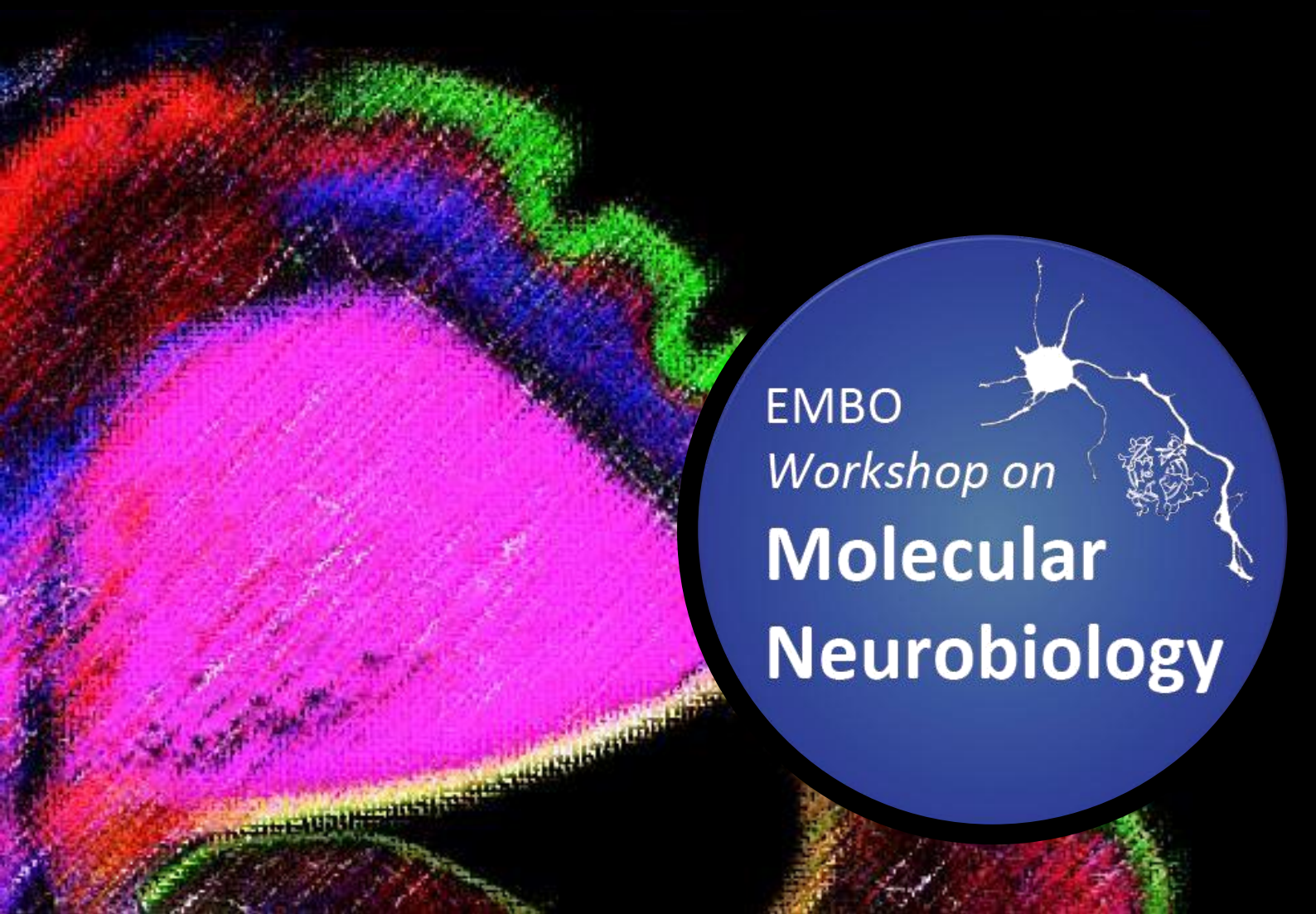
Abstracts of papers presented at the

EMBO Workshop on Molecular Neurobiology

8 – 12 May 2018
Fodele, Crete, Greece



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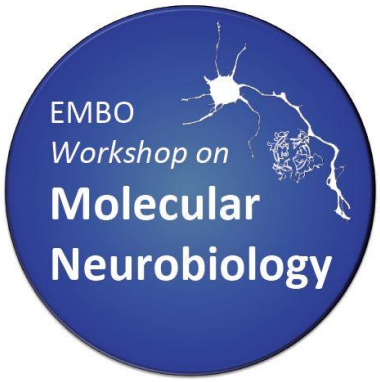

Organizers:

- **Elena Seiradake**
  University of Oxford, UK
- **Rob Meijers**
  EMBL, Germany
- **Rüdiger Klein**
  Max Planck Institute of Neurobiology, Germany
- **Nektarios Tavernarakis**
  IMBB-FORTH & University of Crete, Greece
- **Danieo Choquet**
  Interdisciplinary Institute for Neuroscience, France

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EMBO Workshop "Molecular Neurobiology"

8-12 May 2018 | Crete, Greece

Programme

Tuesday, 8 May 2018	
13:00	**Registration opens**
Molecular Models, Filaments and Environments *Chairs: Elena Seiradake & Rob Meijer*	
14:30-16:30	**Gael McGILL** [Harvard University and Digizyme Inc., Brookline, USA] *New Tools and Techniques for Visualizing Neuronal Molecular Landscapes (Presentations and Practical]*
16:30-17.00	***Coffee break***
17:00-19.00	**Gael McGILL** [Harvard University and Digizyme Inc., Brookline, USA] *New Tools and Techniques for Visualizing Neuronal Molecular Landscapes (Presentations and Practical]*
19:30	***Dinner***
21:00	***Drinks at the bar – Cretan / Greek night – Music and Dancing!***
Wednesday, 9 May 2018	
Session 1: Adhesion and Polarity *Chair: Elena Seiradake*	
09:00-10:00	Lecture 1: **Yvonne JONES** [Oxford University, Division of Structural Biology, Oxford, UK] *The Mechanics of Semaphorin-plexin Cell Guidance Signalling*
10:00-10:30	**Christian SIEBOLD** [Oxford University, Division of Structural Biology, Oxford, UK] *Molecular Mechanisms of the Repulsive Molecules (RGMs)*
10:30-11:00	**Rachelle GAUDET** [Harvard University, MCB, Cambridge, USA] *Clustered Protocadherins as a Case Study in Evolution of Interaction Specificity*
11:00-11:30	***Coffee break***
11:30-12:30	***Hang up Posters & Free Time***
12:30-14:00	***Lunch***
Chair: Rüdiger Klein	
14:00-14:30	**Larry SHAPIRO** [Columbia University, New York, USA] *Visualization of the Clustered Protocadherin Self-recognition Complex*
14:30-15:00	**Yimin ZOU** [UC San Diego, Division of Biological Sciences, La Jolla, USA] *Signaling Mechanisms for Glutamatergic Synapse Formation*
15:00-15:15	**Tuhin BHOWMICK** [European Molecular Biology Laboratory, Hamburg, Germany] *Draxin Recruits Netrin1 to DCC to Mediate Adhesion and Axon Guidance*
15:15-15:30	**Verity JACKSON** [MRC-LMB, Cambridge, UK] *Teneurin Structure: An Ancient Fold for Cell-cell Interaction*
15:30-15:45	**Neil McDONALD** [The Francis Crick Institute, Signalling and Structural Biology, London, UK] *Exploring GDNF-dependent Mechanisms of Neurotrophic Support and Cell Adhesion by Structural Biology*
15:45-16:15	***Coffee break***
16:15-16:30	**Thanos METAXAKIS** [IMBB-FORTH, Heraklion, Greece]

	Neuronal TOR Coordinates Mood and Cognition
16:30-16:45	**Robert HINDGES** [King's College London, Centre for Developmental Neurobiology, London, UK] *Dendritic Structure of Teneurin 3 Positive Amacrine Cells is Critical to Generate Orientation Selectivity in the Vertebrate Retina*
16:45-17:15	**Valerie CASTELLANI** [Institute Neuromyogene, UCBL-CNRS UMR5310-INSERM U1217, Lyon, France] *Sequential Functionalization of Midline Repellents by Spatio-temporal Control of Receptor Dynamics during Commissural Axon Navigation*
17:15-18:30	***Scientific Speed Dating***
18:30-20:00	***POSTER SESSION – RED SESSION - ODD NUMBERS***
20:00	***Dinner***

Thursday, 10 May 2018

Session 2: Migration and Pathfinding

Chair: Rob Meijer

09:00-09:30	**Ruediger KLEIN** [Max Planck Institute Neurobiology, Department of Molecules-Signaling-Development, Martinsried, Germany] *Cell Wrestling and Cortex Wrinkling - Guidance Mechanisms during Neural Development*
09:30-10:00	**Georgios SKINIOTIS** [Stanford University, Department of Molecular and Cellular Physiology, Stanford, USA] *Single-particle CryoEM of G Protein-coupled Receptors*
10:00-10:30	**Junichi TAKAGI** [Osaka University, Department of Biological Sciences, Osaka, Japan] *Plexin Crosslinking by Divalent Artificial Binders differentially Controls its Signaling State*
10:30-11:00	**Bianxiao CUI** [Stanford University, Department of Chemistry, Stanford, USA] *Optical Imaging and Optogenetic Manipulation of Axonal Transport in Neurons*
11:00-11:30	***Coffee break***
11:30-12:00	**Jianping WU** [Princeton University, New Jersey, USA] *Cryo-EM Studies on Excitation-contraction Coupling*
12:00-12:30	**Dietmar SCHMUCKER** [VIB-KU Leuven Center for Brain and Disease Research, Leuven, Belgium] *Molecular Mechanisms of Neurite Branching and Central Synapse Formation*
12:30-14:00	***Lunch***

Chair: Jay Groves

14:00-14:30	**Chenghua GU** [Harvard University, Department of Neurobiology, Boston, USA] *Transcytosis Regulation at the Blood-brain Barrier*
14:30-15:00	**Frank BRADKE** [DZNE, Axon Growth and Regeneration, Bonn, Germany] *ADF/Cofilin-Mediated Actin Turnover Promotes Axon Regeneration in the Adult CNS*
15:00-15:30	**Beatriz RICO** [King's College London, MRC Centre – Developmental Neurobiology, London, UK] *Diverse Molecular Programs Orchestrating the Wiring of Inhibitory Circuitries*
15:30-16:00	***Coffee break***
16:00-16:15	**Katrin GERSTMANN** [Institut NeuroMyoGène, University Lyon 1, Lyon, France] *The Dynamics of Apical Anchoring of Cortical Stem Cells is Balanced by a Dual CSFderived Semaphorin/ Neuropilinsignalling*
16:15-16:30	**Anna ZIEGLER** [German Center for Neurodegenerative Disease (DZNE e.V., Bonn, Germany] *Role of Cell-autonomous Fatty Acid Synthesis for Neuronal Development and Function*
16:30-16:45	**Shiri YANIV** [Weizmann Institute of Science, Molecular Cell Biology, Rehovot, Israel] *Actin Dynamics is Important during Developmental Axon Regrowth*

16:45-17:00	**Yarden OPATOWSKY** [Bar-Ilan University, Ramat Gan, Israel] *SRGAP Truncations Confer Human Brain Advantages and Vulnerabilities*
17:00-17:15	**Bert JANSSEN** [Utrecht University, Bijvoet Center for Biomolecular Research, Utrecht, Netherlands] *Conformational and Oligomeric Rearrangements Control Intercellular Signaling*
17:15-17:45	**Naoko MIZUNO** [Max Planck Institute of Biochemistry, Martinsried, Germany] *Neuronal Cell Shape Formation Controlled by Cytoskeleton*
17:45-18:30	***Free Time***
18:30-20:00	***POSTER SESSION – GREEN SESSION - EVEN NUMBERS***
20:00	🍽 ***Dinner***
Friday, 11 May 2018	
Session 3: Synapses and Signal Transmission I *Chair: Nektarios Tavernarakis*	
09:00-10:00	Lecture 2: **Jay GROVES** [UC Berkeley, Department of Chemistry, Berkeley, USA] *Membrane-mediated RTK Signaling Crosstalk*
10:00-10:30	**Pierre PAOLETTI** [École Normale Supérieure, Department of Biology, Chemistry, Pharmacy, Paris, France] *Illuminating Glutamate Receptor Structure and Function*
10:30-11:00	**Poul NISSEN** [Aarhus University, Department of Molecular Biology and Genetics, Aarhus, Denmark] *Membrane Transporters of the Brain*
11:00-11:30	☕ ***Coffee break***
11:30-12:00	**Bernd FAKLER** [Freiburg University, Institute of Physiology, Freiburg, Germany] *Cell Physiolgy of AMPA-receptors Determined by their Proteome*
12:00-12:15	**Jonathan ELEGHEERT** [University of Oxford, Division of Structural Biology, Oxford, UK] *Synaptic Organizer Proteins: From Structures to Applications in Neuronal Disease*
12:15-12:30	**Vassiliki NIKOLETOPOULOU** [IMBB-FORTH, Heraklion, Greece] *Regulation of Synaptic Plasticity by Autophagic Degradation*
12:30-14:00	🍽 ***Lunch***
Chair: Dietmar Schmucker	
14:00-14:30	**Marina MIKHAYLOVA** [Hamburg University, ZMNH, Hamburg, Germany] *Dendritic actin Cytoskeleton: Structure, Functions and Regulations*
14:30-15:00	**Stephan SIGRIST** [Freie University Berlin, Department of Biology, Chemistry, Pharmacy, Berlin, Germany] *Active Zone Scaffold Proteins Tune Functional Diversity across Brain Synapses*
15:00-15:30	**Scott BLANCHARD** [Cornell University, Department of Physiology and Biophysics, New York, USA] *Single-molecule Analysis of Ligand Efficacy in β_2AR Receptor-G Protein Activation*
15:30-15:45	**Nicole SCHOLZ** [Rudolf Schönheimer Institute of Biochemistry, Faculty of Medicine, University of Leipzig, Leipzig, Germany] *Metabotropic Force Sensing through adhesion GPCRs*
15:45-16:00	**Jone PAESMANS** [Vrije Universiteit Brussel, Structural Biology, Brussels, Belgium] *Revealing the Function of TBC1D24 Mutations in Epilepsy and Related Neurological Diseases*
16:00-16:30	☕ ***Coffee break***
16:30-18:30	**All Participants** - ***Discussion on the future of Molecular Neurobiology***
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19:30	🍽 ***Dinner***

Saturday, 12 May 2018	
Session 4: Synapses and Signal Transmission II *Chair: Yimin Zou*	
09:00-09:30	**Valentin NÄGERL** [Bordeaux University, Interdisciplinary Institute for Neuroscience, Bordeaux, France] *Super-resolution Imaging of Brain Extracellular Space*
09:30-10:00	**Radu ARICESCU** [MRC-LMB, Cambridge, UK] *Structural Insights into GABAA Receptor Gating Mechanisms*
10:00-10:15	**Isabelle BRUNET** [CIRB, College de France, INSERM, Paris, France] *EphrinA4/EphA4 Signaling in Arterial Innervation Development and Physiology: Arteries under Pressure?*
10:15-10:30	**Jaewon KO** [Daegu Gyeongbuk Institute of Science and Technology, Daegu, South Korea] *PTPσ Drives Excitatory Presynaptic Assembly via Various Extracellular and Intracellular Mechanisms*
10:30-10:45	**Pedro GUEDES-DIAS** [University of Pennsylvania, Philadelphia, USA] *Local Microtubule Ccues Specify Presynaptic Cargo Delivery at en passant Synapses*
10:45-11:00	**Wenting GUO** [Laboratory of Neurobiology, VIB, Center for Brain and Disease Research, KU Leuven-Stem Cell Institute, Leuven, Belgium] *HDAC6 Inhibition Reverses Axonal Transport defects in Motor Neurons Derived from FUS-ALS Patients*
11:00-11:30	***Poster Prizes and Coffee Break – End of Workshop***
12:30	🍽 ***Lunch***

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ABSTRACTS

New Tools and Techniques for Visualizing Neuronal Molecular Landscapes

Gaël McGill

Harvard University and Digizyme Inc., Brookline, USA

In this 1/2 day tutorial, participants will learn about the tools and techniques used to create dynamic molecular visualizations. We will begin with an overview of the 3D pipeline and gain an appreciation for the tools and resources available for this kind of work. In particular, we will review the Molecular Maya toolset and several of its specialized kits to rapidly and intuitively model complex molecular models, environments and animations. Participants will become familiar with these tools by crafting several examples of neuro-related molecular models and animations and become acquainted with the resources of Clarafi.com

Learning objectives:

- to become familiar with the capabilities of Molecular Maya (mMaya) and its kits and consider how these may be relevant to visualization in molecular neurobiology
- to be introduced to the range of training, tools and resources available on the new scientific visualization portal Clarafi.com

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The Mechanics of Semaphorin-plexin Cell Guidance Signalling

E. Yvonne Jones

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Cell guidance cues are secreted or cell surface attached proteins that interact with receptors to trigger direct, sub-cellular changes to the cytoskeleton resulting in cell attraction or repulsion. Although cell guidance cues were first characterized by their role in the development of the nervous system they are ubiquitous, functioning both during embryogenesis and in adult tissue homoeostasis. There are four classic cell guidance cue families: the netrins, slits, ephrins and semaphorins [1]. The semaphorins are usually thought of as repulsive guidance cues, however, their effects can be attractive or repulsive. Examples of semaphorin-plexin neuronal functions include axon and dendrite guidance, neuronal migration, target recognition and synaptogenesis. Non-neuronal roles range from vascular patterning through to organogenesis and immune cell function. The first structural studies on semaphorins (from my lab and others) were published in 2003 [2]. I will discuss our current knowledge of the molecular structures and mechanisms underlying semaphorin-plexin signalling system function [3-6].

1. Seiradake et al (2016) Annu. Rev. Cell Dev. Biol. 32, 577-608
2. Love *et al.* (2003) Nature Struct. Biol. 10, 843-848
3. Janssen *et al*. (2010) Nature 467, 1118-1122
4. Bell *et al.* (2011) PLoS Biol. 9, e1001134
5. Janssen *et al.* (2012) Nature Struct. Mol. Biol.19, 1293-1299
6. Kong *et al.* (2016) Neuron 91, 548-560

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Molecular Mechanisms of the Repulsive Molecules (RGMs)

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Repulsive guidance molecules (RGMs) control fundamental processes ranging from cell motility and adhesion to immune cell regulation and systemic iron metabolism. RGMs can directly bind their receptor Neogenin (NEO1), a member of the immunoglobulin superfamily, and this interaction has been implicated in modulating the bone morphogenetic protein (BMP) pathway. We have recently described crystal structures of binary and ternary complexes of RGM with NEO1 and the BMP morphogen BMP2. The RGM structure reveals a novel protein fold, a functionally important auto-catalytic, internal cleavage site and provides a structural framework to explain RGM disease mutations. In the NEO1-RGM complex two RGMB ectodomains, acting as molecular staples, bringing together the juxtamembrane regions of two NEO1 receptors, in a pH-dependent manner. Moreover, our analyses revealed a conserved mode of the BMP-RGM interaction and suggest a mechanism for signal activation based on BMP-mediated clustering of NEO1 that is bridged by RGM.

Moreover, NEO1 also functions as the receptor for another fundamental signalling pathway - the Netrin guidance molecules. NEO1 can act as an attractive guidance receptor in response to Netrin, but in contrast works as a repellent receptor when bound to RGM. Netrins have been implicated as crucial inhibitor of RGM signalling function, however how this inhibition is mediated on a molecular basis is unknown. In this talk, I will also present some of our latest data on the structural and functional characterisation of a ternary RGM-Netrin-NEO1 complex and its implication for NEO1 signalling.

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Clustered Protocadherins as a Case Study in Evolution of Interaction Specificity

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Brain development is orchestrated through synaptic interaction of neighboring neuronal cells. Remarkably, neuronal dendrites distinguish 'self' from 'other,' and avoid forming synapses with dendrites originating from the same cell. This self-avoidance is a key feature in the patterning of neuronal networks and requires neurons to have a unique identity that is provided by the more than 53 isoforms of the clustered protocadherin gene locus. Clustered protocadherins are surface-expressed Ca^{2+}-dependent cadherin superfamily adhesion proteins. Each neuron expresses a collection of these isoforms and homophilic interactions of clustered protocadherins between cells in *trans* dictate self/non-self discrimination.

