sensory neuropathy. 90% of all diabetic patients suffer from type 2 DM, corresponding to more than 220 million people worldwide.
To get more insight into DPN associated with type 2 DM, we decided to use the rodent model of this form of diabetes, the db/db mice.
The progression of pathological changes in db/db mice mimics the ones observed in humans. Initially, db/db mice exhibit obesity and hyperinsulinaemia. Later they become hyperglycemic, and present reduced nerve conduction velocity and small sensory neuropathy (e.g. reduced intraepidermal nerve fiber density). After excluding any myelin related deficits in db/db mice, we further analyzed the node of Ranvier, a critical region for action potential propagation in myelinated fibers.
We observed a strong reduction of Caspr and $K_v1.2$ expression respectively in the paranodal and juxtaparanodal regions. To detect if these changes will lead to any alteration in PNS function we measured compound action potentials in isolated sciatic nerves from control and diabetic animals and showed significant increase in excitability in db/db sciatic nerves. Using pharmacological inhibitors we demonstrated that this hyperexcitability is mostly mediated by the decreased activity of K_v1-channels. Corroborating these results, we noticed aberrant action potential firing after sciatic nerve stimulation also *in vivo*, in db/db mice. Interestingly, nerve hyperexcitability has been previously described in diabetic patients and was correlated to ectopic action potential firing, ataxia, and paresthesiae suggesting that our observations may have a clinical significance.

List of participants

Last name :	First name:	Affiliations :	City:	Country :	Email :
Ait Yahya Graison	Emilie	CIG - University of Lausanne	Lausanne	Switzerland	emilie.aityahyagraison@unil.ch
Albrecht	Urs	University of Fribourg	Fribourg	Switzerland	urs.albrecht@unifr.ch
Aramendy	Marie	University of Fribourg	Fribourg	Switzerland	marie.aramendy@unifr.ch
Arendt	Detlev	EMBL Heidelberg	Heidelberg	Germany	detlev.arendt@embl.de
Azevedo	Joao-Luiz	Federal University of Sao Paulo	Sao Paulo	Brazil	jozevedo.dcir@epm.br
Baruchet	Michaël	CIG - University of Lausanne	Lausanne	Switzerland	michael.baruchet@unil.ch
Bell	Rati	CIG - University of Lausanne	Lausanne	Switzerland	rati.bell@unil.ch
Bendezu	Felipe	CIG - University of Lausanne	Lausanne	Switzerland	felipe.bendezu@unil.ch
Benton	Richard	CIG - University of Lausanne	Lausanne	Switzerland	Richard.Benton@unil.ch
Berthelot-Grosjean	Martine	CIG - University of Lausanne	Lausanne	Switzerland	Martine.Berthelot-Grosjean@unil.ch
Blanchard	Maxime	University of Lausanne	Lausanne	Switzerland	Maxime.Blanchard@unil.ch
Borzée	Amaël	University of Lausanne	Lausanne	Switzerland	amael.borzee@unil.ch
Bovard	David	University of Lausanne	Lausanne	Switzerland	david.bovard@unil.ch
Brechbühl	Julien	University of Lausanne	Lausanne	Switzerland	julien.brechbuhl@unil.ch
Broillet	Marie-Christine	University of Lausanne	Lausanne	Switzerland	Marie-Christine.Broillet@unil.ch
Brüssow	Friederike	University of Lausanne	Lausanne	Switzerland	friederike.bruessow@unil.ch
Buczynski-Ruchonnet	Diane	CIG - University of Lausanne	Lausanne	Switzerland	diane.buczynski-ruchonnet@unil.ch
Canella	Donatella	CIG - University of Lausanne	Lausanne	Switzerland	Donatella.Canella@unil.ch
Capotosti	Francesca	CIG - University of Lausanne	Lausanne	Switzerland	francesca.capotosti@unil.ch
Casals Casas	Cristina	CIG - University of Lausanne	Lausanne	Switzerland	Cristina.CasalsCasas@unil.ch
Chalfie	Martin	Columbia University	New York	United States	mc21@biology.columbia.edu
Chappuis	Sylvie	University of Fribourg	Fribourg	Switzerland	sylvie.chappuis@unifr.ch
Chrast	Roman	University of Lausanne	Lausanne	Switzerland	roman.chrast@unil.ch
Consales	Floriane	CIG - University of Lausanne	Lausanne	Switzerland	floriane.consales@unil.ch
Coupland	George	Max Planck Institute for Plant Breeding Research	Cologne	Germany	coupland@mpiz-koeln.mpg.de
Cousin	Pascal	CIG - University of Lausanne	Lausanne	Switzerland	pascal.cousin@unil.ch
Croset	Vincent	CIG - University of Lausanne	Lausanne	Switzerland	vincent.croset@unil.ch
Curie	Thomas	CIG - University of Lausanne	Lausanne	Switzerland	Thomas.Curie@unil.ch
De Moraes	Consuelo	Penn State University	University Park	United States	czd10@psu.edu
Dean	Caroline	John Innes Centre	Norwich	United Kingdom	caroline.dean@bbsrc.ac.uk

Decosterd	Isabelle	CHUV	Lausanne	Switzerland	isabelle.decosterd@chuv.ch
Degueurce	Gwendoline	CIG - University of Lausanne	Lausanne	Switzerland	gwendoline.degueurce@unil.ch
Demarsy	Emilie	CIG - University of Lausanne	Lausanne	Switzerland	edemarsy@unil.ch
Desplan	Claude	New York University	New York	United States	claude.desplan@nyu.edu
Desvergne	Béatrice	CIG - University of Lausanne	Lausanne	Switzerland	Beatrice.Desvergne@unil.ch
Di Micco	Antonia	CIG - University of Lausanne	Lausanne	Switzerland	Antonia.DiMicco@unil.ch
Ding	Jun	CIG - University of Lausanne	Lausanne	Switzerland	jun.ding@unil.ch
Dorcey	Eavan	University of Lausanne	Lausanne	Switzerland	eavan.dorcey@unil.ch
Dorier	Julien	CIG - University of Lausanne	Lausanne	Switzerland	julien.dorier@unil.ch
Dorsaz	Stéphane	CIG - University of Lausanne	Lausanne	Switzerland	stephane.dorsaz@unil.ch
Doucey	Marie-Agnès	CIG - University of Lausanne	Lausanne	Switzerland	ma_doucey@hotmail.com
Dubochet	Jacques	University of Lausanne	Lausanne	Switzerland	jacques.Dubochet@unil.ch
Dupasquier	Mélanie	CIG - University of Lausanne	Lausanne	Switzerland	melanie.dupasquier@unil.ch
Fankhauser	Christian	University of Lausanne	Lausanne	Switzerland	christian.fankhauser@unil.ch
Farmer	Edward	University of Lausanne	Lausanne	Switzerland	edward.farmer@unil.ch
Fierro	Ivo	CIG - University of Lausanne	Lausanne	Switzerland	Ivo.Fierro@unil.ch
Foster	Russell	University of Oxford	Oxford	United Kingdom	russell.foster@eye.ox.ac.uk
Galliot	Brigitte	University of Geneva	Geneva	Switzerland	brigitte.galliot@unige.ch
Geldner	Niko	University of Lausanne	Lausanne	Switzerland	Niko.Geldner@unil.ch
Genick	Ulrich	Nestlé Research Center	Lausanne	Switzerland	ulrich.genick@rdls.nestle.com
Gilardi	Federica	CIG - University of Lausanne	Lausanne	Switzerland	Federica.Gilardi@unil.ch