We used X-ray crystallography to determine that the *trans* interaction is formed by an antiparallel dimer of the first four (of six) extracellular cadherin (EC) repeats. This dimer is conserved throughout the clustered protocadherins and also in non-clustered protocadherins that are important for the development and maintenance of the nervous system.

The function of clustered protocadherins requires exquisitely specific homophilic interactions. We used bioinformatics, in collaboration with the laboratory of Debora Marks (Harvard Medical School), to determine how specificity between isoforms arose. Isoform-specific conservation and sequence coevolution in combination with structural comparisons indicate that structural differences between isoforms and chemical properties contribute to this specificity between subfamilies and within subfamilies, respectively. Our bioinformatics work, including a coevolution-based statistical interaction energy model, also identified the EC2/EC3 interaction as the primary source of specificity.

In aggregate, our results explain how these proteins encode specificity to ensure self-avoidance. These results provide a framework to explore the role of clustered protocadherins in brain development and to understand why clustered protocadherin mutations are implicated in complex brain disorders such as autism, bipolar disorder and schizophrenia. Furthermore, we have shown that the clustered protocadherin proteins are a valuable system to study the specificity of protein-protein interactions and to develop statistical models for evaluating the role of individual mutations on interaction specificity.

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Visualization of the Clustered Protocadherin Self-recognition Complex

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Neuronal self-avoidance and non-self discrimination are fundamental attributes of all nervous systems, facilitating dendritic arborization and preventing the formation of autapses, while permitting interactions among thousands of neurons. Stochastic cell-surface expression of the ~60 α-, β-, and γ-clustered protocadherin (Pcdh) isoforms provides mammalian neurons with single-cell identities that form the basis of neuronal self-recognition and underpins neuronal self-avoidance. Pcdhs form isoform-specific homophilic *trans* dimers between apposed neuronal membranes, and simultaneously engage in isoform-promiscuous *cis*-dimerization on the same membrane surface. We have used a combination of X-ray crystallography, single-particle cryo-electron microscopy (EM), and fiducial-less cryo-electron tomography (ET) of full length Pcdh ectodomains to determine the molecular arrangement of the Pcdh self-recognition complex. Despite forming discrete tetramers in solution, the crystal structure of Pcdh γB4 reveals an extended zipper-like lattice in the high protein concentration environment of the crystal. Furthermore, when Pcdh ectodomains are tethered to liposome surfaces to mimic a native membrane environment, they spontaneously assemble at membrane contact sites into highly ordered linear zipper-like assemblies of alternating *cis* and *trans* interactions, which we visualized by cryo-ET. The lattice observed in reconstructed tomograms is strikingly consistent with that observed in the crystal structure and mutations targeted to the crystallographically observed interfaces ablate ordered assembly. Our data suggest that formation of linear assemblies by Pcdhs represents the initial step in neuronal self-recognition.

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Signaling mechanisms for glutamatergic synapse formation

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Neuronal synapses are asymmetric structures with hundreds of different types of proteins organized across a 20 nm synaptic cleft between the presynaptic and postsynaptic membranes. The signaling mechanisms that assemble and maintain these polarized cell-cell junctions are not well understood. We showed that components of the planar cell polarity pathway, which forms asymmetric intercellular complexes in cell and tissue polarization, are essential for glutamatergic synapse formation. We now found that components of apical-basal polarity pathway also regulate synapse formation and are testing how these signaling pathways regulate synapse formation and function.

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Draxin Recruits Netrin1 to DCC to Mediate Adhesion and Axon Guidance

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Netrin-1 is an evolutionarily conserved prototypical axon guidance cue at the central nervous system midline and known to trigger chemo-attraction by binding to its canonical receptor Deleted in Colorectal Cancer (DCC). A recently discovered guidance cue Draxin was shown to bind DCC and cause chemo-repulsion required for the development of spinal cord and forebrain commissures (Islam et al. Science. 323, 2009). However, Gao et al. (Cell Reports. 12, 2015) showed that Draxin can modulate Netrin-1 signaling. Here, we present the structural snapshots of Draxin/DCC and Draxin/Netrin-1 complexes using X-ray crystallography. The structures reveal a triangle of interaction involving Netrin-1, Draxin and DCC through a modular binding mechanism utilizing multiple binding sites. Netrin-1 and DCC bind to adjacent sites on Draxin, which appears to capture Netrin-1 and tether it to the DCC receptor. The observation fits well with the recent studies by Dominici C et al. (Nature. 545, 2017) and Varadarajan et al. (Neuron. 94, 2017), which suggest that rather than a freely diffusing gradient, it's the accumulated Netrin-1 on the pial surface that directs axon growth along the adhesive surface. Together, these findings point towards a molecular mechanism involving DCC, which links responses from different cues to promote fasciculation and regulate axon guidance through concerted Netrin-1/Draxin binding.

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Teneurin Structure: An Ancient Fold for Cell-cell Interaction

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Teneurins are ancient cell-cell adhesion receptors, thought to have been important for the evolution of multicellularity in animals. These early cell adhesion receptors are now vital for brain development and synapse organisation. Teneurins originated during early metazoan evolution through a horizontal gene transfer event when a bacterial YD-repeat toxin fused to the epidermal growth factor-like repeats of a eukaryotic receptor. How a protein of bacterial origin has adapted to form a functional brain receptor is unknown.

Here we present an unpublished crystal structure of a large fragment of the Teneurin2 ectodomain, revealing a novel ~200 kDa extracellular super-fold in which eight sub-domains form an intricate structure centred on a spiralling YD-repeat shell. An alternatively spliced loop, which is implicated in homophilic Teneurin interaction and specificity, is exposed and poised for interaction. The N-terminal side of the YD-shell is "plugged" via a novel fibronectin-plug domain, which defines a new class of YD proteins. Structure-guided bioinformatics searches show that this class of YD proteins is also present in a wide variety of bacterial species.

These results provide structural insight into early metazoan receptor evolution from bacterial origins, reveal a novel YD-repeat protein architecture, and suggest a molecular mechanism for Teneurin-mediated trans-synaptic adhesion.

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Exploring GDNF-dependent Mechanisms of Neurotrophic Support and Cell Adhesion by Structural Biology

Neil McDonald, Sarah Adams, Andrew Purkiss, Svend Kjaer

The Francis Crick Institute

REarranged during Transfection (RET) is a receptor tyrosine kinase activated by glial cell line-derived neurotrophic factor (GDNF) family ligands when presented by membrane anchored or transmembrane GFR-alpha co-receptors (Ibáñez CF, Andressoo JO. 2017). GDNF triggers neurotrophic support through RET activation, a process crucial for neuronal and kidney development (Mulligan LM. 2014) . We have explored the architecture, maturation and ligand recognition properties of RET (Goodman, 2014). Our current progress in understanding GDNF-GFRa1-dependent RET activation will be presented. GDNF also exhibits RET-independent functions such as promoting synapse formation through ligand-induced cell adhesion (Ledda et al. 2007). We have explored this second function of GDNF in vitro to investigate how an adhesive complex may form contribute to synaptogenesis. Our data suggest how two orthogonal complexes involving GDNF can contribute either to a trophic support when components present on the same membrane or an adhesive function when presented in trans between two membranes.

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Neuronal TOR Coordinates Modd and Cognition

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Autophagy is essential for healthspan and lifespan extension in animal models. Moreover, it has been extensively implicated in cognitive impairment and mood stabilization. However, the relevant mechanisms are not fully understood. Here, we investigated the cellular and molecular mechanisms by which autophagy affects cognition in three animal models: worms, flies and zebrafish. Acute rapamycin treatment, known to induce autophagy through TORC1 inhibition, impaired memory in all three species. In all cases, memory loss was associated with reduced phosphorylation of NMDA receptor 2 at Tyr1472, a site which is involved in receptor endocytosis, in vertebrates. Combined biochemical and behavioral analyses revealed that upregulation of an evolutionary conserved serotonin receptor upon rapamycin treatment, is necessary for rapamycin induced memory loss in all three animal models. Loss of the serotonin receptor increases Tyr1472 phosphorylation of NMDA in fly brains, and abrogates enhanced longevity of rapamycin treated flies and worms. In addition, a single-fly training scheme revealed a tight link between cognitive impairment and mood improvement upon rapamycin treatment, which is coordinated by the serotonin receptor. Our preliminary results indicate that neuronal autophagy coordinates mood and cognition through an evolutionary conserved interplay between serotoninergic and glutamatergic signaling pathways.

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Dendritic Structure of Teneurin 3 Positive Amacrine Cells is Critical to Generate Orientation Selectivity in the Vertebrate Retina

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In the vertebrate retina, visual information is pre-processed before being sent to higher visual centres through parallel feature-specific neuronal pathways. They are generated through distinct connectivity between retinal cell subtypes. How the underlying circuitry is established, however, is poorly understood. Here we show a role for the cell adhesion molecules teneurins, which are expressed in subsets of retinal cells. We find that all four teneurins are localised synaptically, consistent with a possible role in controlling synaptic partner matching. Using zebrafish BAC transgenesis, we genetically identify a class of GABAergic amacrine cells (ACs) with elongated dendritic arbours expressing Teneurin-3 (Tenm3). Using in vivo two-photon calcium imaging reveals that these cells show orientation-selective responses to drifting gratings. These Tenm3+ ACs respond maximally when the orientation of elongated visual stimuli coincides with their dendritic field orientation. Selective optogenetic ablation of Tenm3+ ACs and pharmacological interference show that these cells generate orientation selectivity in retinal ganglion cells (RGCs) through GABAergic inhibition. Structural analyses suggest that Tenm3+ ACs connect to orientation-selective RGCs and that they require Tenm3 for their dendritic morphology. Our results outline how molecularly defined retinal cell types form a circuit to detect elongated visual stimuli and provide orientation-specific information to the brain.

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Sequential Functionalization of Midline Repellents by Spatio-temporal Control of Receptor Dynamics during Commissural Axon Navigation

Aurora Pignata[1], Hugo Ducuing[1], Leila Boubakar[1], Karine Kindbeiter[1], Muriel Bozon[1], Julien Falk[1], Olivier Thoumine[2], Valérie Castellani[1,*]

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Several repulsive signals orchestrate midline crossing during commissural axon guidance. Whether they act concomitantly or sequentially and how they are timed with axon progression remain highly challenging questions. We designed a set-up for live imaging and super resolution analysis of repulsive guidance receptors in commissural axons navigating in their native environment. Four key receptors mediating Slit and Semaphorin repulsion, Robo1, Robo2, PlexinA1 and Neuropilin2, were monitored from the pre-crossing to the post-crossing stages of commissural axon navigation. Our study revealed remarkably unique profiles of receptor membrane sorting in commissural growth cones. This supports that spatio-temporal control of cell-surface delivery of guidance receptors is a key mechanism for patterning midline repulsive activities.

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Cell Wrestling and Cortex Wrinkling - Guidance Mechanisms during Neural Development

Ruediger Klein

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Eph receptors and their membrane-tethered ephrin ligands control repulsive and attractive responses between opposing cells, thus influencing tissue morphogenesis. Cell repulsion is promoted by bi-directional trans-endocytosis of Eph/ephrin complexes at cell interfaces. I will describe our progress in identifying the underlying intracellular signaling pathways for Eph/ephrin trans-endocytosis that removes the physical tether between cells. Interestingly, we find that the signaling mechanisms resemble those that regulate phagocytic processes. EphB2/ephrinB trans-endocytosis requires the Rac-specific guanine nucleotide exchange factor Tiam2, activating Rac subfamily GTPases leading to actin cytoskeleton rearrangement and ligand–receptor internalization. EphB2/ephrinB engagement also recruits the phagocytosis adaptor protein Gulp1, which cooperates with Tiam2 for binding to EphB2/ephrinB1 complexes, and leads to recruitment of dynamin, an essential component of vesicle formation in receptor-mediated endocytosis. These findings reveal mechanistic similarities between phagocytosis and trans-endocytic processes that promote contact repulsion.

Folding of the cerebral cortex into valleys (sulci) and ridges (gyri) represents a fascinating evolutionary mechanism that impacts on neuronal networking and cognitive capacities of large mammals. While recent studies suggest that gyri develop in areas with an amplification of basal progenitors, the developmental mechanisms controlling sulci formation remain largely unknown. Previously, we have established that genetic ablation in mice of FLRT3, a member of the FLRT family of cell adhesion molecules leads to an altered distribution of pyramidal neurons during cortical development, forming a repeated pattern of clusters along the tangential axis. Here, I report that FLRT1-/-;FLRT3lx/null;Nestin-cre double mutant mice show enhanced pyramidal neuron clustering and develop macroscopic cortical folds during embryogenesis. This process appears to happen independently of cell proliferation. Analyses and simulations suggest that sulcus formation in the absence of FLRT1/3 results from reduced intercellular adhesion, increased neuron migration, and clustering in the cortical plate. Notably, FLRT1/3 expression is low in the human cortex and in future sulcus areas of ferrets, suggesting that intercellular adhesion is a key regulator of cortical folding across species. Current efforts in the lab aim at elucidating the relative contributions of progenitor amplification and cell migration to cortex folding.

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Single-particle CryoEM of G Protein-coupled Receptors

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Recent technological breakthroughs have enabled single-particle electron cryo-microscopy (cryoEM) to achieve atomic resolution structures of macromolecular complexes. The methodology is now displaying its hidden potential, and has already become a principal choice of method for characterizing the structure of large and dynamic macromolecular assemblies. GPCR complexes have been challenging targets for cryo-EM analysis, both because of the relatively instability of such assemblies but also due to their relatively small size, which limits accurate alignments for high-resolution 3D reconstructions. Nevertheless, near atomic resolution cryoEM maps are now within reach, opening up unprecedented opportunities for structure determination in the GPCR field. Here I will describe our efforts in cryo-EM visualization of GPCR complexes.

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Plexin Crosslinking by Divalent Artificial Binders differentially Controls its Signaling State

Junichi Takagi

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Axon guidance molecule semaphorins are homodimeric ligands for cell surface receptor plexins and their signaling mechanism is thought to involve receptor dimerization and subsequent modulation of the cytoplasmic GAP activity. Structural analyses of plexin ectodomain in complex with semaphorin ligand have advanced our understanding about the structural mechanism of plexin activation, but clear and definitive picture of active and signal-producing plexin dimer is yet to emerge, precluding the design of specific plexin modulators. We have previously reported that agonistic and antagonistic anti-plexin A1 antibodies can differentially crosslink the receptor in a face-to-face and back-to-back manner, respectively [1]. This suggested a possibility that one can design artificial divalent molecules to control the plexin function. By using a macrocyclic peptides that bind specifically to plexinB1 ectodomain [2], we synthesized various dimeric versions of peptides and tested their effect on the semaphorin 4D-induced cellular collapse. As a result, we successfully obtained strong plexin B1 antagonist that shows signal inhibition at nanomolar concentrations. Furthermore, dimerization of a non-functional plexin B1-binding peptide converted it to an artificial agonist. Structural analysis of peptide-plexin complex suggested that, as in the case of anti-plexin A1 antibodies, the functional outcome of the divalent agents correlated with the two contrasting dimer assemblies.

[1] Suzuki et al. PLoS One, 11, e0156719 (2016)
[2] Matsunaga et al. Cell Chem. Biol., 23, 1341 (2016)

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Optical Imaging and Optogenetic Manipulation of Axonal Transport in Neurons

Bianxiao Cui

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Long-distance transport of vesicular cargoes are essential for the function and survival of neurons. Defects in this transport process are linked to a range of neurodegenerative disease such as Alzheimer's disease and Huntingtin's disease. Physically stalling the cargoes would be one of the most direct means to perturb a cargo transport process, which, however, are technically challenging in live cells. We engineered optogenetic and magnetic forces that specifically stall a population of axonal cargoes that contain magnetic or optical nanoparticle probes at the trapping area. Using a combination of force manipulation and high resolution microscopy methods, we show that mechanical tugs-of-war and intracellular motor regulation are complimentary features of the axonal transport process.

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Cryo-EM Studies on Excitation-contraction Coupling

Jiaping Wu

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Molecular Mechanisms of Neurite Branching and Central Synapse Formation

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We have established an experimental system for a systematic genetic analysis of neurite branching and synaptogenesis in the fly CNS (Urwyler et al. 2015). We used this system to apply reverse genetics in order to identify novel molecular regulators. We screened all Drosophila kinases and phosphatases to identify several novel signaling molecules and pathways directly linked to axonal branching and/or central synapse formation. I will discuss our findings on neuron-intrinsic molecular mechanisms enabling single axons to connect to multiple postsynaptic targets in the CNS. A previously identified key factor regulating early events of axon branching is the hypervariable receptor Dscam1. In mechanosensory neurons (ms-neurons), the loss of Dscam1 results in a complete block of axon branching, where the axons can reach the CNS and initiate branching, but those branches become aberrantly entangled and collapse. Furthermore, neurons with normal levels of Dscam1 yet an experimentally reduced repertoire of isoforms show normal axon growth, yet these axons cannot form any axon collaterals. We find evidence suggesting an important role for the kinases msn and tao1 in restricting the formation of axon collaterals. We will present genetic and biochemical results suggesting that Dscam1 via msn/tao1 can locally and likely directly control cytoskeletal regulatory molecules and simultaneously intiating a transcriptional feedback program that leads to a switch from normal axon growth to an axon branching mode. Currently we are investigating what effector pathways underlie this Dscam1-dependent switch.

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Transcytosis Regulation at the Blood-brain Barrier

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The blood-brain barrier (BBB) provides a safe and constant homeostatic brain environment that is essential for proper neural function. Low rates of vesicular transport (transcytosis) maintain BBB function by limiting transcellular trafficking across central nervous system (CNS) endothelial cells. However, it is not known how vesicle formation and transcytosis are maintained at this unusually low levels in brain endothelial cells for BBB integrity. Here, we demonstrate that CNS endothelial cells possess a program that actively inhibits a transcytotic route readily used in the periphery. We identify that Mfsd2a acts at the BBB to regulate a specific vesicular trafficking pathway, caveolae-mediated transcytosis, in CNS endothelial cells by suppressing caveolae pit formation and cargo uptake at the plasma membrane. The lipids transported by Mfsd2a establish a unique lipid environment that inhibits caveolae vesicle formation in CNS endothelial cells to suppress transcytosis and ensure BBB integrity. Indeed, an unbiased lipidomic analysis reveals significant differences in endothelial cell lipid signatures from the CNS and periphery, which underlie a suppression of caveolae vesicle formation and trafficking in brain endothelial cells. This lipid-mediated mechanism is a key mechanism to regulate transcytosis and thus BBB permeability.

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ADF/Cofilin-Mediated Actin Turnover Promotes Axon Regeneration in the Adult CNS

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Injured axons fail to regenerate in the adult central nervous system, which contrasts their vigorous growth during embryonic development. It has been postulated that similar neuron-intrinsic pathways regulate both the axon growth and regeneration states. However, the molecular effectors and the involved mechanisms underlying axon regeneration have remained unclear. Here, genetic loss- and gain-of-function experiments followed by time-lapse microscopy and in-vivo-analysis revealed that axon regeneration is fueled by elevated actin turnover. The members of the actin depolymerizing factor (ADF)/Cofilin family, which regulate neurite formation during development, coordinate actin turnover and axon regeneration after spinal cord injury through their actin severing activity. This suggests that ADF/Cofilin acts as key regulator for growth competence and, thereby, dictates the regenerative fate by recapitulating developmental processes. Thus, our work provides fundamental insights into the effectors facilitating axon regeneration after CNS trauma and identifies ADF/Cofilin as a key target for future regenerative interventions.

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Diverse Molecular Programs Orchestrating the Wiring of Inhibitory Circuitries

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Understanding brain function and dysfunction begins with the knowledge of how neuronal connections are established and organized in functional networks. The remarkable diversity and connectivity patterns of cortical interneurons, place them in a unique position to orchestrate functionally relevant circuit-specific roles and critically shape cortical function. Consistently, GABAergic dysfunction has been implicated in several neurological and psychiatric disorders. While some progress has been made towards understanding the molecular and structural components that broadly distinguish inhibitory synapses and their assembly, the molecular mechanisms underlying interneuron subtype-specific assembly are largely unknown. Here we provide the transcriptional dynamics of a sample of interneurons with a restricted targeting area into the pyramidal cells, the dendritic, somatic and axonal initial segment compartments (AIS) during synapse formation. We then coupled the gene expression longitudinal profiles with loss-of-function experiments using a systematic virus-mediated gene knockdown strategy. These experiments showed that the identified cell-specific molecular signatures support interneuron early wiring and underlie the specification of different patterns of connectivity.

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The Dynamics of Apical Anchoring of Cortical Stem Cells is balanced by a Dual CSF-derived Semaphorin/Neuropilin-signalling

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During brain development the precise regulation of apical adhesion is crucial for cortical integrity and function. Neural stem cells are tightly attached to adjacent neighbours at the ventricular surface and loss of apical adhesion is associated with precocious delamination and differentiation. However, cells that are committed to differentiate reduce their apical adhesion and disengage from the neuroepithelium. Therefore, controlling the adhesive properties of cortical stem cells is crucial for maintaining the ventricular zone architecture and for fate determination of mitotic cells. The mechanisms controlling this process remain to be elucidated. We observed that extrinsic Class3-Semaphorins and their Neuropilin-receptors are expressed by the embryonic choroid plexus and are released into the cerebrospinal fluid (CSF). The molecules form soluble complexes that bind to Plexins, which are present on the apical endfeet of cortical stem cells and the resultant signalling regulates the adhesive properties of cortical stem cells. Sema3B/Nrp2-signalling increases apical attachment and favours maintenance of cortical stem cells, whereas Sema3F/Nrp1-interactions reduce apical adhesiveness and promote delamination. Altogether our results reveal a novel role for Semaphorin/Neuropilin interactions in regulating the apical attachment and positioning of cortical stem cells to control the number of proliferating cells and postmitotic neurons.

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Role of Cell-autonomous Fatty Acid Synthesis for Neuronal Development and Function

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Around 60 % of the brain consists of lipids. Recently, the fatty acid synthesis master regulator sterol regulatory binding protein 1 (srebp1) has been identified as a new risk locus for sporadic Parkinson´s disease. However, the consequences of a SREBP1 malfunction on neuronal morphology and function are not sufficiently studied. We have used the complex, nociceptive Drosophila class four dendritic arborization (CIVda) neurons as a model to study the role of SREBP on neuronal morphology and function. Using in vivo imaging we show that neurite expansion in CIVda neurons relies on cell-autonomous fatty acid production via the transcription factor SREBP and it´s down-stream target genes such as fatty acid synthase or acetyl-CoA carboxylase. In mutant srebp CIVda neurons, dendritic structures are correctly established at early developmental stages, but fail to scale with the animal´s growth. As a consequence dendritic trees are severely simplified in late larval stages. Additionally, we observed length-dependent, progressive axon loss. The dendrite simplification in mutant CIVda neurons is accompanied by hypersensitivity to the neurons stimuli. These data are in support of a clear cell-autonomous control for lipid production in neurons and help to gain first insights into the consequences of SREBP misexpression on neurite morphology and function.

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Actin Dynamics is Important during Developmental Axon Regrowth

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What determines the growth state of a neuron during development and following injury is not well understood. An attractive model for studying intrinsic control of growth state is the stereotypical developmental remodeling of the Drosophila mushroom body (MB) γ neurons. These neurons first undergo initial outgrowth, then during metamorphosis they prune larval connections followed by developmental regrowth, in a process that we have shown is distinct from initial outgrowth and involves transcriptional regulation.

To further explore the mechanisms that control developmental regrowth we performed developmental RNAseq of MB-γ neurons and found that regulators of actin dynamics were upregulated prior to regrowth. We performed a mini-screen of genes involved in actin dynamics and found that Chickadee (Chic, profilin) and Enabled (Ena), but not other nucleators such as formins or the arp2/3 complex, are required for axon regrowth but not for initial axon outgrowth.

Using a combination of genetic experiments in vivo and primary cultures, where we combined genetics, pharmacology and time-lapse imaging, we found that a hierarchical actin network that is amenable for compensatory regulation to achieve maximal robustness of axon growth. Ultimately, our work should increase our understanding of how actin dynamics promotes axon growth in different cellular contexts.

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SRGAP Truncations Confer Human Brain Advantages and Vulnerabilities

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In the development of the human brain, human-specific genes are considered to play key roles, conferring its unique cognitive advantages and vulnerabilities. At the time of Homo lineage divergence from Australopithecus, Slit-Robo GAP2C (SRGAP2C) emerged through a process of partial duplication and mutagenesis from ancestral SRGAP2A (3.4-2.4 million years ago (mya)). Remarkably, ectopic expression of SRGAP2C endows cultured mouse brain cells, with human-like characteristics, specifically, increased dendritic spines length and density. On the other hand, similarly truncated SRGAP isoforms appear in schizophrenia, and SRGAP deletions inflict mental retardation and early infantile epileptic encephalopathy. To understand the molecular mechanisms underlying these seemingly opposite neuronal outcomes, we determined the structure of SRGAP2A, and studied the interplay between the intact and truncated SRGAP isoforms. To determine the crystal structure, we have applied an exhaustive molecular symmetry search approach that took advantage of the anti-parallel two-fold biological symmetry of the protein. We found that homo- and hetero-dimerization guides the function of SRGAP proteins. Based on the site of truncation, some of the short isoforms are inhibitors, while others stimulate activity. It is by maintaining a precise balance between SRGAP activation and inhibition, that the human brain achieves its phenomenal accuracy in elaboration and connectivity.

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Conformational and Oligomeric Rearrangements Control Intercellular Signaling

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Intercellular communication, orchestrated by cell-surface expressed proteins, is a fundamental aspect of the formation, function and pathology of all tissues and organs. Protein structure, interaction and conformational change determine signaling and adhesion events. Using two target systems with central roles in the formation and maintenance of our nervous system; transmembrane receptors Myelin associated glycoprotein (MAG) and Sortilin, we show how interactions and conformational changes on the cell surface and between cells underlie the molecular mechanisms of signal transduction and adhesion.

This work required a hybrid approach of structural biology to resolve protein structures and conformational rearrangements, biophysical methods to determine protein interactions and cellular assays to unify these mechanistic insights with function in our nervous system. MAG controls myelin formation and maintenance, and inhibits axon regeneration. We show that MAG dimerization on the myelin surface regulates bidirectional axon-myelin signaling and we reveal how MAG adhesion maintains the myelin-axon spacing by binding to neuronal glycolipids. Neuronal expressed Sortilin internalizes signaling proteins and sorts them for degradation or recycling. We reveal that Sortilin undergoes a pH and concentration dependent conformational change plus oligomeric switch that underlies cargo release after endocytosis and Sortilin recycling. These are detailed mechanistic insights into central neuronal signaling and adhesion events.

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Neuronal Cell Shape Formation Controlled by Cytoskeleton

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Neurons are highly polarized cells whose shape is controlled by cytoskeleton networks. The formation of neuronal protrusions such as dendrites and axons is mediated by the dynamic nature of microtubules, and it is the basis of neuronal development. Particularly at axon branches, signaling processes trigger actin re-formation leading to the recruitment of microtubules to reinforce the branching site; however, little is known about this remodeling mechanism.

Combining the interdisciplinary methods of cryo-EM, biophysics, and cell biology, we focus on elucidating the mechanism of neuronal cell shape formation and accompanying cytoskeleton remodeling.

We will present our recent discovery of a novel factor promoting axon branch formation. To understand the underlying mechanism of branch promotion, we have characterized the interaction of the protein with tubulin and reconstituted its microtubule nucleation process *in vitro*. Moreover, cryo-EM revealed the molecular mechanism of how microtubule remodeling leads to the formation of branches. Mutagenesis experiments in primary neurons correlate the molecular remodeling activity with the formation of axon branches.

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Membrane-mediated RTK Signaling Crosstalk

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Illuminating Glutamate Receptor Structure and Function

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Reprogramming receptors and channels to artificially respond to light has wide-ranging applications in molecular studies and interrogation of biological functions. Light confers high temporal and spatial resolution and, combined with genetics, provides unique control on the cellular and molecular level. Recently, we set out to develop a set of NMDA receptor (NMDAR) subunits that can be precisely controlled by light using a variation of receptor engineering methodologies. NMDARs are glutamate-gated ion channels that play crucial roles in brain development and function. NMDARs exert control over many forms of synaptic plasticity that underlie learning and memory. They are also targets of therapeutic interest since their dysfunction is associated to numerous neurological and psychiatric disorders such as schizophrenia, mental retardation and epilepsy. Light sensitivity was successfully endowed to GluN1 and GluN2 subunits by either attaching photoswitchable ligands or by directly encoding light-sensitive amino acids by means of the genetic code expansion technology. Optically-controlled two-electrode voltage-clamp (TEVC) and patch-clamp recordings revealed robust photoresponses combining high temporal precision, bi-directionality (photopotentation or photoinhibition) and molecular (subunit) specificity. Photocontrol of key receptor properties including channel open probability, agonist sensitivity and ion permeation was achieved. Our results demonstrate the feasibility and utility of these approaches to probe the structure and biophysics of an important family of neurotransmitter receptors. They also bear general applicability to other membrane receptors and ion channels. We are now aiming at implementing these innovative optochemical tools in more native situations for *in vivo* optogenetic exploration of specific neuronal receptor functions.

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Membrane Transporters of the Brain

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Active transport plays a major role in brain. Depending on the brain region, Na,K-ATPase activity alone accounts for an estimated 40-70% of ATP hydrolysis, and also Ca2+-ATPases of the same P-type ATPase family contribute critically to ion homeostasis in the brain. The ionic gradients thus generated activate the ion channel receptors, the secondary transporters such as neurotransmitter transporters and chloride transporters, and potentiate osmotic changes and fluidics that regulate ionic conditions and pH of the cytosol and interstitial space. These activities are fundamental to brain physiology, and malfunction is linked to diseases of the brain, such as neurodegenerative, neurological and psychiatric disorders.

Using primarily membrane protein crystallography combined with biochemical and electrophysiological studies, single-molecule FRET, molecular dynamics simulations, modelling, and *in vivo* models, we have obtained deep insight into the functional cycle of the mammalian Na,K-ATPase and Ca2+-ATPase ion pumps. Furthermore, we have investigated fundamental aspects of the Na+ gradient coupled mechanism of the SLC6 neurotransmitter:sodium symporter family based on the bacterial homologues MhsT and LeuT.

In the lecture I will cover both methodological considerations and rationales as well basic concepts and mechanisms of active transport revealed by structural biology. I will also share new insights obtained from cryoEM and X-ray/neutron scattering studies.

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Cell Physiolgy of AMPA-receptors Determined by their Proteome

Bernd Fakler

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AMPA-type glutamate receptors (AMPARs), the key elements of fast excitatory neurotransmission, are fundamental for normal operation of the brain. These ionotropic receptors mediate a large part of the excitatory postsynaptic currents (EPSCs) that drive point-to-point transmission in glutamatergic synapses and control both propagation of the electrical signal and the influx of calcium ions into the postsynaptic spine. By these means, AMPARs promote formation and maturation of new synapses and trigger a variety of activity-dependent processes that lead to alterations of both amplitude and properties of the EPSCs. In combination, changes in signal transduction and wiring are thought to endow excitatory neurotransmission with the activity-initiated plasticity that underlies learning and memory formation.

I will discuss the molecular basis of some of the aforementioned processes as encoded in the comprehensive *proteome* (or *interactome*) that we obtained with native AMPARs isolated from the rodent brain. This will include subunit-function relation(s) of macromolecular AMPAR complexes, as well as the processes determining their biogenesis and activity-dependent dynamics.

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Synaptic Organizer Proteins: From Structures to Applications in Neuronal Disease

Jonathan Elegheert[1], Wataru Kakegawa[2], Vedrana Cvetkovska[4], Kunimichi Suzuki[2], Inseon Song[5], Alexander Dityatev[5], Ann Marie Craig[4], Michisuke Yuzaki[2], A. Radu Aricescu[1, 3], et al.

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Synaptic organizer protein complexes span the synaptic cleft to link pre- and post-synaptic sites and induce synaptic differentiation. As such, they profoundly modulate neuronal signaling and neurotransmission. I will present structural and functional studies of such complexes, focusing on interactions within the neuroligin–neurexin (NL–NRX) signaling hub. NL-NRX complexes organize excitatory and inhibitory synapses throughout the brain and aberrant signaling in the pathway is linked to disorders such as autism and schizophrenia.

Additionally, I will present data showing that synthetic synaptic organizer proteins with defined functionalities can be applied in models of neurodegenerative disease that are characterized by loss of synapses. One such molecule we designed is able to restore excitatory neuronal transmission and plasticity in the hippocampus, as well as spatial and contextual memories in Alzheimer's disease (AD) model mice.

Methods employed are protein crystallography, biophysics, neuronal co-culture, electrophysiology, and animal models of neuronal disease.

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Regulation of Synaptic Plasticity by Autophagic Degradation

Vassiliki Nikoletopoulou, Emmanouela Kallergi, Akrivi-Dimitra Daskalaki, et al.

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Converging evidence supports a pivotal role for long-term depression (LTD) in memory, learning and cognitive functions that demand behavioral flexibility. Consistently, LTD impairment has been implicated in autism spectrum disorders and neurodegeneration. LTD is mediated by shrinkage and elimination of pre- and post-synaptic elements, however, the pathways that facilitate these structural changes are not fully understood. Our results indicate that LTD critically relies on autophagic degradation of synaptic proteins, a process we coin “synaptophagy”. Moreover, we have identified the group of synaptic proteins that are degraded by autophagy during LTD and demonstrated that the conditional ablation of autophagy in the nervous system or its acute impairment with a selective inhibitor completely abolish LTD. Taken together, our findings reveal that persistent depression of synaptic strength relies on the regulation of the autophagic machinery in synapses which in turn degrades synaptic components to ensure the elimination of synaptic structures necessary for neuronal plasticity and associated behaviors.

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Dendritic actin Cytoskeleton: Structure, Functions and Regulations

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The actin cytoskeleton plays a major role in dendritic structure and function. In the dendrite, actin is highly enriched in dendritic spines but also present in the dendritic shaft. Spinous F-actin is segregated onto several sub-compartments: periodic F-actin structures aligning the neck of dendritic spines, a stable F-actin pool is enriched in the base of spine head, and dynamic branched actin filaments are located near the PSD. Calcium-dependent plasticity is directly linked to rapid actin remodeling in dendritic spines. We show that the Ca^{2+} sensor caldendrin orchestrates nano-domain actin dynamics. Steep elevation in spinous $[Ca^{2+}]_i$ disrupts an intramolecular interaction of caldendrin and allows cortactin binding. The fast on and slow off rate of this interaction keeps cortactin in an active conformation, and protects F-actin at the spine base against cofilin-induced severing. This indicates that caldendrin-cortactin directly couple $[Ca^{2+}]_i$ to preserve a minimal F-actin pool that is required for actin remodeling in the early phase of LTP. F-actin in dendritic shafts is present in form of the periodic actin-spectrin lattice, F-actin cables, and F-actin 'hot spots'. Our findings suggest that the local organization of F-actin is decisive for positioning of the Golgi satellites and lysosomes within dendritic compartments.

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Active Zone Scaffold Proteins Tune Functional Diversity across Brain Synapses

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Recently, high throughput electron microscopy has started to reveal complete wiring diagrams of single circuits and whole brain regions, for example in the Drosophila olfactory sensory and learning center. However, efficacy, timing, and frequency tuning of synaptic vesicle release are highly diversified across the development of brain circuitry. Systematic knowledge regarding the functional features of synapse types will be required for a satisfactory understanding and functional modeling of neural circuits. Using light superresolution microscopy, we provide evidence that presynaptic active zone scaffold protein diversity controls functional diversity across Drosophila brain synapses: distinct patterns of scaffold complexes differentially recruit specific Unc13 isoforms to steer transmission dynamics in a neuron-specific manner by conferring diverse nanometer-precise positioning of vesicle release sites to Ca2+ channels. In this manner, a compositional code of such stereotypic release modules diversifies synapse response properties. Our analysis provides 'nanoscopic molecular fingerprints' of synapse types which helps in understanding specific synaptic features in circuit modeling.

Key publications:

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Single-molecule Analysis of Ligand Efficacy in β_2AR Receptor-G Protein Activation

G. Glenn Gregorio[1*], Matthieu Masureel[2*], Daniel Hilger[2*], Daniel S. Terry[1], Manuel Juette[1], Hong Zhao[1], Zhou Zhou[1], Jose Manuel Perez-Aguilar[1,9], Maria Hauge[3,5,7,8], Signe Mathiasen[3,5], Jonathan A. Javitch[3,4,5], Harel Weinstein[1,6], Brian K. Kobilka[2‡], Scott C. Blanchard[1‡]

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G protein-coupled receptor (GPCR)-mediated signal transduction is central to human physiology and disease intervention, yet the molecular mechanisms responsible for ligand-dependent signaling responses remain poorly understood. In Class A GPCRs, receptor activation and G protein coupling entail outward movements of transmembrane segment 6 (TM6). Using single-molecule Fluorescence Resonance Energy Transfer (smFRET) imaging, we examine TM6 motions in the β_2 adrenergic receptor (β_2AR) upon exposure to orthosteric ligands with different efficacies, in the absence and presence of the G_s heterotrimer. We show that partial and full agonists affect TM6 motions in a manner that differentially regulates the rate at which GDP-bound β_2AR-G_s complexes are formed and the efficiency of nucleotide exchange leading to G_s activation. These data also reveal transient nucleotide-bound β_2AR-G_s species distinct from known structures and single-molecule perspectives on the allosteric link between ligand and nucleotide binding pockets that shed new light on the G protein activation mechanism.

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Metabotropic Force Sensing through adhesion GPCRs

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The Adhesion-class of G protein-coupled receptors (aGPCRs) builds one of the largest yet least understood GPCR family. aGPCRs feature an extraordinary blueprint signified by very large and complex ectodomains, which promote interactions with insoluble ligands as well as an auto-catalytically active domain, which splits the receptor into two fragments that are kept together by a non-covalent link. While these features may reflect the newfound role of aGPCR as metabotropic mechanosensors, the activating mechanisms and fundamental signaling principles of aGPCRs remain incompletely understood.

Utilizing Drosophila as an in vivo test tube to study the biology of aGPCRs we showed that Latrophilin/dCIRL localizes to a specific set of mechanosensory neurons. Here, dCIRL acts to optimize the gating properties of ionotropic receptors through an cAMP-dependent pathway thereby shaping the initiating step of mechanosensation. Structure-function analyses of different dCIRL alleles uncovered that the mechanosensitivity of these neurons i) subsides with increasing length of the ectodomain, ii) depends on a tethered agonist of the receptor and iii) is independent of self-cleavage of the receptor. Thus, aGPCRs enable cells to detect and respond to the highly dynamic mechanical habitat and add a yet to be explored layer of functional complexity to the superfamily of GPCRs.

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Revealing the Function of TBC1D24 Mutations in Epilepsy and Related Neurological Diseases

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Mutations in TBC1D24 cause severe epilepsy and DOORS syndrome, but the molecular mechanisms underlying these pathologies remained unresolved. We solved the crystal structure of the TBC domain of the Drosophila ortholog Skywalker, revealing an unanticipated cationic pocket conserved among TBC1D24 homologs. Cocrystallization and biochemistry showed that this pocket binds phosphoinositides phosphorylated at the 4 and 5 positions. The most prevalent patient mutations affect the phosphoinositide-binding pocket and inhibit lipid binding. Using in vivo photobleaching of Skywalker-GFP mutants, including pathogenic mutants, we showed that membrane binding via this pocket restricts Skywalker diffusion in presynaptic terminals. Additionally, the pathogenic mutations cause severe neurological defects in flies, including impaired synaptic-vesicle trafficking and seizures, and these defects are reversed by genetically increasing synaptic PI(4,5)P2 concentrations through synaptojanin mutations. Hence, we discovered that a TBC domain affected by clinical mutations directly binds phosphoinositides through a cationic pocket and that phosphoinositide binding is critical for presynaptic function.