Goldschmidt-Clermont	Michel	University of Geneva	Geneva	Switzerland	michel.goldschmidt-clermont@unige.ch
Gomez Diaz	Carolina	CIG - University of Lausanne	Lausanne	Switzerland	Carolina.GomezDiaz@unil.ch
Gurba	Alexandre	University of Neuchâtel	Neuchâtel	Switzerland	alexandre.gurba@unine.ch
Hall	Matthew	CIG - University of Lausanne	Lausanne	Switzerland	matthew.hall@unil.ch
Hann	Dagmar	University of Basel	Basel	Switzerland	dagmar.hann@unibas.ch
Hardtke	Christian	University of Lausanne	Lausanne	Switzerland	christian.hardtke@unil.ch
Harewood	Louise	CIG - University of Lausanne	Lausanne	Switzerland	louise.harewood@unil.ch
Harshman	Keith	CIG - University of Lausanne	Lausanne	Switzerland	keith.harshman@unil.ch
Heinemann	Matthias	ETHZ-Zurich	Zurich	Switzerland	heinemann@imsb.biol.ethz.ch
Hernandez	Nouria	CIG - University of Lausanne	Lausanne	Switzerland	nouria.hernandez@unil.ch
Herr	Winship	CIG - University of Lausanne	Lausanne	Switzerland	winship.herr@unil.ch
Hersch	Micha	University of Lausanne	Lausanne	Switzerland	micha.hersch@unil.ch
Hodroj	Wassim	CIG - University of Lausanne	Lausanne	Switzerland	wassimhodroj@unil.ch

Hurni	Nicolas	University of Lausanne	Lausanne	Switzerland	nicolas.hurni@unil.ch
Huser	Delphine	University of Lausanne	Lausanne	Switzerland	delphine.huser.2@unil.ch
James Faresse	Nicole	CIG - University of Lausanne	Lausanne	Switzerland	nicole.jamesfaresse@unil.ch
Kaessmann	Henrik	CIG - University of Lausanne	Lausanne	Switzerland	Henrik.Kaessmann@unil.ch
Kami	Chitose	CIG - University of Lausanne	Lausanne	Switzerland	chitose.kami@unil.ch
Katsanou	Vicky		Lausanne	Switzerland	vkatsanou@hotmail.com
Keller	Laurent	University of Lausanne	Lausanne	Switzerland	laurent.keller@unil.ch
Kohnen	Markus	CIG - University of Lausanne	Lausanne	Switzerland	Markus.Kohnen@unil.ch
Kokkoris	Kyriakos	CIG - University of Lausanne	Lausanne	Switzerland	kyriakos.kokkoris@unil.ch
Krishnan	Jaya	ETHZ-Zurich	Zurich	Switzerland	jaya.krishnan@cell.biol.ethz.ch
Kroeber	Thomas	University of Neuchâtel	Neuchâtel	Switzerland	thomas.kroeber@unine.ch
La Spada	Francesco	CIG - University of Lausanne	Lausanne	Switzerland	francesco.laspada@unil.ch
Lahiri	Shawon	CIG - University of Lausanne	Lausanne	Switzerland	shawon.lahiri@unil.ch
Laverrière Loss	Alexandra	CIG - University of Lausanne	Lausanne	Switzerland	alexandra.laverriereloss@unil.ch
Leuenberger	Nicolas	CIG - University of Lausanne	Lausanne	Switzerland	Nicolas.leuenberger@chuv.ch
Lingner	Joachim	EPFL	Lausanne	Switzerland	joachim.lingner@epfl.ch
Lo Presti	Libera	CIG - University of Lausanne	Lausanne	Switzerland	Libera.LoPresti@unil.ch
Lorrain	Séverine	CIG - University of Lausanne	Lausanne	Switzerland	severine.lorrain@unil.ch
Maiolo	Elena	University of Fribourg	Fribourg	Switzerland	Elena.Maiolo@unifr.ch
Mehr	Marco	Swiss Paraplegic Research	Nottwil	Switzerland	m_mehr_ksw@hotmail.com
Mescher	Mark	Penn State University	University Park	United States	mcmescher@psu.edu
Michalik	Liliane	CIG - University of Lausanne	Lausanne	Switzerland	liliane.michalik@unil.ch
Michlig Gonzalez	Stéphanie	Nestlé Research Center	Lausanne	Switzerland	stephanie.michliggonzalez@rdls.nestle.com