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Super-resolution Imaging of Brain Extracellular Space

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The extracellular space (ECS) of the brain provides the physical stage and signaling platform where neuronal and glial players perform in concert. While the ECS takes up a fifth of brain volume, its topology is incredibly complex and miniaturized, defying traditional investigative approaches. Consequently, despite a marked interest in the physiological roles of brain ECS, its structure and dynamics remain largely inaccessible for experimenters. We combined 3D-STED microscopy and fluorescent labeling of the extracellular fluid to develop super-resolution shadow imaging (SUSHI) of brain ECS in living organotypic brain slices. SUSHI enables quantitative analysis of ECS structure and reveals dynamics on multiple scales in response to a variety of physiological stimuli. Because SUSHI produces sharp negative images of all cellular structures, it enables unbiased imaging of unlabeled brain cells with respect to their anatomical context. Moreover, the extracellular labeling strategy greatly alleviates problems of photobleaching and phototoxicity associated with traditional imaging approaches. As a straightforward variant of STED microscopy, SUSHI provides unprecedented access to the structure and dynamics of live brain ECS and neuropil.

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Structural Insights into GABAA Receptor Gating Mechanisms

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Type-A gamma-aminobutyric acid receptors (GABAARs) are pentameric ligand-gated ion channels and the principal mediators of inhibitory neurotransmission in the human brain. They are know to bind a broad range of endogeneous molecules and synthetic drugs, potent sedative, analgesic, anticonvulsant and anaesthetic agents. How these molecules interact with and modulate GABAARs remains, however, unknown. I will present recent structural results describing mechanisms of action for several classes of GABAAR ligands, and discuss the new insights these provide into understanding the basic biology of human GABA-ergic signalling.

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Ephrin-A4/EphA4 Signaling in Arterial Innervation Development and Physiology: Arteries under Pressure?

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Autonomic sympathetic nerves innervate peripheral resistance arteries, thereby regulating vascular tone and controling blood supply to organs. Despite the fundamental importance of blood flow control, how sympathetic arterial innervation develops remains largely unknown. Here, we identify the axon guidance cue Ephrin-A4 as an essential factor required for development of arterial innervation in mice. Ephrin-A4 is produced by arterial smooth muscle cells (SMCs) at the onset of innervation and signals via its receptor EPHA4 on sympathetic growth cones to triggers axonal repulsion. Function-blocking approaches including cell-type specific deletion of the gene encoding EphA4 in sympathetic neurons led to severe and selective increase of sympathetic innervation and to enhanced vasoconstriction in resistance arteries. As a result, arterial peripheral resistance rose significantly, provoking systemic hypertension from sympathetic origin.

These findings reveal a novel role for Ephrin-A4 and EPHA4 critical for the control of arterial innervation and systemic blood pressure regulation.

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PTPσ Drives Excitatory Presynaptic Assembly via Various Extracellular and Intracellular Mechanisms

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Running title: Presynaptic organization by LAR-RPTPs

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Leukocyte common antigen-receptor protein tyrosine phosphatases (LAR-RPTPs) are hub proteins that organize excitatory and inhibitory synapse development through binding to various extracellular ligands. Here, we report that knockdown (KD) of the LAR-RPTP family member PTPσ reduced excitatory synapse number and transmission in cultured hippocampal neurons, whereas KD of PTPδ produced comparable decreases at inhibitory synapses, in both cases without altering expression levels of interacting proteins. Extensive rescue experiments revealed that various extracellular and intracellular mechanisms are involved in heterologous synapse formation and development mediated by LAR-RPTPs. Strikingly, extracellular interactions of PTPσ with Slitrks are important for the excitatory synapse development. We also found that the D2 domain of PTPσ is required for induction of heterologous synapse formation by Slitrk1 or TrkC, suggesting that interaction of LAR-RPTPs with distinct intracellular presynaptic proteins drives presynaptic machinery assembly. Consistent with this, double-KD of liprin-α2 and -α3 or KD of PTPσ substrates (N-cadherin and p250RhoGAP) in neurons inhibited PTPσ-mediated heterologous synapse formation activity induced by Slitrk6, but re-expression of a PTPσ mutant containing the PTPδ intracellular domain in PTPσ-deficient neurons restored the impaired excitatory heterologous synapse formation observed in PTPσ-deficient neurons. We propose a synaptogenesis model in presynaptic neurons involving LAR-RPTP–organized retrograde signaling cascades, in which both extracellular and intracellular mechanisms are critical in orchestrating distinct synapse types.

Keywords: LAR-RPTPs/PTPσ/presynaptic assembly/protein-protein interaction/synaptic adhesion molecule

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Local Microtubule Ccues Specify Presynaptic Cargo Delivery at en passant Synapses

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The formation and maintenance of presynaptic sites are dependent on local delivery of presynaptic cargo, including synaptic vesicle precursors (SVPs). However, the mechanisms specifying the local delivery of SVPs to presynaptic sites, particularly the en passant synapses of the central nervous system, remain unclear. Using live-cell microscopy in hippocampal neurons and in vitro single-molecule reconstitution assays, we investigated how the organization of the axonal microtubule network affects vesicular motors to direct cargo delivery to the presynapse. We found that microtubule plus-ends are enriched at presynapses and that presynaptic delivery of SVPs occurs preferentially in the anterograde transport direction. Critically, anterograde delivery of SVPs to presynaptic sites is curtailed when local microtubule plus-end organization is disrupted. In vitro, we observed that the SVP anterograde motor KIF1A interacts weakly with plus-end-like microtubules, and that KIF1A processive runs are mainly limited by the microtubule length and terminate preferentially at the plus-ends of microtubules. Further, we found that presynaptic regions have low levels of microtubule glutamylation and KIF1A binds slower to non-glutamylated microtubules, suggesting that low glutamylation may act as a retention cue at presynapses. Finally, we identified KIF1A mutants that have altered microtubule binding properties are associated with neurological disorders.

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HDAC6 Inhibition Reverses Axonal Transport defects in Motor Neurons Derived from FUS-ALS Patients

Wenting Guo[1, 2], Maximilian Naujock[3], Laura Fumagalli[1], Tijs Vandoorne[1], Pieter Baatsen[4], Ruben Boon[2], Matthew Jarpe[7], Delphine Bohl[5], Pieter Vanden Berghe[6], Catherine Verfaillie[2], Ludo Van Den Bosch[1], et al.

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Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder due to selective loss of motor neurons (MNs). Mutations in the fused in sarcoma (FUS) gene can cause both juvenile and late onset ALS. We generated and characterized induced pluripotent Q8 stem cells (iPSCs) from ALS patients with different FUS mutations, as well as from healthy controls. Patient-derived MNs show typical cytoplasmic FUS pathology, hypoexcitability, as well as progressive axonal transport defects. Axonal transport defects are rescued by CRISPR/Cas9-mediated genetic correction of the FUS mutation in patient-derived iPSCs. Moreover, these defects are reproduced by expressing mutant FUS in human embryonic stem cells (hESCs), whereas knockdown of endogenous FUS has no effect, confirming that these pathological changes are mutant FUS dependent. Pharmacological inhibition as well as genetic silencing of histone deacetylase 6 (HDAC6) increases α-tubulin acetylation, endoplasmic reticulum (ER)–mitochondrial overlay, and restore the axonal transport defects in patient-derived MNs.

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Poster - 01

A Novel Interaction Partner for Caspr2 in the Developing Cerebellum

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Despite receiving renewed attention thanks to the revelation it is involved in higher cognitive functions, we still know little about how the cerebellum develops and operates. Studies suggest Caspr2, a member of the neurexin superfamily, has a function in cerebellar development. However, the cellular and molecular bases for this remain unknown.

To address this, we searched for Caspr2 interactors using a pull down assay combined with mass spectrometry analysis. Unexpectedly, and for the first time, we identified a Calcium ion channel as a cognate partner of Caspr2 at synapses in the cerebellum. Immunohistochemistry experiments coupled with confocal microscopy revealed that this interaction is sufficient to affect cellular morphology. In addition, we used Calcium imaging, immunoprecipitation and biophysical techniques to demonstrate that this functional effect is likely driven by Caspr2 binding directly to the pore region of the ion channel and modulating its activity, thus adjusting synaptic Calcium currents.

Together, these unpublished, interdisciplinary data reveal novel cellular and molecular roles for Caspr2 in the developing cerebellum. As well as improving our understanding of the nervous system, knowledge such as this will likely be increasingly clinically relevant, given the previously overlooked links between the cerebellum and cognition.

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Poster - 02

Study of the Involvement of the MAP6 Partners, CRMP4, in the Semaphorin3E Signaling Pathway

Boulan Benoit[1], Ravanello Charlotte[1], Denarier Eric[1], Bosc Christophe[1], Delphin Christian[1], Fournier Alyson[2], Andrieux Annie[1], Gory-Fauré Sylvie[1], Deloulme Jean-Christophe[1]

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Structural microtubule-associated proteins (MAPs) stabilize microtubules, a property that is thought to be essential for development, maintenance and function of neuronal circuits. Our group has demonstrated a role of MAP6 in brain wiring. We found that MAP6 deletion is associated with a lack of post-commissural fornix fibers in mice brain. MAP6 contributes to fornix development by regulating axonal elongation induced by Semaphorin3E. We have recently identified three members of the Collapsin Response Mediator Proteins (CRMP) family as protein partners of MAP6. These CRMPs were originally identified for their function in semaphorin signaling. In this study, we demonstrated the function of CRMP4 in the MAP6-dependant axonal outgrowth induced by Sema3E by using an homemade ImageJ macro able to automatically quantify neuronal arbor in primary culture. We next showed an axonal growth deficit of the fornix in CRMP4-KO mice, and confirming the involvement of CRMP4 in this neuronal tract. Furthermore, the interbreeding of CRMP4-KO mice with MAP6-KO mice revealed a genetic interaction between those genes. Bearing in mind that disorders in the fornix formation are associated with schizophrenia, a better understanding of the fornix formation would provide new evidence in favor of the neurodevelopmental origin of psychiatric diseases.

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Poster - 03

The Molecular Identity of Autistic Synapses: A SHANK3 Perspective

Michael Bucher[1, 2], Hans-Jürgen Kreienkamp[3], Dmitry Molodenskiy[4], Dmitri Svergun[4], Rob Meijers[4], Michael Kreutz[1, 2], Marina Mikhaylova[1]

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The SH3- and ankyrin-rich repeat (SHANK) proteins are considered as master organiser of the post-synaptic density (PSD). By interaction with proteins such as Homer or Cortactin, SHANKs are linking to receptors at the PSD on one side and synaptic actin dynamics on the other. These postsynaptic scaffolds exist in three major isoforms (SHANK1–3). Each isoform shows a brain-region specific expression pattern that is generally restricted to excitatory post-synapses. Among others, distinct missense mutations within the canonical SHANK3 isoform have been proposed as causative for the development of autism spectrum disorders (ASDs). Indeed, distinct mutations can alter the morphology of dendritic spines and affect synaptic transmission. However, a molecular explanation for such phenotypes is largely missing. Using diverse biophysical, biochemical and cell biology techniques, we characterize the molecular impact of selected missense mutations of SHANK3 in detail. We hypothesize that mutation-induced structural rearrangements of SHANK3 can be correlated with an alteration of the postsynaptic interactome, which culminates in the disruption of distinct synaptic signalling pathways. Hence, the major goal of this study is to show that SHANK3-mutation induced disruptions of postsynaptic signalling pathways represent a general principle in the development of ASD.

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Poster - 04

The Role of Autophagy in Shaping Inhibitory Synapses

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Institute of Molecular Biology and Biotechnology (IMBB)

Work from our laboratory and from others has identified autophagy as a novel mechanism contributing to protein homeostasis at the synapse. In line with these findings,our recent findings indicates that modulation of autophagy is crucial for synaptic plasticity in excitatory neurons. While autophagy upregulation can impair long-term potentiation (LTP) of synaptic strength, local induction of autophagy at the synapse is necessary to induce long-term depression (LTD), highlighting the immediate consequences of autophagy modulation on synaptic plasticity. Excitatory neurons represent the vast majority in the forebrain and synaptic plasticity traditionally studied in these cells has been shown to underlie key cognitive functions such as memory and learning. Therefore, work so far has focused on delineating the role of autophagy in excitatory neurons, ignoring the minority interneuron populations responsible for brain inhibition. Here, we characterise the role of autophagy in shaping inhibitory synapses and compare the network effects and behavioural deficits associated with impairment of autophagy in excitatory or inhibitory neurons. Moreover, we explore the modulation of autophagy as a means of restoring impaired brain inhibition and of reinstating normal behaviour in disorders such as epilepsy and schizophrenia that entail impaired excitation/inhibition balance in neural networks.

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Poster - 05

Regulation of Cerebral Cortex Folding by Controlling Neuronal Migration via FLRT Adhesion Molecules

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The folding of the mammalian cerebral cortex into sulci and gyri is thought to be favored by the amplification of basal progenitor cells and their tangential migration. Here we provide a molecular mechanism for the role of migration in this process by showing that changes in intercellular adhesion of migrating cortical neurons result in cortical folding. Mice with deletions of FLRT1 and FLRT3 adhesion molecules develop macroscopic sulci with preserved layered organization and radial glial morphology. Cortex folding in these mutants does not require progenitor cell amplification, but is dependent on changes in neuron migration. Analyses and simulations suggest that sulci formation in the absence of FLRT1/3 results from reduced intercellular adhesion, increased neuron migration and clustering in the cortical plate. Notably, FLRT1/3 expression is low in the human cortex and in future sulcus areas of ferrets, suggesting that intercellular adhesion is a key regulator of cortical folding across species.

Currently, we aim to enhance neurogenesis in mice with deletions of FLRT1 and FLRT3 in order to combine progenitor amplification with lateral dispersion of neurons. We are also comparing the relative contributions of FLRT1 and FLRT3 in regulating cortical neuron adhesion, clustering and migration.

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Poster - 06

Traumatic Brain Injury (TBI) as a Modulator of Neural Fate Specification in Reactive Astrocytes

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TBI contribute to about 30% of all injury deaths and, due to the poor regenerative ability of the central nervous system (CNS), those who survive can face effects as impaired memory, movement and sensation. After a TBI, reactive astrocytes perform different roles, as the maintenance of the inflammatory response, secretion of factors that modify the extracellular matrix and/or the synaptic reorganization. In vivo, reactive astrocytes remain in the astroglial fate; however, in vitro these cells undergo a process of dedifferentiation to neural stem cells (NSC), acquiring the potential of self-renewal and differentiation. Which are the regulatory mechanisms involved in the establishment of specific transcriptional programs after a TBI? How can a TBI define gene expression programs, gene regulatory circuitry and cellular diversity? We perform an assessment of NSC-related signaling pathways (WNT, SHH, NOTCH), regulatory mechanisms and gene expression in reactive astrocytes of mice submitted to a TBI model. To address these questions we use a combination of cell culture techniques and molecular biology. Considering the crosstalk among these pathways to be relevant for NSC maintenance in the neurogenic niches, we expect to elucidate the role of TBI in the modulation of neural fate.

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Poster - 07

Dynamic Tuneable G Proteincoupled Receptor Monomerdimer Populations

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G protein-coupled receptors (GPCRs) play a pivotal role in cellular signalling, highlighted by the fact that they form the target for ~40% of pharmaceuticals. While evidence has been accumulating for the existence and functional significance of GPCR oligomers, the matter remains contraversial, in part due to lack of consensus on e.g. the receptor interfaces involved in oligomerisation, and their possible dynamic nature [1]. Neurotensin receptor 1 (NTS1) has previously been shown to dimerise in lipid bilayers [2], is one of few GPCRs that can be produced in E. coli, and holds therapeutical potential for a variety of conditions including schizophrenia and cancer. Using a combination of single-molecule [3], and ensemble FRET, DEER spectroscopy, and Monte Carlo and molecular dynamics simulations, we demonstrate the presence of a concentration-dependent dynamic equilibrium between NTS1 monomers and dimers, with multiple co-existing dimer interfaces. These finding could rationalise previous seemingly contradicting results, and may provide a means of regulation of receptor signalling in vivo.

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Synaptic Organizer Proteins: From Structures to Applications in Neuronal Disease

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Synaptic organizer protein complexes span the synaptic cleft to link pre- and post-synaptic sites and induce synaptic differentiation. As such, they profoundly modulate neuronal signaling and neurotransmission. I will present structural and functional studies of such complexes, focusing on interactions within the neuroligin–neurexin (NL–NRX) signaling hub. NL-NRX complexes organize excitatory and inhibitory synapses throughout the brain and aberrant signaling in the pathway is linked to disorders such as autism and schizophrenia.

Additionally, I will present data showing that synthetic synaptic organizer proteins with defined functionalities can be applied in models of neurodegenerative disease that are characterized by loss of synapses. One such molecule we designed is able to restore excitatory neuronal transmission and plasticity in the hippocampus, as well as spatial and contextual memories in Alzheimer's disease (AD) model mice.

Methods employed are protein crystallography, biophysics, neuronal co-culture, electrophysiology, and animal models of neuronal disease.

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Lentiviral Transduction of Mammalian Cells for Fast, Scalable and High-level Production of Soluble and Membrane Proteins

Jonathan Elegheert[1], Ester Behiels[1], Benjamin Bishop[1], Suzanne Scott[1,2], Rachel E. Woolley[1], Samuel C. Griffiths[1], Veronica T. Chang[2], David I. Stuart[1], E. Yvonne Jones[1], Christian Siebold[1], A. Radu Aricescu[1,2]

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Structural, biochemical and biophysical studies of eukaryotic soluble and membrane proteins require their production to milligram amounts. Although large-scale protein expression strategies based on transient or stable transfection of mammalian cells are well established, they are associated with high consumable cost, limited transfection efficiency or long and tedious selection of monoclonal cell lines.

Lentiviral transduction is an efficient method for the delivery of transgenes to mammalian cells and unifies the ease of use and speed of transient transfection with the robust expression of stable cell lines. We have designed a lentiviral plasmid suite, termed pHR-SIN-CMV-TetO_2, for the constitutive or inducible large-scale production of soluble and membrane proteins in HEK293 cell lines.

The method is optimized for simplicity, speed and affordability, leads to milligram-scale amounts of protein in 3-4 weeks, and routinely achieves a ~3-10-fold improvement in protein production yield per number of cells as compared to transient transfection. Advanced features include bicistronic expression of fluorescent marker proteins for enrichment of co-transduced cells using cell sorting, and of biotin ligase for *in vivo* biotinylation. We demonstrate the efficacy of the method for a set of soluble proteins, the G-protein coupled receptor (GPCR) Smoothened (SMO), and the Type-A γ-aminobutyric acid receptor ($GABA_AR$) β3 homopentamer.

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Clinical Development of Anti-Semaphorin 4D Antibody for Huntington's Disease

Elizabeth Evans[1], Terence Fisher[1], John Leonard[1], Danielle Fisher[1], Leslie Balch[1], Alan Howell[1], Crystal Mallow[1], Ernest Smith[1], Maurice Zauderer[1], Andrew Feigin[1]

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SEMA4D triggers activation of inflammatory glial cells, inhibits differentiation of oligodendrocyte precursor cells, and disrupts the blood-brain barrier. Chronic inflammation, neuronal degeneration, and disruption of BBB are believed to play important roles in neurodegenerative diseases. Antibody neutralization of SEMA4D ameliorates neurodegenerative processes in preclinical models including HD transgenic mice.

SIGNAL is a randomized double-blind phase 2 clinical trial enrolling late prodromal and early manifest HD subjects to evaluate the safety and efficacy of VX15/2503, a first-in-class antibody to SEMA4D. Endpoints include clinical features of HD and imaging, including volumetric MRI, considered an early biomarker with prognostic significance for HD, and FDG-PET measures of glucose metabolism in prospectively defined brain regions of interest (ROI).

The recently completed first cohort demonstrated that VX15/2503 was well tolerated and appeared to prevent loss of brain volume and restore metabolic activity. VX15/2503 treatment trended toward stabilization of disease-related reduction in MRI volume and favored VX15 over placebo in 24/31 ROI. FDG uptake also favored VX15 in all 31 ROI, including p-values

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The Dynamics of Apical Anchoring of Cortical Stem Cells is balanced by a Dual CSF-derived Semaphorin/Neuropilin-signalling

Katrin Gerstmann[1], Karine Kindbeiter[1], Ludovic Telley[2], Muriel Bozon[1], Denis Jabaudon[2], Frederic Moret[1], Valerie Castellani[1]

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During brain development the precise regulation of apical adhesion is crucial for cortical integrity and function. Neural stem cells are tightly attached to adjacent neighbours at the ventricular surface and loss of apical adhesion is associated with precocious delamination and differentiation. However, cells that are committed to differentiate reduce their apical adhesion and disengage from the neuroepithelium. Therefore, controlling the adhesive properties of cortical stem cells is crucial for maintaining the ventricular zone architecture and for fate determination of mitotic cells. The mechanisms controlling this process remain to be elucidated. We observed that extrinsic Class3-Semaphorins and their Neuropilin-receptors are expressed by the embryonic choroid plexus and are released into the cerebrospinal fluid (CSF). The molecules form soluble complexes that bind to Plexins, which are present on the apical endfeet of cortical stem cells and the resultant signalling regulates the adhesive properties of cortical stem cells. Sema3B/Nrp2-signalling increases apical attachment and favours maintenance of cortical stem cells, whereas Sema3F/Nrp1-interactions reduce apical adhesiveness and promote delamination. Altogether our results reveal a novel role for Semaphorin/Neuropilin interactions in regulating the apical attachment and positioning of cortical stem cells to control the number of proliferating cells and postmitotic neurons.

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New Insights on 'Unconventional' Glycine Excitatory GluN1/GluN3A NMDA Receptors

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NMDA receptors (NMDARs) are classically composed of two obligatory glycine-binding subunits GluN1 and two glutamate-binding subunits GluN2. A third glycine-binding subunit, GluN3 (A and B), can assemble as di- or tri-heteromeric receptors. In tri-heteromeric GluN1/GluN2/GluN3 receptors, GluN3 has a dominant negative effect on receptor activity, while the di-heteromeric assembly GluN1/GluN3 leads to the formation of unconventional NMDARs gated by glycine alone. To date, glycine excitatory NMDARs have only been observed in heterologous expression systems and have proved difficult to study since: i) their apparent expression is low, ii) they undergo fast desensitization, iii) they lack proper pharmacology. Combining molecular pharmacology, site-directed mutagenesis and cellular electrophysiology, we uncover two striking properties of recombinant GluN1/GluN3A receptors. First, we identify a compound which dramatically enhances GluN1/GluN3A responses, converting tiny and fully-desensitizing currents into massive and stable responses. Second, we identify a few critical residues within distinct receptor regions (agonist-binding domains, linkers) which have profound effects on agonist sensitivity and gating kinetics, suggesting that the receptors may operate either under a tonic or phasic regime. Overall, our study reveals novel properties of GluN1/GluN3A receptors and provide new means to study the mechanisms and function of the yet enigmatic glycine excitatory NMDARs.

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Poster - 12

Structural Basis and Signalling Implications for Neogenin Receptor Assembly by Extracellular Ligands

Sam Griffiths

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A number of secreted ligands control neuronal pathfinding via binding to extracellular receptor Neogenin (NEO1). Repulsive Guidance Molecule (RGM) ligands trigger growth cone collapse; conversely, Netrin (NET) ligands elicit axon outgrowth. Additional binding sites on the surface of RGM ligands are also present for secreted Bone Morphogenetic Protein (BMP) ligands. The mechanism of signal transduction via NEO1 through multiple ligands remains poorly understood. In our laboratory, we have solved crystal structures of binary complexes between NEO1:NET1 and NEO1:RGM, as well as ternary complexes between NEO1:NET1:RGM and NEO1:RGM:BMP2. Combined validation of these structures via biophysical and cellular experiments shows that assembly of defined oligomeric states of NEO1 by various ligands is the true driver of signalling output. Utilisation of therapeutics to target uncovered interaction epitopes and modulate cell surface architectures of NEO1 may prove to be key to nervous system regeneration and cancer therapeutics.

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Poster - 13

Role of the MonoADPribose Polymerase, TIPARP, in the Cerebral Cortex

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The mono-ADP-ribose transferase, TIPARP, is an aryl hydrocarbon receptor (AHR) target gene, which regulates AHR activity and protects against dioxin toxicity. Previous studies have shown that exposure to dioxin impairs memory and learning abilities in mice. How TIPARP contributes to this and the role of this enzyme in the brain as well as in neurodevelopment is unknown. Here we show that TIPARP is physiologically expressed in the brain, specifically in the cortex, cerebellum and hippocampus of both human and mouse. We observed that TIPARP is highly upregulate during differentiation of human neural stem cells. We generated a CRISPR/Cas Tiparp knockout line of these cells and analyzed its differentiation and migration potential. Furthermore, our Tiparp knockout mice have a disorganized cerebral cortex, where the layers appear ill-defined. Taken together these results suggest that Tiparp and perhaps mono-ADP-ribosylation play a central role in neuronal differentiation and migration which could affect memory and learning.

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Poster - 14

Identification of Novel Regulators of GABAergic Synaptogenesis in the Nematode Caenorhabditis elegans

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To identify novel genes and mechanisms involved in the formation and regulation of inhibitory synapses, we used the inhibitory GABAergic neuromuscular junction of the nematode C. elegans as a genetically tractable model. After random mutagenesis of a knock-in strain expressing fluorescently tagged GABAAR, we screened for mutants with abnormal fluorescence pattern in vivo. We analyzed 36 mutant strains using a novel WGS strategy to simultaneously map and identify causative mutation without any prior time-consuming genetic mapping. We found 7 alleles of genes already known to be involved in synaptogenesis.

We undertook the analysis of a non-characterized gene, tentatively named nsp-3, which encodes an evolutionarily conserved transmembrane protein. nsp-3 deletion using CRISPR technology causes ectopic localization of GABAAR in intracellular compartments of the muscle cell. We found partial colocalization of these ectopic receptors with early and late endosomal markers. nsp-3 is expressed in neurons, muscles and epidermis and colocalizes with GABAARs. Preliminary rescue experiments showed that NSP-3 acts, at least, in muscles. We are now investigating NSP-3 subcellular localization and its role in GABAAR trafficking and localization. Our data should identify novel functions of these proteins in the traffic and/or synaptic localization of neurotransmitter receptors.

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HDAC6 Inhibition Reverses Axonal Transport Defects in Motor Neurons derived from FUS-ALS Patients

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Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder due to selective loss of motor neurons (MNs). Mutations in the fused in sarcoma (FUS) gene can cause both juvenile and late onset ALS. We generated and characterized induced pluripotent Q8 stem cells (iPSCs) from ALS patients with different FUS mutations, as well as from healthy controls. Patient-derived MNs show typical cytoplasmic FUS pathology, hypoexcitability, as well as progressive axonal transport defects. Axonal transport defects are rescued by CRISPR/Cas9-mediated genetic correction of the FUS mutation in patient-derived iPSCs. Moreover, these defects are reproduced by expressing mutant FUS in human embryonic stem cells (hESCs), whereas knockdown of endogenous FUS has no effect, confirming that these pathological changes are mutant FUS dependent. Pharmacological inhibition as well as genetic silencing of histone deacetylase 6 (HDAC6) increases α-tubulin acetylation, endoplasmic reticulum (ER)–mitochondrial overlay, and restore the axonal transport defects in patient-derived MNs.

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Integrated Approach to Study Netrin Complex Formation

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Netrin-1, a guidance molecule, helps in migrating neurons and can act as chemo-attractant and chemo-repellent (bi-functional) guidance cue depending on the presence of its receptors DCC and UNC5. The function of Netrin is not only restricted to the nervous system but it is also involved in other developing organs like mammary gland, lung etc., anti-inflammatory responses, angiogenesis, cell adhesion and cell survival in later stages of life. During embryogenesis, defective Netrin signaling can cause developmental defects and also in adult's life it is involved in cancer and neurodegenerative diseases.

To study the complexes between Netrin and its receptors, we are performing an integrated Approach combining X ray crystallography with biophysical methods (incl. Dynamic Light Scattering, Analytical Ultra Centrifugation, Size Exclusion Chromatography-Multi Angle Light Scattering, Micro Scale Thermophoresis and Small-Angle X-ray Scattering) and in-depth functional assays. Moreover, negative staining electron microscopy is used to get information about the arrangement of the ligand and receptor in complex. The detailed structural information of different ligand-receptor complexes will help to gain a molecular understanding of netrin-mediated complex formation.

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Dynamic VGCC Nanodomains contribute to Variability of Neurotransmitter Release

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Neuronal communication at chemical synapses is initiated by vesicular release of neurotransmitters, a process triggered by the transient influx of calcium ions. To successfully induce vesicle exocytosis, spatial proximity between voltage-gated calcium channels (VGCCs), mainly CaV2.1 and CaV2.2, and vesicular calcium sensors is essential. Despite their key function in synaptic transmission, little is known about the synaptic targeting of VGCCs and their local organization over time. Using functional imaging of presynaptic characteristics, we identified differences in calcium influx and evoked glutamate release of synapses populated by different CaV2.1 splice variants. Further, we localized VGCCs within active synapses and determined their surface dynamics using single particle tracking photoactivation localization microscopy (sptPALM). We found that VGCCs transiently dwell (100-200 ms) in nanodomains of 100 nm in size. To investigate the impact of channel surface dynamics on synaptic transmission, we performed temporary optogenetic clustering of CaV2.1 and observed a general recruitment of VGCCs into the synapse reflected in enhanced presynaptic calcium transients. However, only the CaV2.1 splice variant, having a high affinity to scaffold proteins, effectively changed synaptic transmission properties. We postulate that short-term plasticity underlies a dynamic remodeling of presynaptic VGCC nanodomain localization that can be regulated via alternative splicing of VGCCs.

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Convergent Evolution of Clustered Protocadherins (cPcdhs)

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Clustered protocadherins (cPcdh) genes are thought to have important functions in mammalian brain wiring. It has been proposed that heteromeric cPcdh- alpha, cPcdh - beta, and cPcdh -gamma receptors provide unique and highly diverse surface tags involved in neurite self- recognition in mammals. While Xenopus tropicalis and zebrafish cPcdh clusters do not contain cPcdh-beta isoforms, we found evidence that through alternative splicing of the cytoplasmic domain the X. tropicalis cPcdh-gamma1 gene cluster may generate a beta-type form of cPcdh isoforms. Loss-of-function mutants of full-length cPcdh gamma1 isoforms cause dramatic and wide spread defects in nervous system development of X. tropicalis tadpoles. In contrast, alternatively spliced shorter gamma1 isoforms that resemble beta-type isoforms appear to be specifically required for the differentiation of a subset of retinal neurons. This function cannot be compensated by full-length gamma1 isoforms. Similar results were obtained for zebrafish cPcdh-gamma cluster, although the splicing mechanisms differ between those two species. We hypothesize that this functional conservation represents a form of convergent evolution and reveals a unique specialization of cPcdh-beta receptors.

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Analyses of Receptor Variants of the Adhesion GPCR Latrophilin/CIRL

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Latrophilin/CIRL (Calcium independent receptor of α-latrotoxin) belongs to the Adhesion G protein-coupled receptor family (aGPCR), which has been shown to function in different physiological settings (Langenhan et al., 2009; Silva et al., 2011; Monk et al., 2009; Matsushita et al., 1999). However, its molecular functions remain incompletely understood. The sole Latrophilin locus in Drosophila, named dCirl, encodes a protein that localizes in a specific set of mechanosensory neurons. Electrophysiological and genetic analyses suggest dCIRL's relevance for the mechanosensing capability of these neurons (Scholz et al., 2015; Scholz et al., 2017). RNA-sequencing analysis predicts 8 dCirl mRNAs, which seem to be the result of alternative splicing events. Interestingly, these mRNAs encode receptor variants that differ in the number of transmembrane-spanning regions and composition of their extracellular domains (FBgn0033313). Cell-specific expression of different receptor variants and/or development-specific expression profiles may thereby tailor cellular functions based on the provided receptor layout. Moreover, it will be interesting to clarify the impact of structural alterations of the receptor on mechanosensation. Finally, we hypothesize that this naturally occuring set of receptors visions enables the coverage of a broad stimulus detection and signaling range, which in turn may lend functional diversity to enable appropriate cellular behaviors.

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Paracellular Mechanisms may contribute to Early Blood-brain Barrier Leakage after Cerebral Ischemia and Reperfusion

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The mechanisms underlying early-onset blood-brain barrier (BBB) hyperpermeability after ischemia/reperfusion (I/R) injury remain controversial. This study investigated the roles of the transcellular and paracellular pathways in early BBB leakage after I/R injury. In vitro, human brain microvessel endothelial cells (HBMECs) cultured in transwells were subjected to 60-min of oxygen-glucose deprivation (OGD). In vivo, male C57BL/6J mice underwent 60-min middle cerebral artery occlusion with time-lapse two-photon microscopic imaging of cortical parenchymal microvessels. BBB integrity was evaluated by extravasation of fluorescent tracers and transendothelial electrical resistance (TEER). The role of caveolin-1-mediated transcytosis was investigated using caveolin-1-/- mice and lentivirus-mediated knockdown of caveolin-1 in vitro. Progressive transendothelial leakage to small-sized dextrans (0.95-4.4kDa) was observed in cultured HBMECs 1-3h after OGD. Leakage was not blocked by caveolin-1 shRNA knockdown ($n=4$, $p>0.05$). Consistently, TEER was decreased by 25% after OGD ($p\leq0.01$). In vivo two-photon imaging revealed that biocytin-tetramethylrhodamine-869Da (TMR-869Da) extravasates into cerebral parenchyma as early as 1h after injury (5/5 wild-type mice) and this leakage was absent in sham-operated mice (n=3). Despite inhibited endothelial transcytosis in caveolin-1-/- mice, I/R-induced TMR-869Da extravasation was not reduced (n=4). These data suggested that paracellular rather than transcellular mechanisms contribute to early BBB disruption after brain I/R injury.

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Molecular Basis for the Regulation of Neurotransmission by Artemisinins

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The frontline anti-malarial drug artemisinins have additionally been implicated in the modulation of multiple cellular activities in mammals. In the absence of structures of any protein bound to artemisinins, the molecular mechanism of action of these sesquiterpenes remains enigmatic. We determined crystal structures of the inhibitory postsynaptic organizer gephyrin in complex with artesunate and artemether at 1.5 Å resolution, revealing for the first time how artemisinins are recognized by a target protein. Artemisinins occupy the prominent universal receptor-binding pocket residing in the C-terminal E-domain. Calorimetric and membrane sheet assays demonstrate the competition of artemisinins and inhibitory neurotransmitter receptors for an overlapping pocket on gephyrin. Electrophysiology measurements reveal a significant reduction in neurotransmission with an obligatory dependence on gephyrin. Clustering analysis of primary hippocampal neurons demonstrate a prominent reduction of gephyrin and receptor clustering in a time-dependent manner. Dysfunctional inhibitory neurotransmission manifests in lethal neurological disorders such as Alzheimer's, epilepsy and hyperekplexia. As artemisinins have been shown to cross the blood-brain barrier, our data will not only open up avenues in drug discovery against the aforementioned neurological diseases but also establish artemisinins as a potent tool to impair neuronal activity, thus to better understand the physiology of the human brain.

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Microfluidic Co-Culture System to Expose Synapses to CHO Cell-Secreted Aβ42

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Our genome-wide association studies have identified a number of Alzheimer's disease (AD) genetic risk factors; however, the mechanisms by which they contribute to the disease are poorly understood. One such gene (PTK2B) expresses Pyk2, a tyrosine kinase closely related to FAK, which regulates synapse function and plasticity in the mouse hippocampus by mediating dendritic spine remodeling. To specifically analyze Pyk2 at the postsynaptic level, we developed a multi-compartmental microfluidic device that isolates synapses of primary neurons. The device employs microchannels of varying length, thus permitting axons and dendrites, or only axons, emanating from distant chambers, to reach the so-called synapse chamber. The synapse chamber is directly accessible to introduce toxic oligomeric Amyloid-β (Aβ), a hallmark of AD, or potential therapeutic compounds. The synapse chamber is also connected to a fourth chamber, where Chinese Hamster Ovary (CHO) cells over-expressing wild-type APP or APP with London mutation are cultured. CHO cell secretion provides long-term exposure to pathologically-relevant levels of Aβ, thus mimicking disease conditions. Our preliminary data suggest that both synthetic and secreted Aβ decreases synaptic connectivity. The experiments where we selectively under- or over-express Pyk2 in postsynaptic neurons to dissect its role in synapse plasticity and failure are ongoing.

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Interplay between mTOR Kinase and the Retromer Complex in Neuronal Development

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Neuronal development and function is regulated by different cellular processes, many of which are dependent on mTOR kinase function. Our preliminary data revealed a new substrate of mTOR - TBC1D5, a Rab7 GAP that regulates retromer activity. Since impairment of retromer was shown to affect dendritogenesis, we tested whether mTOR could regulate dendritogenesis at least partially via control of retromer function. We show that the uptake of fluorescently labeled Shiga Toxin subunit B, a known retromer cargo, is slowed down upon mTOR inhibition with rapamycin, which suggests an interplay between mTOR and the retromer. Next, via kinase assay and mass spectrometry analysis, we show that TBC1D5 is phosphorylated by mTOR, and we identify mTOR-dependent phosphorylation sites. The overexpression of unphosphorylatable mutants of TBC1D5 increases the dispersal of cellular Vps35, as assessed by immunofluorescence analysis in HeLa cells. Furthermore, overexpression of TBC1D5 mutants in cultured rat hippocampal neurons causes a significant simplification of their dendritic arbors.This study has revealed mTOR as a potential regulator of the retromer complex, and the contribution of mTOR-retromer interplay in neuronal development. This work has been supported by Polish National Science Centre OPUS grant 2012/07/E/NZ3/00503.

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Structural Investigations into cis/trans Dimerization of Human DSCAM

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Down Syndrome Cell Adhesion Molecule (DSCAM) belongs to the immunoglobulin (Ig) superfamily of cell-surface receptors and is implicated in cell adhesion and neuronal wiring. The Drosophila Dscam gene can give rise to more than 19,000 distinct ectodomain isoforms through differential splicing in three Ig domains, Ig2, Ig3, and Ig7. The diversity is used to generate a repertoire of homophilic interaction partners, exclusively amongst identical isoforms. This high degree of specificity in homophilic recognition is a key regulator in neurite self-avoidance and tiling in anthropods. The human genome contains two DSCAM genes (DSCAM and DSCAM-Like1), which do not undergo extensive alternative splicing. Nevertheless, Dscam and DSCAM share similar biological roles. We have performed structural studies on human DSCAM to investigate whether homophilic dimerization is conserved in other species. Here, we report a 1.85Å X-ray structure of human DSCAM immunoglobulin domains, which shows the presence of homophilic dimers in the crystal lattice and uncovers a hot spot for homodimerization. Complementary biophysical studies indicate a possible mechanism for cis/trans homodimerization, similar to protocadherins.

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Angiomotins – A Novel Family of Proteins Involved in Neuronal Organization and Mice Behavior

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Angiomotin family comprises of three closely related scaffold proteins Amot, Amotl1 and Amotl2 that regulate actin cytoskeleton and the Hippo pathway signaling. Their function in the central nervous system is unknown. Our experiments demonstrate that all three Angiomotins are widely expressed in the brain and localize to synaptic compartments of mature neurons. However, at earlier stages of neuronal development, Amot protein localizes to dendritic and axonal processes. We showed that in neurons Amot interacts with transcription co-activator Yap1, which has similar localization to Amot in juvenile and mature neurons. Subsequently, using cultured hippocampal neurons and conditional knockout mice we demonstrate that both Amot and Yap1 play a critical role in proper organization of dendritic tree, cerebellar development and locomotor coordination in Rota Rod tests.

In contrast to Amot, neuronal deletion of Amotl1 does not affect motor coordination, but instead impairs social behavior of mutant animals. Amotl1 animals exhibit reduced anxiety, impaired nesting behavior as well as deficit in social novelty preference tests.

Collectively, our research identified a novel family of proteins that regulate neuronal organization and behavior of living animals.

This research was supported by the National Science Center (NCN) grants Sonata-Bis 2012/05/E/NZ3/00487, Preludium 2015/19/N/NZ3/02346.

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Chromatin Remodeling Complex and Notch Signalling Pathway in Apoptosis of Drosophila Larval Neural Stem Cells

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Most of the genes and biological pathways are conserved across all species. We choose Drosophila melanogaster as our model organism to understand central nervous system (CNS) development. We have recently shown that the combinatorial action of three transcription factors(TFs) namely Hox, Extradenticle and Grainyhead on enhancer is required for transcriptionally activating the death genes and initiate larval neural stem cells (Nbs) apoptosis (Khandelwal et al,2017). To further understand role of niche and epigenetic regulation, we did an in-vivo RNAi screen for identifying the Nbs fate regulators. Further, we have identified signalling pathway and chromatin remodelers that regulate apoptosis and differentiation of Nbs.