Modi	Honey	CIG - University of Lausanne	Lausanne	Switzerland	Honey.Modi@unil.ch
Montanaro	Mauro	CIG - University of Lausanne	Lausanne	Switzerland	mauro.montanaro@unil.ch
Moreno	Silvia	University of Lausanne	Lausanne	Switzerland	silvia.moreno@unil.ch
Mottaz	Hélène	CIG - University of Lausanne	Lausanne	Switzerland	helene.mottaz@unil.ch
Mounien	Lourdes	CIG - University of Lausanne	Lausanne	Switzerland	lourdes.mounien@unil.ch
Nawathean	Pipat	CIG - University of Lausanne	Lausanne	Switzerland	pipat.nawathean@unil.ch
Nawrath	Christiane	University of Lausanne	Lausanne	Switzerland	Christiane.Nawrath@unil.ch
Nenniger Tosato	Monique	University of Lausanne	Lausanne	Switzerland	Monique.NennigerTosato@unil.ch
Neyen	Claudine	EPFL	Lausanne	Switzerland	claudine.neyen@epfl.ch
Paillusson	Alexandra	CIG - University of Lausanne	Lausanne	Switzerland	alexandra.paillusson@unil.ch
Parisod	Christian	University of Neuchâtel	Neuchâtel	Switzerland	christian.parisod@unine.ch

Paszkowski	Uta	University of Lausanne	Lausanne	Switzerland	uta.paszkowski@unil.ch
Patel	Dhaval	CIG - University of Lausanne	Lausanne	Switzerland	Dhaval.Patel@unil.ch
Pertin	Marie	CHUV-University of Lausanne	Lausanne	Switzerland	marie.pertin@unil.ch
Petit	Christine	Collège de France, Institut Pasteur	Paris	France	cpetit@pasteur.fr
Poirier	Yves	University of Lausanne	Lausanne	Switzerland	yves.poirier@unil.ch
Preitner	Maria	CIG - University of Lausanne	Lausanne	Switzerland	Maria.Preitner@unil.ch
Preuten	Tobias	CIG - University of Lausanne	Lausanne	Switzerland	tobias.preuten@unil.ch
Quadroni	Manfredo	CIG - University of Lausanne	Lausanne	Switzerland	manfredo.quadroni@unil.ch
Ragni	Laura	University of Lausanne	Lausanne	Switzerland	laura.ragni@unil.ch
Ramdya	Pavan	CIG - University of Lausanne	Lausanne	Switzerland	ramdya@gmail.com
Rando	Gianpaolo	CIG - University of Lausanne	Lausanne	Switzerland	gianpaolo.rando@unil.ch
Raymond	Frédéric	Nestlé Research Center	Lausanne	Switzerland	frederic.raymond@rdls.nestle.com
Reina Copete	Jaime Humberto	CIG - University of Lausanne	Lausanne	Switzerland	jaime.reina@unil.ch
Renaud	Marianne	CIG - University of Lausanne	Lausanne	Switzerland	marianne.renaud@unil.ch
Reppert	Steven	University of Massachusetts	Worcester	United States	Steven.Reppert@umassmed.edu
Reymond	Alexandre	CIG - University of Lausanne	Lausanne	Switzerland	alexandre.reymond@unil.ch
Reymond	Philippe	University of Lausanne	Lausanne	Switzerland	Philippe.Reymond@unil.ch
Richter	Hannes	CIG - University of Lausanne	Lausanne	Switzerland	hannes.richter@unil.ch
Ripperger	Juergen	University of Fribourg	Fribourg	Switzerland	juergenalexandereduard.ripperger@unifr.ch
Rodriguez	Ivan	University of Geneva	Geneva	Switzerland	Ivan.Rodriguez@unige.ch
Rossier	Bernard	University of Lausanne	Lausanne	Switzerland	Bernard.Rossier@unil.ch
Rubino	Ivana	CHUV-University of Lausanne	Lausanne	Switzerland	reverendivi@hotmail.com
Saina	Michael	CIG - University of Lausanne	Lausanne	Switzerland	michael.saina@unil.ch
Sambeat	Audrey	CIG - University of Lausanne	Lausanne	Switzerland	Audrey.Sambeat@unil.ch
Sanno	Hitomi	CIG - University of Lausanne	Lausanne	Switzerland	hitomi.sanno@unil.ch