We find that chromatin remodeling complex members are important for apoptosis of larval neural stem cells in Drosophila. Our genetic experiments with chromatin remodeling complex and Notch confirm that they work together to controlling the apoptosis of larval neural stem cells. We further observe that chromatin remodeling complex and Notch signaling are important for maintenance of the apoptotic enhancer, which in turn is important for activating the downstream apoptotic genes. Taken together, our results indicate that fine tuning between TFs, epigenetic regulators & niche is important for programmed cell death of larval Nbs.

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Behaviour of the Nicotinic Acetylcholine Receptor at Ultra-high Temporal Resolution

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Embryonic muscular nicotinic receptors (nAChRs) contain two different binding sites, alpha-delta and alpha-gamma. The developmental switch from embryonic to adult receptors, which possess alpha-delta and alpha-epsilon sites equips neuromuscular junctions with channels signified by elevated single channel conductances and fast desensitisation kinetics. To uncover additional functional differences, we employed ultra-low noise patch clamping to measure single channel currents of mouse adult nAChRs at an unprecedented temporal resolution of 5 µs. Unexpectedly four, instead of three, types of openings, characterised by time constants of their open period distributions, were detected: tau-open1, 3 µs; tau-open2, 40 µs; tau-open3, 183 µs; tau-open4, 752 µs. For the first time, it was possible to selectively block either of the two binding sites. This allowed the exploration of single receptor behaviour during activation by a single ligand. Analysis of resulting currents supported the conclusion that tau-open2 and tau-open3 stem from monoliganded alpha-epsilon-sites, tau-open1 from monoliganded alpha-delta-sites and tau-open4 from diliganded receptors. In sharp contrast to the embryonic receptor, where tau-open1 dominate at very low agonist concentrations, the adult receptor displayed intermediate length openings tau-open2 and tau-open3. We conclude that the developmental replacement of alpha-gamma by highly affine and more effective alpha-epsilon-sites strengthens the synapse at low agonist concentrations.

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Voltage-sensing Nanoparticles for Super-resolution Voltage Imaging in Neurons

Anastasia Ludwig[1], Joonhyuck Park[3], Yung Kuo[3], Jack Li[3], Omri Bar-Elli[2], Dan Oron[2], Shimon Weiss[3], Antoine Triller[1]

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In the last decade, rapidly developing optical imaging field has significantly improved our understanding of the information processing principles in the brain. Although a number of promising tools have been designed, sensors of membrane potential are lagging behind the rest. In this project we aim to characterize in neurons an innovative voltage sensor that is fundamentally different from the existing ones. Our sensor is based on semi-conductor voltage-sensing nanorods (vsNRs) coated with transmembrane peptides to facilitate membrane insertion. vsNRs offer unique advantages of large voltage sensitivity, fast response times in the range of ns, and high photon flux. Such vsNRs can potentially record action potentials at a single particle level, at multiple sites and across a large field-of-view.

We optimized conditions for loading vsNRs into primary dissociated cortical neurons and performed initial series of experiments aimed to establish the relationship between the membrane potential and the fluorescent signal of vsNRs. Our data indicate that vsNRs are responsive to depolarizing voltage steps that are imposed on neurons in whole-cell voltage clamp configuration.

vsNRs has a potential to become the long-looked-for single-emitter voltage sensor that will open up a new avenue for the super-resolution voltage imaging in living cells.

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SorCS2-dependent Protein Sorting in Neurons: New Targets Implicated in Epilepsy

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SorCS2 is an intracellular sorting receptor expressed in neurons of the CNS. The receptor has been linked to several neurological disorders, including bipolar disorder and ADHD. Here, we show that SorCS2 expression is induced in epileptic human brains and that loss of SorCS2 expression in mice aggravates the outcome of PTZ kindling, an experimental model of epilepsy. To dissect the underlying molecular mechanisms, we compared the surface proteome in primary neurons from wild type and SorCS2-deficient mice to identify novel receptor cargo missorted upon loss of SorCS2. These studies uncovered altered cell surface exposure of several proteins involved in glutamatergic transmission in SorCS2-KO neurons, suggesting a role for SorCS2 in neuronal excitability. We currently characterise the relevance of these protein interactions for the neuroprotective role of SorCS2 in epilepsy.

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Direct Visualization of Conformational Gating in a Cyclic Nucleotidegated Ion Channel

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Cyclic nucleotide-gated (CNG) ion channels are non-selective cation channels key to signal transduction. The free energy difference of cyclic-nucleotide (cAMP/cGMP) binding/unbinding is translated into mechanical work to modulate the open/closed probability of the pore, i.e. gating. Despite the recent advances in structural determination of CNG channels, the conformational changes associated to gating remain unknown. Here we examine directly the conformational dynamics of a prokaryotic homolog of cyclic nucleotide-gated channels, using high-speed atomic force microscopy (HS-AFM) and electrophysiology. Single-channel electrophysiology shows that SthK channels are gated by cAMP binding to the cyclic nucleotide-binding domain (CNBD), whereas cGMP inhibits channel activity. HS-AFM of SthK 2D-crystals in lipid bilayers shows that the CNBDs undergo dramatic conformational changes during the interconversion between the resting and the activated states: The CNBDs approach the membrane and splay away from the 4-fold channel axis accompanied by a clockwise rotation with respect to the pore domain. Furthermore, our data suggests that these conformational changes in the CNBDs may be accompanied by a rearrangement in the voltage sensor domains (VSDs). In summary, we provide direct and compelling evidence that CNG channel gating is associated with concerted structural changes implicating long-range interactions between orthogonal protein domains in the channel.

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Robo1 Forms a Compact Assembly that Undergoes Slit2N Mediated Removal from the Cell Surface

Andrew McCarthy, et al.

EMBL-Grenoble

Roundabout (Robo) receptors provide an essential replusive cue in neuronal development following Slit ligand binding. This important signaling pathway can also be hijacked in numerous cancers, making Slit-Robo an attractive therapeutic target. However, little is known about how Slit binding mediates Robo activation. I present the crystal structure of Robo1 Ig1-Ig4 and Robo1 Ig5 together with a negative stain electron microscopy (EM) reconstruction of the Robo1 ectodomain [1]. The EM reconstruction shows that the Robo1 ectodomain forms compact dimers, mainly mediated by the central Ig domains, that can further interact in a ‘back-to-back‘ fashion to generate a tetrameric assembly. Complementary fluorescence light microscopy experiments show that Robo1 does not undergo any oligomeric change upon Slit2 binding on the cell surface, suggesting that a Robo1 monomer to oligomer transition upon addition of Slit2-N does not occur. I will also present more recent live cell imaging studies showing that upon interaction with Slit2-N, but not Slit2 D2, Robo1 can form concentrated assemblies on the cell surface that are subsequently removed. Taken together with previous studies we therrefore propose that Robo1 activation is mediated by a conformational change upon Slit binding that results in endocytosis and subsequent cell signaling.

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Insights into Teneurin3 Dimerization in the Neuronal Synapse using Single-particle Cryo-electron Microscopy

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Neurons are joined into functional circuits through connections called synapses. Intact neural circuitry is essential for all brain function, whereas faulty neural networks may result in severe disorders. Teneurins, a family of type II transmembrane proteins, have recently been characterized as synaptic cell adhesion molecules in forward-genetic screens for synaptogenesis in fruitfly Drosophila. A crucial role for Teneu-rin3 in synapse formation has since been established in the vertebrate visual system. We aim to under-stand the role of Teneurins using cryo-electron microscopy in combination with biophysical and cellular assays. We produced the extracellular portion of Teneurin3 in mammalian HEK cells and collected cryo-EM images of purified sample on a Talos Arctica with K2 camera. A 3.8 Å reconstruction of monomeric Teneurin3 reveals a novel superfold for synaptic cell adhesion, containing a six-bladed beta-propeller fol-lowed by a cocoon-like YD-barrel. The YD-barrel is sealed from the N-terminal side by a novel fibron-ectin plug domain and by its own inward spiral on its C-terminal end. Preliminary results of ongoing cryo-EM studies of the Teneurin3 dimer reveal that Teneurin3 dimerization is flexible and allows hetero- and homodimeric trans-synaptic interactions. Further structure-function studies will provide increased understanding on how Teneurins enable trans-synaptic interactions and synapse formation.

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Oxytocin alters the Morphology of Hypothalamic Neurons via the Transcription Factor Myocyte Enhancer Factor 2 (MEF2)

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Oxytocin (OT) has gained attention not only as anxiolytic drug and as potential treatment option for autistic children; it also acts as a growth and differentiation factor in neuronal cells. While behavioral effects of OT have been studied in detail, knowledge about its cellular effects is relatively sparse. We present evidence for three hypotheses: 1) OT leads to neurite retraction in hypothalamic neurons via the OT receptor (OTR) 2) The transcription factor MEF-2 is a central regulator of OT-induced neurite retraction, and 3) The MAPK pathway is critical for OT-induced MEF-2 activation. In more detail, activation of the OTR in rat hypothalamic H32 cells resulted in a significant retraction of neurites over time, accompanied by increased nuclear compartment size and cell viability. The molecular mechanism that controls OT-induced reduction of neurite outgrowth includes dephosphorylation of the transcription factor MEF-2A at Serine 408, resulting in a transcriptional activation which can be blocked by an inhibitor of the MAPK pathway. Also a knockdown of MEF-2A via siRNA prevented the OT-induced neurite retraction revealing a previously unknown OTR-coupled MAPK-MEF-2A pathway, which is responsible for OT-mediated morphological alterations in hypothalamic neurons.

This work was supported by the German Research Foundation DFG (GRK2174).

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Taking Phase-Contrast Electron Microscopy to the Limits

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Transmission electron microscopy (TEM) has advanced rapidly, culminating in the 2017 Nobel prize for the development of cryo-electron microscopy. Realizing its full potential requires phase-contrast imaging, which has already shown dramatic enhancement in imaging individual macromolecular assemblies and in cellular tomography. Stable, controllable and virtually lossless generation of phase contrast at the limits allowed by physics is possible by manipulating electrons with a powerful laser beam. We will present the current state of the laser-based phase plate based on resonant amplification of an infrared laser inside a focusing Fabry-Pérot resonator. We have experimentally demonstrated such cavity, and reached a laser power sufficient to produce a 30° phase shift if the electron energy is 80 keV. We plan to achieve a further tenfold power increase, which will allow for a full 90° phase shift for 300 keV electrons using state-of-the-art mirror coatings and improved heat management. We will then proceed to develop a laser phase plate module that will be inserted in the conjugate Fourier plane of a TEM. Cryo-electron microscopy close to its theoretical limit will create an unprecedented tool to determine the state of cells at a molecular level, for the purposes of diagnosing disease, predicting outcomes and helping inform therapeutic interventions.

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Optogenetics: HT4 Cells can be stably Transfected using AAV to Express Opsin from Carbydea Rastonii in order to Create Light Activation of the cAMP Pathway

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Type II opsins stimulate unique G-protein coupled pathways. JellyOp from the box jelly fish (carbydea rastonii) is a type II opsin that was recently shown to activate the GαS-cAMP. We used JellyOP in a unique recombinant AAV construct to express the opsin in cells derived from the mouse hippocampal cell line (HT4 cells). After transfection of HT4 cells, we did a light stimulation experiment. The transfected cells were exposed to interrupted light stimulation of 10s pulses for a period of 10 minutes. Non-transfected cells and cells not exposed to light throughout the experiment were used as controls. We then estimated the levels of cAMP-dependent kinase (PKA) levels on light exposure.

Our results show for the first time, that transfection of HT4 cells using a recombinant AAV2 vector, carrying a transgene construct of the opsin from carbydea rastonii is feasible and sufficient to cause robust expression. pVASP expression levels were equivocal, but a small trend is noted (p=0.2 Further experiments with this construct are needed to show expression of cAMP-dependent pathway activation, which in turn would lead to phenotype changes in neuronal cells, which would have important therapeutic implications.

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Neuronal Cell Shape Formation Controlled by Cytoskeleton

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Neurons are specially shaped cells with long extensions whose shape depend on the cytoskeleton. The dynamic feature of microtubules controls the growth of dendrites and axons and it is the basis of neuronal development and network plasticity. Particularly at axon branches, the local remodeling of microtubules is induced by upstream signaling and further transmitted via actin, however, little is known about the remodeling mechanism. Using combinations of the complementary methods of cryo-EM, biophysics, and cell biology, we focus on elucidating the mechanism of neuronal cell shape formation and downstream cytoskeleton remodeling. We will present our recently discovery of a novel axon branch promoting factor. To understand the underlying mechanism, we have reconstituted the interaction of the factor with tubulin biophysically as well as structurally, to show how nucleation of microtubules is mediated. Furthermore we show how the resulting remodelling of microtubules leads to the formation of axon branches.

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TDP-43 Modulates Translation of Specific mRNAs Linked to Neurodegenerative Disease

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The RNA-binding protein TDP-43 is the major component of cytoplasmic aggregates that are pathological hallmarks of neurodegenerative diseases ALS and FTD. Numerous patient mutations in TARDBP gene, combined with data from animal and cell-based models, imply that altered RNA regulation by TDP-43 causes disease. However, underlying mechanisms remain unresolved. Increased cytoplasmic TDP-43 levels in diseased neurons suggest a potentially important role in this cellular component. Here we used 'Ribosome footprint profiling' of motor neuron cell lines and primary cortical neurons, to identify mRNAs whose translation is altered by TDP-43 patient mutant. This revealed a small number of translational target mRNAs of mutant TDP-43, including some affected in both cell types. We validated some of them for increased ribosome density by polysome profiling and demonstrated direct TDP-43 binding by CLIP. Two target mRNAs encode proteins directly linked to ALS and other neurodegenerative diseases. For another target, which was previously shown to bind to microtubules and affect its stabilization, mutant TDP-43 expression altered levels of the encoded protein in cultured neuronal cells and in spinal cord neurons in a mouse model of ALS. Thus, our study shows that TDP-43 function as mRNA specific translational enhancer suggesting that this function might contribute to disease.

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Involvement of Monocarboxylate Transporters in Cognition and Plasticity in vivo

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The astrocyte-neuron lactate shuttle proposes that glutamate-induced neuronal activity leads in astrocytes to a large increase in the production of lactate which is released in the extracellular space through the monocarboxylate transporter 4 (MCT4) to be taken by neurons via MCT2 and used as an energy substrate to sustain neurotransmission [Pellerin and Magistretti, 1994]. It has been reported that lactate and MCTs could be involved in the formation of memory [Newman et al. 2011; Suzuki et al., 2011]. On this work, we use the Cre-LoxP technology to create an inducible model to delete the MCT2 (in neurons) and MCT4 (in astrocytes) in the hippocampal formation to study the involvement of these transporters in a cell-specific manner and in different cognitive tasks. Our results show that the deletion of MCT2 or MCT4 does not alter the short-term memory but significantly decreases the retrieval of the recognition information in long-term. We are now studying possible changes in the expression of plasticity-related genes, as well as morphological changes to clarify the basis of this alteration. The understanding of the roles of the MCTs in these fundamental cognitive functions will open the possibilities for developing novel therapeutic strategies, based on improving energy metabolism.

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Regulation of Synaptic Plasticity by Autophagic Degradation

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Converging evidence supports a pivotal role for long-term depression (LTD) in memory, learning and cognitive functions that demand behavioral flexibility. Consistently, LTD impairment has been implicated in autism spectrum disorders and neurodegeneration. LTD is mediated by shrinkage and elimination of pre- and post-synaptic elements, however, the pathways that facilitate these structural changes are not fully understood. Our results indicate that LTD critically relies on autophagic degradation of synaptic proteins, a process we coin "synaptophagy". Moreover, we have identified the group of synaptic proteins that are degraded by autophagy during LTD and demonstrated that the conditional ablation of autophagy in the nervous system or its acute impairment with a selective inhibitor completely abolish LTD. Taken together, our findings reveal that persistent depression of synaptic strength relies on the regulation of the autophagic machinery in synapses which in turn degrades synaptic components to ensure the elimination of synaptic structures necessary for neuronal plasticity and associated behaviors.

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NMDA Receptor Mediated Cation Influx during Neuronal Differentiation

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Immortal neuroblastoma cell lines enable investigating neuronal processes in vitro as they undergo neuronal differentiation upon retinoic acid (RA) treatment. We used SH-SY5Y neuroblastoma cell line to explore cation intake through NMDA receptors during differentiation under the effect of RA. We have shown that intracellular calcium ion (Ca+2) levels increase during differentiation which was attenuated by memantine treatment, an NMDA receptor antagonist. Supplementing differentiation medium with zinc ions (Zn+2) further increased total divalent cation content which was neutralized by intracellular chelation of Zn+2 and memantine treatment. We have used Oregon Green BAPTA-AM as a divalent cation indicator and flow cytometry to relatively measure intracellular divalent cation content and a selective Zn+2 chelator to differentially monitor Zn+2 and Ca+2 levels. Our results have shown an NMDA receptor mediated increase in intracellular Ca+2 and Zn+2 levels during neuronal differentiation of neuroblastoma cells.

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Revealing the Function of TBC1D24 Mutations in Epilepsy and Related Neurological Diseases

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Mutations in TBC1D24 cause severe epilepsy and DOORS syndrome, but the molecular mechanisms underlying these pathologies remained unresolved. We solved the crystal structure of the TBC domain of the Drosophila ortholog Skywalker, revealing an unanticipated cationic pocket conserved among TBC1D24 homologs. Cocrystallization and biochemistry showed that this pocket binds phosphoinositides phosphorylated at the 4 and 5 positions. The most prevalent patient mutations affect the phosphoinositide-binding pocket and inhibit lipid binding. Using in vivo photobleaching of Skywalker-GFP mutants, including pathogenic mutants, we showed that membrane binding via this pocket restricts Skywalker diffusion in presynaptic terminals. Additionally, the pathogenic mutations cause severe neurological defects in flies, including impaired synaptic-vesicle trafficking and seizures, and these defects are reversed by genetically increasing synaptic PI(4,5)P2 concentrations through synaptojanin mutations. Hence, we discovered that a TBC domain affected by clinical mutations directly binds phosphoinositides through a cationic pocket and that phosphoinositide binding is critical for presynaptic function.

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Mitochondrial Turnover and Neuronal Homeostasis in C. elegans

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Mitochondria are essential for energy production and have vital roles in calcium signalling and storage, metabolite synthesis and apoptosis in eukaryotic cells. Neuronal cells are dependent, perhaps more than any other cell type, on proper mitochondrial function. Therefore, maintenance of neuronal homeostasis necessitates a tight regulation of mitochondrial biogenesis, as well as, the elimination of damaged or superfluous mitochondria. Mitochondrial dysfunction has been associated with several age-related neurodegenerative disorders. Mitochondria selective autophagy mediates the removal of damaged mitochondria, and serves as the major degradation pathway, by which cells regulate mitochondrial population in response to metabolic state. However, little is known about the effects of mitophagy deficiency in neuronal physiology. To address this question, we developed two composite, in vivo imaging systems to monitor mitophagy in neurons. Neuronal mitophagy is induced in response to oxidative stress. Mitochondrial dysfunction leads to transportation of axonal mitochondria in neuronal cell body in a calcium- and an AMPK-dependent manner. Genetic depletion of autophagy increases mitochondrial number in neurons of age-matched nematodes and abolishes mitochondrial axonal transport upon stress. Additionally, mitophagy deficiency results in enhanced cell death in C. elegans models of neurodegeneration. Our results indicate that mitophagy contribute to preserve mitochondrial homeostasis and neuronal health.

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DNA Damage-induced Autophagy and Necrotic Neurodegeneration during Ageing

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Accumulation of DNA damage is a key determinant of ageing and has been implicated in neurodegeneration. Although it is well known that ultraviolet (UV) radiation induces apoptosis, the contribution of necrotic cell death to DNA damage-related pathology remains elusive. To address this question, we developed a nematode model for DNA damage-induced neurodegeneration by using UV-C irradiation to trigger DNA damage in C. elegans neurons. Initial observations using this model show a marked increase of cytoplasmic calcium concentration upon UV irradiation. To examine whether this acute cytoplasmic calcium elevation triggers necrosis in neurons, we exposed DNA repair-defective mutants to UV light. These mutant animals are hypersensitive to UV irradiation and exhibit widespread necrotic cell death in somatic tissues upon exposure, while neurons are particularly affected. Runaway autophagy has previously been implicated in necrotic neurodegeneration. In this context, we investigated the contribution of autophagy in DNA damage-induced cellular pathology and nuclear dynamics. Notably, we found that DNA damage induces autophagic flux and alters nuclear dynamics both in nematodes and mouse cells. We are currently dissecting the interplay between DNA damage-induced autophagy, nuclear membrane alterations and necrotic cell death, aiming to identify evolutionarily conserved molecular mechanisms interfacing these processes.

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The Role of Neuronal DEG/ENaC Ion Channels in Organismal Stress Responses

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The integration of sensory stimuli to appropriately modulate behavioral responses to environmental signals is critical for organismal survival. The molecular mechanisms that underlie such responses are not fully understood. Dopamine signaling is involved in several forms of behavioral plasticity. In Caenorhabditis elegans (italics) the functionality of the dopamine and serotonin pathways can be easily assessed by monitoring specific locomotory responses to environmental food availability cues, termed basal and enhanced slowing. We found that the members of the DEG/ENaC family of ion channels DEL-2, DEL-3 and DEL-4 are expressed in dopaminergic, serotonergic, sensory or motor neurons. Furthermore, we showed that these ion channel proteins modulate basal and/or enhanced slowing responses and responses to gustatory stimuli. They act through DOP-2 and DOP-3 dopamine receptors and affect the signaling at the neuromuscular junction, as inferred by behavioral studies. Degenerin effects are largely influenced by stress conditions, such as heat and starvation. Notably, the stress response transcription factors DAF-16/FOXO and SKN-1/Nrf couple degenerin ion channel function to environmental conditions and behavioral output.

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The Punctin-Neuroligin Partnership Regulates the C. elegans Inhibitory Synapse

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Synaptic defects are linked to neuropsychiatric impairments, highlighting the need for a better understanding of the molecular mechanisms responsible for correct synaptic function. The cell adhesion proteins Neuroligin and Neurexin act as synaptic organizers, while their mutations are associated with synaptic malfunction. In contrast to the Neuroligin-Neurexin interaction, that is well characterized in mammals, the mechanisms regulating GABAA receptor clustering to the postsynaptic membrane are unclear. Punctin, a multidomain protein secreted in the synapse, was identified as a novel partner of Neuroligin, critical for post-synaptic recruitment of GABAA receptors in C. elegans. Punctin is thought to regulate the identity of the post-synaptic membrane and the gene encoding the human orthologue has been identified as susceptible to cause schizophrenia. By biophysically characterising the Punctin-Neuroligin interaction, we provide insights in the nature of this partnership and the molecular determinants responsible for specific recognition of Neuroligin by Punctin. Further investigation in the interaction of these partners in C. elegans will allow us to extrapolate a molecular mechanism for the function and regulation of the human neuronal synapse, key to our understanding of how neuropsychiatric conditions develop.

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Structural Basis of Myelin-associated Glycoprotein Adhesion and Signaling

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Myelin-associated glycoprotein (MAG; Siglec4) constitutes 1% of total CNS myelin protein and is expressed along the internode on the adaxonal leaflet of the plasma membrane. MAG-/- mice show severe myelination distortions, most notably a widening of the periaxonal diameter. MAG binds specific neuronal gangliosides, bridging the periaxonal space. This has led to the hypothesis that MAG acts as a regulator of the periaxonal diameter. Other work has shown that MAG is involved both in axon-to-myelin and myelin-to-axon signalling functions. Myelin-to-axon signalling is in part responsible for the lack of regeneration after injury in the central nervous system.

Using X-ray crystallography we were able to determine the structure of the extracellular domain of MAG and a complex with a sialylated ligand. The structures were used to generate mutants that were analyzed in neurite outgrowth assays and by biophysical techniques such as small-angle X-ray scattering, analytical ultracentrifugation and liposome surface plasmon resonance. These studies revealed new mechanisms that explain biological function and phenotypes. Furthermore, the structure gives new insights into the mechanism of regeneration inhibition in the central nervous system by MAG.

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C1QL-mediated Complexes, a Novel Molecular Logic in Synapse Adhesion

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Proper brain function is based on neuronal networks, which are based on synapses, the fundamental structural unit of neuronal communication. Synaptic adhesion proteins bind across the synaptic cleft forming membrane tethered complexes, and have important functions in synapse homeostasis. Dysfunction of synaptic adhesion proteins are linked to complex brain disorders, 'synaptopathies'. Members of the family of complement component 1, q subcomponent-like proteins (C1QL1-3) act as synapse organizers. C1QLs are secreted into the synaptic cleft and bind to a post-synaptically localized adhesion GPCR B3 (ADGRB3). We hypothesize that C1QLs bidirectionally coordinate a trans-synaptic complex by interacting with ADGRB3 and a yet unknown pre-synaptic partner. Building on our in-vivo interactome data that identified such pre-synaptic binding partner, our research focusses on X-ray crystallography and electron microscopy studies to elucidate the stoichiometry and identify binding surfaces of this new C1QL-mediated complex. Additionally, C1QL proteins can form distinct higher oligomer species, which together with calcium specificity, dictate the nature of binding and stoichiometry, resulting in a novel mechanism of how trans-synaptic adhesion is achieved. Our discovery of a novel trans-synaptic complex will reveal an entirely new biochemical pathway that achieves synapse formation and maintenance in a unique way with an unusually complex stoichiometry.

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Axonal Growth in Three Dimensions

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The physiological growth of neurons occurs in three dimensions (3D) and it has been indicated in other dynamic cell types that the dimensionality affects cytoskeletal organization, molecular pathways and cell dynamics. Nevertheless, the conventional cultures so far are made on a flat surface. Here, collections of experiments in a simple, well-described method demonstrate a more physiological way to study axonal growth in vitro. Interestingly, overall neuronal growth is increased and the growth pattern is more comparable to what is physiologically observed in 3D. Furthermore, the growth cone morphology is drastically changed, suggesting a set of artifacts caused by the conventional two-dimensional (2D) in vitro systems. Moreover, this work sheds a first light on the forces involved in axonal growth. We demonstrate, for the first time, how a 3D cell culture method can offer insights on neuronal physiological growth and thereby tighten the gap between in vitro and in vivo.

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Heparan Sulfate Switches Netrin-receptor Selection in Axon Guidance

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The development of neuronal and vascular patterning in humans relies on a communication hub involving the guidance cue netrin. Different assemblies of netrin with the receptors DCC and Unc5 mediate opposing behaviors in cellular organization: attraction/adhesion versus repulsion/de-adhesion. We are investigating a mechanistic basis of this fundamental observation in addition to the more complex roles of co-receptors in modifying netrin-receptor selection and circuitry. Specifically, the post-translational attachment of heparan sulfate (HS) is presented on the cell surface by proteoglycans such as glypicans. In vitro, HS alters the site-specific binding patterns of both netrin-DCC and netrin-Unc5B and results in a reversal of netrin-receptor selection at one of the multivalent netrin binding sites. Similarly, in human cells expressing wildtype proteins, HS promotes inclusion of Unc5B in netrin-DCC assemblies. These findings suggest an essential component in the 'sugar code' of cellular communication with HS proteoglycans acting as switches in netrin interaction networks.

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The role of Neuronal Pentraxin 2 in Retinal Ganglion Cell Growth

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Axonal growth represents a critical step in functional recovery following traumatic central nervous system (CNS) injury. Activity-dependent signaling molecules, such as neuronal pentraxin 2 (NP2), play a significant role in neural development and neuroplasticity. The role of NP2 in the injured CNS remains unclear. The aim of this study was to characterize whether NP2 had any beneficial effects on retinal ganglion cell growth, using an ex vivo retinal explant model system. Given that the regenerative ability of neurons diminishes with age, neurite outgrowth was assessed in both embryonic-day 18 (E18) and postnatal day 7 (P7) retinal explants after exposure to NP2. The average number of neurites that grew beyond 500 μm, from the edge of the explant, were quantified. Treatment with NP2 significantly increased neurite outgrowth in both E18 and P7 retinal explants, compared to controls. These results suggest that NP2 is a regeneration-inducing factor that could be manipulated toward promoting regeneration and repair of the damaged CNS.

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POMC Processing is Directly Regulated by Saturated Fat in the Hypothalamus

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In outbred mice, susceptibility or resistance to diet-induced obesity is dependent on early oscillations in hypothalamic POMC levels following the consumption of dietary fats. Here, we employed obese prone (OP) and obese resistant (OR) Swiss mice to test three hypothesis: i, OP and OR mice fed on high-fat diet (HFD) promote early change in gut microbiota leading to increased fatty acid harvesting in OP mice; ii, independently of gut microbiota, OP mice fed on HFD present increased blood fatty acid levels; iii, fatty acids act directly in the hypothalamus to differentially regulate POMC expression and processing in OP and OR mice. Hypotheses i and ii were discarded once OP and OR mice fed on HFD presented similar changes in the gut microbiota and lipid harvesting. Upon testing of hypothesis iii, we demonstrate that in OP mice, palmitate induces an early increase in hypothalamic POMC, followed by increased expression of PC1/3. This also occurs in human hypothalamic cells differentiated from stem cells. Lentiviral inhibition of hypothalamic PC1/3 increased caloric intake and body mass in both OP and OR mice. Thus, direct regulation of POMC by dietary saturated fat emerges as an important mechanism involved in the development of diet-induced obesity.

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Sound Perception and Brain Wiring Enabled by Exceptional Cadherins

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Members of the cadherin superfamily of proteins are involved in diverse biological processes such as epithelial morphogenesis, sound transduction, and neuronal connectivity. Key to cadherin function is their extracellular domain containing heterogeneous cadherin "repeats", which can mediate interactions responsible for adhesion, force transduction, and cell signaling. Here I will present our recent work on various cadherin extracellular domains showing the complex and diverse structural determinants of their function in hearing and brain wiring. These structures also revealed the biochemical basis of the pathogenic effects of various missense mutations causing deafness and epilepsy, with broad implications for the function of various cadherin superfamily members.

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Function of the SPIRE Actin Nucleators in Emotional Fear Learning

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SPIRE proteins and FMN-subgroup formins cooperate in nucleating actin filaments at vesicle membranes to facilitate myosin V dependent transport processes. The brain is the major tissue of mammalian SPIRE1 and FMN2 expression. Contextual fear conditioning experiments of FMN2 knockout mice showed an impairment of fear extinction at young age and a memory loss at old age. In contrast SPIRE1 mutant mice exhibit increased fear. The discrepancy in fear behaviour might result from a recently discovered SPIRE1 function in mitochondrial dynamics. The mammalian SPIRE1 gene locus encodes an alternatively spliced exon (E13), which targets the SPIRE1E13 protein towards the outer mitochondria membrane. In brain we identified by qPCR a significant higher expression of vesicle associated SPIRE1 isoforms in contrast to the mitochondrial isoform SPIRE1E13. Live cell imaging experiments revealed a fragmented mitochondria phenotype in primary cells of SPIRE1 mutant mice. The SPIRE1 mutant mitochondria were metabolically active and had the same ATP production level as wildtype mitochondria. Enhanced fear expression in SPIRE1 mutant mice is most likely not caused by a metabolic dysfunction of mitochondria. As SPIRE1 mutant mice lack both, the expression of vesicular and mitochondrial SPIRE1, a SPIRE1 exon 13 knockout mouse was established for further investigations.

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O-linked N-beta-acetylglucosamine (O-GlcNAc) Post-Translational Modifications Dynamically Enhance Axon Regeneration

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Axonal regeneration within the mammalian central nervous system following traumatic damage is limited and interventions to enable regrowth a crucial goal in regenerative medicine. The nematode Caenorhabditis elegans is an excellent model to identify the intrinsic genetic programs that govern axonal regrowth. Here we demonstrate that alterations in O-linked N-beta-acetylglucosamine (O-GlcNAc) post-translational modifications can increase the regenerative potential of individual neurons. O-GlcNAc are single monosaccharide protein modifications that occur on serines/threonines in nucleocytoplasmic compartments. O-GlcNAc signaling is a sensor of cellular nutrients and acts in part through the insulin-signaling pathway. Loss of O-GlcNAc via mutation of the O-GlcNAc Transferase (OGT) enhances regeneration by 70%. Likewise, pharmacological inhibition of OGT increases regeneration in both C. elegans and mammalian neuronal culture. Remarkably, hyper-O-GlcNAcyation via mutation of the O-GlcNAcase (OGA) also enhances regeneration in C. elegans by 40%. Our results shed light on this apparent contradiction by demonstrating that these mutants differentially modulate the insulin-signaling pathway. OGT mutants act through AKT1 to modulate glycolysis. In contrast, OGA mutants act through the FOXO/DAF-16 transcription factor to improve the mitochondrial stress response. These findings reveal for the first time the importance of O-GlcNAc post-translational modifications in axon regeneration.

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In vivo Investigation of the Newly-identified SlitC/PlexinA1 Signaling during Commissural Axon Navigation

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During embryonic development, commissural axons cross the spinal cord midline and gain responsiveness to local repellents which prevent them from crossing back and expel them away. Sema3B acts via NP2/PlexinA1 receptor complex. SlitN binds to Robo1 and Robo2 receptors and mediates Slit repulsive activity. SlitC has long been considered as inactive, until we recently demonstrated that it binds to PlexinA1 and mediates repulsion, independently of the Robos and the Neuropilins. Conversely to Sema3B, SlitC repulsive activity requires the phosphorylation of PlexinA1 tyrosine Y1815. We generated a mouse strain, PlexinA1Y1815F, in which SlitC signaling is expected to be specifically altered. Analysis of spinal cord commissural axon trajectories revealed the presence of axons turning back and recrossing the floor-plate in mutant embryos. These phenotypes are reminiscent of those observed in PlexinA1-/- and Slits-/- embryos and support that the midline barrier function is ensured by SlitC/PlexinA1 signaling. In order to decipher the mechanisms regulating this signaling pathway, we set up cellular tools (i) to track Slit cleavage with a fluorescent cleavage reporter, (ii) to map in space and time SlitC/PlexinA1 interaction by BiFC. More broadly, PlexinA1Y1815F mice should allow us to identify yet unknown functions of SlitC in the developing nervous system.

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DNA Methylation and Demethylation in Cocaine Withdrawal

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An increasing number of reports have provided crucial evidence that epigenetic modifications, such as DNA methylation, may be involved in initiating and establishing psychostimulant-induced stable changes at the cellular level by coordinating the expression of gene networks, which then manifests as long-term behavioural changes. Recent discoveries suggest that ten-eleven translocation enzymes (TET1-3) participate in the DNA demethylation process and might also play a role in cocaine action. However, there are no studies that have focused on the complex role of DNA methylation and demethylation in the mechanisms of psychostimulant-induced addiction. In this study, we show that cocaine withdrawal upregulates mRNA levels of DNA methyltransferases (Dnmts) and downregulates mRNA levels of Tets in the nucleus accumbens (NAc) of mice and that these changes correlate tightly with Dnmt and Tet mRNA levels in peripheral blood cells. Our data show that cocaine withdrawal increases DNMT activity but decreases TET activity in the NAc and that these changes are associated with enhanced global DNA methylation levels. Thus, our data indicate that cocaine withdrawal may disturb the equilibrium between DNA methylation and demethylation processes and cause global changes in DNA methylation in the NAc.

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Differential Expression of Perineuronal Nets in the Mouse Spinal Cord

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Perineuronal nets (PNNs) are a specialized form of extracellular matrix surrounding cell bodies of selected neurons that stabilize synaptic connections in the adult CNS and restrict neuroplasticity. In the spinal cord, PNNs contribute to the potent molecular inhibition hindering axon regrowth after injury. Formation of PNNs is dependent on the expression of link proteins (Crtl1 and Bral2), which are essential for the interaction between its components. We examined the expression and regional distribution of key PNN proteins in the spinal cord of developing and adult mouse. The results show temporal and regional differences along the dorso-ventral axis in link protein expression suggestive of underlying PNN heterogeneity. Double labelling experiments are being carried out to determine whether PNN formation is related to specific classes of spinal neurons. An in vitro model using mouse embryonic stem cells (wild-type and Crtl1 link protein knock-out) differentiating toward neuronal and/or glial phenotype was used to study the molecular composition and formation of PNNs. Understanding the role of PNNs in regulating plasticity in specific spinal neurons will provide an experimental avenue for selectively targeting synaptic plasticity to specific neural circuits and provide opportunity to direct the formation of new synaptic connections after an injury.

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New Insights in the Nucleotidedependent Conformational Cycle of Roco Proteins and the Parkinson's Disease-associated Protein LRRK2

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Mutations in LRRK2 are a common cause of genetic Parkinson's disease (PD). LRRK2 is a multi-domain Roco protein, harbouring kinase and GTPase activity. In analogy with a bacterial homologue, LRRK2 was proposed to act as a GTPase activated by dimerization (GAD), while recent reports suggest LRRK2 to exist under a monomeric and dimeric form in vivo. It is however unknown how LRRK2 oligomerization is regulated. We show using a combination of structural and biophysical methods that oligomerization of a homologous bacterial Roco protein depends on the nucleotide load. The protein is mainly dimeric in the nucleotide-free and GDP-bound states, while it forms monomers upon GTP binding, leading to a monomer-dimer cycle during GTP hydrolysis. An analogue of a PD-associated mutation stabilizes the dimer and decreases the GTPase activity. This work thus provides new insights into the conformational cycle of Roco proteins and suggests a link between oligomerization and disease-associated mutations in LRRK2.

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Studies of Neurexin-Neurexophilin Interactions

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Neurexins are pre-synaptic cell adhesion molecules that are expressed as thousands of isoforms in the brain. Neurexins interact with a multitude of ligands in an isoform-dependent manner and through these interactions can differentially specify the functional properties of synapses. In this way, Neurexins constitute part of a molecular code that contributes to the complex functional organization of the brain. Of the many Neurexin ligands, the Neurexophilins are a family of secreted neuropeptide-like glycoproteins encoded by four genes (Nxph1-4). The Neurexophilins are only conserved in vertebrates and share virtually no homology with any other proteins. The Neurexophilins bind to alpha-Neurexin isoforms at the second Laminin/Neurexin/Sex-hormone-binding globulin (LNS2) domain. Neurexophilin-1 is highly expressed in distinct populations of inhibitory interneurons and is likely involved in modulating inhibitory neurotransmission. Here we present structural and biophysical studies of Neurexin-Neurexophilin interactions.

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Unraveling the Role of Endocrine Pancreas Innervation through in vivo Time-lapse Imaging and Optogenetic Control of Nerve Activity

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Autonomic innervation has been implicated as an important modulator of pancreas development and function. However, innervation studies in mammals have been limited to specific snapshots in time and tissue depth. Characterization of innervation establishment should provide insight into the nerve-endocrine interactions and their roles in modulating pancreas development. The zebrafish is well suited for in vivo studies of pancreatic islet development with time-lapse imaging due to its rapid embryogenesis and transparency during embryonic/early larval stages. With reporters labeling neuronal and endocrine cells, we determined the sequence of events leading to pancreatic innervation. Our studies revealed that endocrine pancreas innervation begins early in development, prior to dorsal and ventral pancreatic bud fusion. We identified a key sub-population of neural-crest-derived neurons that are crucial for pancreatic innervation. These neurons are in close contact with endocrine cells at early developmental stages and extend axons towards the islet as they surprisingly migrate away. Upon targeted-ablation of these neurons, we observed diminished innervation. We are focused on deciphering the functional roles of selective neurons with optogenetic control of nerve activity and simultaneous imaging of calcium dynamics in endocrine cells. This research can have a major impact on our understanding of pancreatic innervation dynamics, signaling, and function.