Schmutz	Isabelle	University of Fribourg	Fribourg	Switzerland	isabelle.schmutz@unifr.ch
Schnell	Anna	University of Fribourg	Fribourg	Switzerland	anna.schnell@unifr.ch
Schweizer	Fabian	University of Lausanne	Lausanne	Switzerland	fabian.schweizer@unil.ch
Silbering	Ana Florencia	CIG - University of Lausanne	Lausanne	Switzerland	ana.silbering@unil.ch
Sivasubramaniam	Anantha Krishna	CIG - University of Lausanne	Lausanne	Switzerland	ananthakrishna.sivasubramaniam@unil.ch
Stadler	Frédéric	University of Fribourg	Fribourg	Switzerland	frederic.stadler@unifr.ch
Stasiak	Alicja	CIG - University of Lausanne	Lausanne	Switzerland	Alicja.Stasiak@unil.ch
Stasiak	Andrzej	CIG - University of Lausanne	Lausanne	Switzerland	Andrzej.Stasiak@unil.ch
Staub	Olivier	University of Lausanne	Lausanne	Switzerland	olivier.staub@unil.ch

Suarez	Philippe	University of Lausanne	Lausanne	Switzerland	philippe.suarez@unil.ch
Sung	Tzu-Ling	CIG - University of Lausanne	Lausanne	Switzerland	tzu-ling.sung@unil.ch
Thomas	Jérôme	CIG - University of Lausanne	Lausanne	Switzerland	jerome.thomas@unil.ch
Thore	Stéphane	University of Geneva	Geneva	Switzerland	stephane.thore@unige.ch
Thorens	Bernard	CIG - University of Lausanne	Lausanne	Switzerland	bernard.thorens@unil.ch
Thottathil Oommen	Sajit	CIG - University of Lausanne	Lausanne	Switzerland	sajit.thottathiloommen@unil.ch
Vanoaica	Liviu	CIG - University of Lausanne	Lausanne	Switzerland	Liviu.Vanoaica@unil.ch
Vassalli	Anne	CIG - University of Lausanne	Lausanne	Switzerland	anne.vassalli@unil.ch
Vosshall	Leslie	Rockefeller University	New York	United States	leslie@mail.rockefeller.edu
Vuillet	Laurie	CIG - University of Lausanne	Lausanne	Switzerland	laurie.vuillet@unil.ch
Wahli	Walter	CIG - University of Lausanne	Lausanne	Switzerland	Walter.Wahli@unil.ch
Wawrzyniak	Marta	CIG - University of Lausanne	Lausanne	Switzerland	marta.wawrzyniak@unil.ch
Weber	Johann	CIG - University of Lausanne	Lausanne	Switzerland	Johann.Weber@unil.ch
Witwicki	Robert	CIG - University of Lausanne	Lausanne	Switzerland	RobertMateusz.Witwicki@unil.ch
Wurm	Yannick	University of Lausanne	Lausanne	Switzerland	yannick.wurm@unil.ch
Yessoufou	Akadiri	CIG - University of Lausanne	Lausanne	Switzerland	Akadiri.Yessoufou@unil.ch
Zenker	Jennifer	University of Lausanne	Lausanne	Switzerland	Jennifer.Zenker@unil.ch

Posters authors

Last name	First name	Poster Nr
Albrecht	Urs	23
Alix	Karine	18
Arnaud	Estelle	28
Ban	N.	26
Barg	Sebastian	27
Bell	Rati	1
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Rando	Gianpaolo	20
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Rutter	Guy A.	27
Rytz	Raphaël	24
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Sanno	Hitomi	22
Schepens	Isabelle	6
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Silbering	Ana Florencia	24
Stadler	Frédéric	21
Stasiak	Andrzej	7
Steinle	Lea	11
Stratmannn	M.	21
Suarez	Philippe	25
Tamanini	F.	21
Tarussio	David	17
Thore	Stéphane	26
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Trevisan	Martine	13, 16
Vanderhorst	G.	21
Wahli	Walter	20, 27
Yessoufou	Akadiri	27
Zaugg	Judith	12
Zenker	Jennifer	28
Zoete	Vincent	20