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Local Microtubule Ccues Specify Presynaptic Cargo Delivery at en passant Synapses

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The formation and maintenance of presynaptic sites are dependent on local delivery of presynaptic cargo, including synaptic vesicle precursors (SVPs). However, the mechanisms specifying the local delivery of SVPs to presynaptic sites, particularly the en passant synapses of the central nervous system, remain unclear. Using live-cell microscopy in hippocampal neurons and in vitro single-molecule reconstitution assays, we investigated how the organization of the axonal microtubule network affects vesicular motors to direct cargo delivery to the presynapse. We found that microtubule plus-ends are enriched at presynapses and that presynaptic delivery of SVPs occurs preferentially in the anterograde transport direction. Critically, anterograde delivery of SVPs to presynaptic sites is curtailed when local microtubule plus-end organization is disrupted. In vitro, we observed that the SVP anterograde motor KIF1A interacts weakly with plus-end-like microtubules, and that KIF1A processive runs are mainly limited by the microtubule length and terminate preferentially at the plus-ends of microtubules. Further, we found that presynaptic regions have low levels of microtubule glutamylation and KIF1A binds slower to non-glutamylated microtubules, suggesting that low glutamylation may act as a retention cue at presynapses. Finally, we identified KIF1A mutants that have altered microtubule binding properties are associated with neurological disorders.

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A Novel Synthetic Microneurotrophin Protects Oligodendrocytes against Cuprizone-induced Death, through NGF Receptors

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BNN27, a member of a new family of C17-spiroepoxy derivatives of the neurosteroid DHEA, has been shown to regulate neuronal survival and differentiation through its selective interaction with NGF receptors (TrkA and $p75^{NTR}$), but its role on glial populations has not been studied. Here we present evidence that BNN27 provides trophic action (rescue from apoptosis), in a TrkA-dependent manner, to mature oligodendrocytes when they are challenged with the cuprizone toxin *in vitro*. BNN27 treatment also increases oligodendrocyte process branching. Deletion of $p75^{NTR}$ decreases oligodendrocyte arborization, not affecting the protective role of BNN27. The effect of BNN27 on oligodendrocytes *in vivo* in the cuprizone mouse model of demyelination has also been investigated. In this model, that does not directly implicate the immune system, BNN27 is able to protect from demyelination without affecting the remyelinating process. BNN27 positively regulates mature oligodendrocyte and oligodendrocyte precursor numbers during demyelination *in vivo*, while reducing microgliosis and astrogliosis. Our findings suggest that BNN27 may serve as a lead molecule to develop neurotrophin-like, blood brain barrier (BBB)-permeable protective agents of oligodendrocyte populations and myelin, with potential applications in the treatment of demyelinating disorders.

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The Function of the Adhesion Molecule Contactin-2/TAG-1 in Oligodendrocytes in Health and Demyelinating Pathology

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The oligodendrocyte maturation process and the transition from the pre-myelinating to the myelinating state are extremely important during development and in pathology. In the present study we have investigated the role of the cell adhesion molecule TAG-1 on oligodendrocyte proliferation, differentiation, myelination and function during development and under pathological conditions. With the combination of *in vivo*, *in vitro*, ultrastructural and electrophysiological methods we have mapped the expression of TAG-1 protein in the oligodendrocyte lineage during the different stages of myelination and its involvement on oligodendrocyte maturation, branching, myelin-gene expression, myelination and axonal function. The cuprizone model of CNS demyelination was further used to assess TAG-1 in pathologies of the oligodendrocyte population.
During development, TAG-1 can transiently affect the expression levels of myelin and myelin-regulating genes, while its absence results in reduced oligodendrocyte branching, hypomyelination of fiber tracts and impaired axonal conduction. In pathology, TAG-1 absence does not affect the extent of de- and remyelination. However, during remyelination, a novel, TAG-1-independent mechanism is revealed that is able to re-cluster voltage gated potassium channels (VGKCs) resulting in the improvement of fiber conduction.

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EMBO Workshop
"Molecular Neurobiology"

8 – 12 May 2018
Fodele, Heraklion, Crete, Greece

Survivor's Guide...

❖ Transportation from Heraklion Airport "N. Kazantzakis" [HER]

Organizers have arranged for two buses from the airport to the venue [Fodele Beach and Water Park Holiday Resort (http://www.fodelebeach.gr)] on the 7th of May 2018 when the majority of the participants arrive. Buses will leave the airport at **16.00** and **20.30**. You can locate the bus in the airport parking just outside the arrivals behind the tour operator's kiosks. The bus will have this sign in the front window:

For those who will not be served by the buses, please find bellow alternative ways of transportation from the airport to the hotel.

Please note that the airport is very close to the city center. So, if you arrive early, you can leave your luggage to the 'left luggage' at the airport, take the city bus to the city center for a short visit (ticket 1,20 € - see also 'public transport' below) and return to the airport for the bus.

TAXI

Taxi ride from Heraklion "Nikos Kazantzakis" Airport [HER] to the Hotel at Fodele costs around 45 Euros. TAXIs are outside the arrival room on the left.

There is an offer from our partner organizer CCBS-Greece. For the same price (45 € per taxi), the TAXI driver will wait for you holding a sign with your name on it. The price is fixed from Heraklion to Fodele Beach. If you wish to take advantage of the service you are kindly requested to send an e-mail directly to sales@ccbsgreece.gr, Ms Katerina Koronaiou, indicating your name, your arrival flight number and your arrival date and time in Heraklion airport.

PUBLIC TRANSPORT

Heraklion airport is close to the city center; only 15 minutes by any city bus (blue bus), which leaves from just outside the airport. You need to buy a 1,20 € ticket (colored orange) at the bus stop kiosk; you will enter at the front door and the bus driver will tear half of your ticket apart. Ask the driver to drop you off at the "KTEL for Chania", which is the bus station for the RETHYMNO-CHANIA intercity coach (green bus). Buy a ticket to FODELE BEACH inside the station (for ~3,00 €), and tell the driver on the bus where to stop (FODELE BEACH Hotel Stop). The short ride should take no more than 30 minutes. It's a final 300m walk to the hotel from there (public transportation plan – see page 4). There are also … buses to the hotel reception. See the plan for more information.

Bus schedule: City buses leave from the airport to the city center every 10 minutes or so. Please ask the driver to let you know the bus stop for KTEL. Intercity coaches leave from the KTEL bus station near the port every hour on the half hour from 05:30 until 20:30 and after that, at 21:45 (city map and location of KTEL - see page 5).

Please, be careful, the public bus station across the street from airport arrivals, does not serve West Crete and Fodele.

❖ Arriving at the Hotel / Registration on the 8th

- ❖ Upon arrival at the hotel you must check-in your room. You don't need any voucher. Just state your name at the reception. You will get the "all inclusive" colored bracelet put on your wrist (list of "all inclusive service" attached – see page 6); also attached is a plan of the hotel (see page 7)
- ❖ Since your reservation is made through the meeting organizers, for any pending accommodation extras, please contact the person from CCBS-Greece during registration and throughout the Workshop. Additional charges (e.g. city tax, telephone, internet access, mini bar, etc) are not included in your accommodation. Please remember to take care of these directly at your hotel, upon checking out. City tax has also to be paid at the reception upon check out. ***City tax for 5 stars hotel is 4,00 € per night/per room.***
- ❖ Upon registration (starting at 13.00 on Tuesday, 8 May) you will be given an EMBO bag containing the following:
  - Bag / Notepad / Pen
  - Course Program Booklet & Posters List
  - Name badge
  - Badge strip
  - Leaflets

  * The Abstract Book will be distributed electronically before the Workshop in order for you to have it in you electronic devices.

Registration will take place at the Workshop Secretariat, outside the Conference Room
(No 35 at the hotel plan – see page 7)

If you are a speaker:

There will be a data projector connected to a PC (Windows – Microsoft Office) so kindly prepare your presentation file(s) accordingly. There will be assistance inside the conference room, at your disposal for any technical assistance. Please ask the secretariat for more detailed information. You should not forget to contact the assistant during the break *prior to* your presentation's session and hand over to them your presentation data (CD, memory stick, notebook/laptop). Assistants will wear yellow colored badges.

- If you are a Mac user, please don't forget to bring the thunderbold compatible with your computer in order to connect it to the projector cable.

If you are presenting a poster:

Poster Room: No 34 "Games Room" at the hotel plan (see page 7)
Poster boards will be ready for presentation mounting. You are not allowed to use push-pins or any other mount material which could damage boards. Mounting materials will be distributed during registration. Remember to consult the detailed poster presentation guidelines (attached, see page 8). **POSTERS SHOULD BE PORTRAIT ORIENTED**. See poster panel dimension on page 8.
All posters should be up for the whole duration of the workshop.

There are 2 Poster sessions: **ODD NUMBERS - Wednesday, 9 May 2018 @ 18:00** and **EVEN NUMBERS - Thursday, 10 May 2018 @ 18:00**. There will be a poster list where you can check the poster session you present in and your poster number/board. You will also be notified for your poster session during registration.

* Please note that you have to bring your poster ready to be up. There is no poster printing service available on site.

❖ Frequently Asked Questions

Will I have Internet access during the conference?

On your check-in you will get a small paper with your password for the internet. ***Please note that the connection is only for ONE device. What we suggest is to connect a device which can be a hot spot (e.g. smartphone) and share the wifi to the rest of your devices.***

If you want additional connections, you will need to buy an access card from the Reception of the hotel. The prices are: 3 days → 5,00 €, 7 days → 12,00 €.

Free internet, low standard bandwidth, is provided in the central square outside the conference and poster room, close to Starlight Bar (No 18 in the Hotel Plan), in the Water Park (No 38 in the Hotel Plan) and the Beach.

What if I want to keep my room after 12 noon on checkout day?

12.00 is the regular check-out time. If you wish to keep your room past 12.00, you should notify the reception of the hotel in advance to check for availability. In case of extended day stay, you can contact the course secretariat before the end of the course. Bear in mind that after 18.00 a full overnight stay charge is applicable.

Do I have any options outside the conference area?

The person in charge from CCBS-Greece, Ms. Katerina Koronaiou, will be happy to advice you on short visits or day schedules all around Crete and will be more than willing to arrange such off-conference activities for you and/or your escorts.

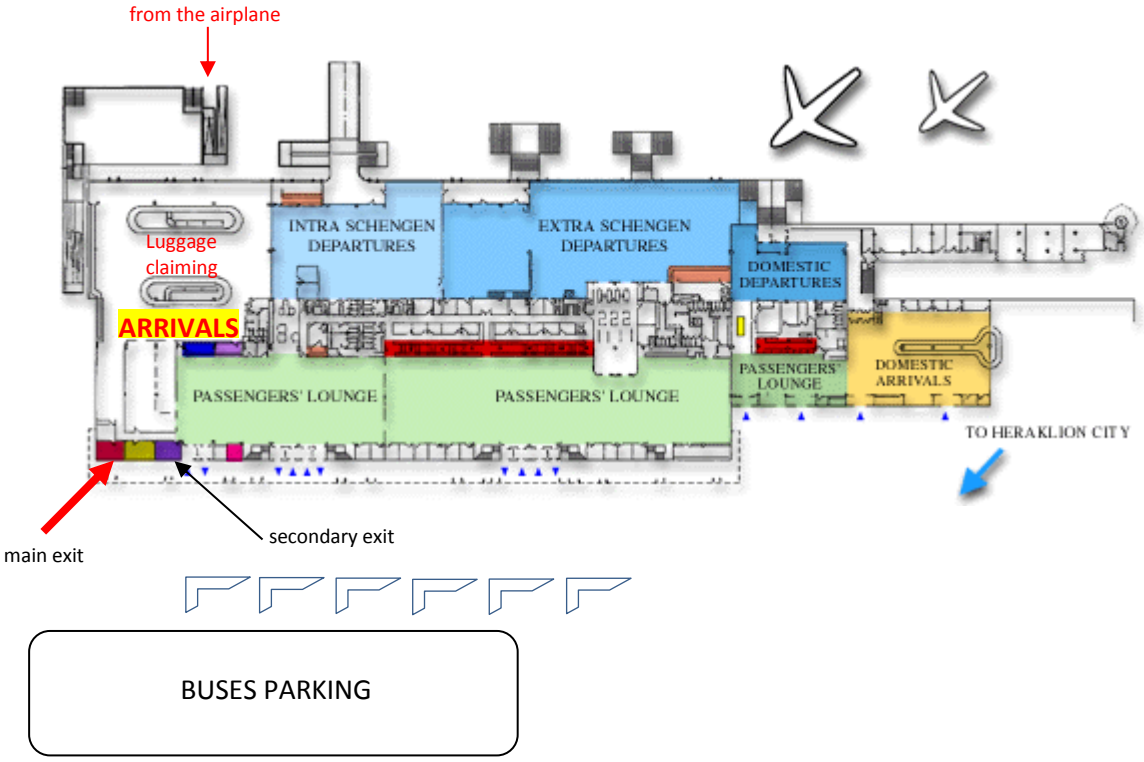
- Last but not least, unless you are unlucky, weather should be perfect as usual in early May; warm and sunny, even tempting for a swim. Check the weather and bring you swimsuit!

We are all looking forward for a very interesting conference!

The organizers,

Elena Seiradake, Rob Meijers, Rüdiger Klein, Nektarios Tavernarakis, Daniel Choquet

Transfers Meeting Point



Public Transportation

<u>From Heraklion to Fodele – Hotel Bus Station (daily):</u>

05:15 06:30 07:30 08:30 09:30 10:30 11:30 12:30 13:30*
14:30 15:30 16:30 17:30 18:30 19:30 20:30 21:45

*Stops outside the hotel reception

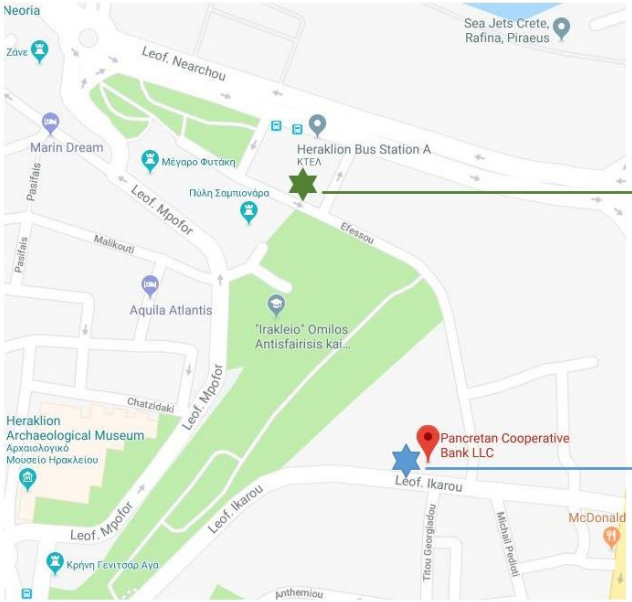
HERAKLION CITY MAP

Here is where you catch the (green) bus to Chania. You should ask the driver to stop to Fodele Beach Hotel. You will have to walk about 300 meters to reach the hotel from the bus stop.

Price per way: ~ 3,00 Euros.

TAXI terminals
Airport to the hotel: around 45 Euro.

1. Tourist Police
2. Police
3. Traffic Police
4. Telephone Office
5. Loggia - Town Hall
6. Ntl Tourist Organization
7. Daskalogianni Square
8. Post Office
9. Natural History Museum
10. Valide tzami
11. Archaelogical Museum
12. St. Ekaterini Museum
13. Eleftherias Square
14. Grave of N. Kazantzakis
15. Morozini Fountain
16. Old Venetian Harbour
17. Open Market
18. Koules Venetian Castle
19. St. Marcus Church
20. St. Titus Church
21. St. Minas Church
22. El-Greco Park



Fodele Beach and Water Park Holiday Resort

All Inclusive Description

Food & Beverage Services

Main Restaurant

All meals are served in a buffet style

- **Early Breakfast**: (05:00-07:00) Main Restaurant available upon request one day in advance at reception.
- **Continental Breakfast** (07:00-07:30) Main Restaurant "Amadeus"
- **Full Buffet Breakfast** (07:30-10:00) Main Restaurant "Amadeus"
- **Late Continental Breakfast** (10:00-11:00) at Snack Bar "Margherita"
- **Lunch Buffet + Show Cooking** (12:30-14:30) Main Restaurant "Amadeus"
- **Children Dinner** (from 01/07 until 31/08, upon arrangement with the chief animator)
- **Dinner Buffet + Show Cooking** (18:30-21:30) Main Restaurant "Amadeus"
- **Late Dinner** (21:30-23:00) Light Buffet – Snacks ,Main Restaurant "Amadeus"
- **Lunch Baskets**: available upon request at reception one day in advance until 19:00.
- **Greek Night**: Once a week in our Main Restaurant "Amadeus" (music & dance in the hotel)
- **4 theme buffets in 2 weeks stay** (Greek, Asian, Mediterranean and International , in our Main Restaurant "Amadeus"

Drinks, during meals in main restaurant: water, soft drinks, juices, local beer & local wine.

A La Carte Restaurants* (19:00 - 21:30) supplement required

1. **Cretan Restaurant *Elia*** (Cretan cuisine)
2. **International Restaurant *Ambrosia*** (International Cuisine)

Accompanied by water, soft drinks, juices, local beer & local wine.

**upon reservation one day in advance at the Main Restaurant.*

Snacks Outlets

A. *Margarita Snack* Bar at the main swimming pool (10:00 -18:00).
B. *Windmill Snack* Bar* at the Hotel's Water Park open on specific hours
C. *After Dark* Snacks in the Main Restaurant (21:30 -23:00).
Accompanied by water, soft drinks, juices, local beer & local wine.
** Open air, weather permitting*

Bars

1. ***Belvedere Cocktail* Bar** at the Hotel's lobby, self service. Belvedere Coctail Bar is open from17:30 -01:00.All inclusive is valid though till 23:00.
2. Offering a big variety of International and Local Alcoholic Drinks, Cocktails, Soft drinks, Juices, Aperitifs, Local Beer, House Wine and Coffee.
3. ***Starfish Beach* Bar*** at the beach, self service (10:00 -18:00). Soft Drinks, Juices, Aperitifs, Local Beer, House Wine, Filter Coffee and Light Snacks.
4. ***Starlight* Bar*** at Hotel main plaza, self service. Starlight Bar is open from 17:30-24:00. All Inclusive is valid till 23:00. Offering a big variety of International and Local Alcoholic Drinks, Soft drinks, Juices, Aperitifs, Local Beer, House Wine and Coffee.

**open air, weather permitting.*

Sports Activities*

- **Floodlit Tennis Court** 08:00 – 20:00 (One hour a day/reservation required one day in advance / free equipment)
- **Mini Golf**: please contact our reception desk
- **Water Park**: with 7 slides and 6 Pools
- **Table Tennis**: just outside the snack bar
- **Mini Football (on the beach):** Please contact our animation team.
- **Basketball court**
- **Beach Volley**
- **Archery**
- **Boccia**

****There might be a time limit in the use of the sports facilities and equipment.***

Animation - Entertainment

Day & Evening Animation programme six days a week, for more details please check the information board.

Water polo, Darts, Gymnastics, Aerobics, Aqua Gym, Evening Shows, Quiz, Games , ance competitions, Bingo, Various tournaments, Mini Club 4-12 years old, Mini Disco (20:30 -21:30, 6 days a week)

Beach Facilities (Sandy Beach) 10:00 - 18:00

Sunbeds and umbrellas, Showers – Changing cabins – WC, Lifeguard on duty 1st June – 30th September

Water Sports

Pedaloes, Canoe, Wind surfing, Water Skiing, Scuba diving , Diving lessons, Banana

HOTEL PLAN


1 MAIN ENTRANCE
2 MAIN BUILDING ENTRANCE
3 RECEPTION
4 MAIN BAR
5 MAIN RESTAURANT
6 INTERNET CORNER
7 A LA CARTE RESTAURANT "AMBROSIA"
8 SNACK BAR
9 BEACH BAR
10 DISCO
11 MINI CLUB
12 MEDICAL CENTER
13 FITNESS ROOM (GYM)
14 SAUNA
15. MAIN SWIMMING POOL
16 HEATED SWIMMING POOL
17 PLAZZA
18 STAR LIGHT BAR
19 SWIMMING POOL
20 MINI GOLF
21 TENNIS COURTS
22 BASKET BALL COURT
23 MINI MARKET
24 HAIRDRESSING SALON
25 RENT A CAR
26 BEACH
27 SEA SPORTS
28 AMPHITHEATRE
29 LUGGAGE ROOM
30 PARKING
31 ARCHERY
32 BEACH SOCCER
33 BEACH VOLLEY
34 GAMES ROOM
35 CONFERENCE ROOM
36 DIVING CENTER
37 ATM
38 WATERPARK
39 SNACK BAR "WINDMILL"
40 BOCCIA
41 A LA CARTE RESTAURANT
FODELE BEACH HOLIDAYS RESORT
P.O.BOX 1354
GR - 71500 HERAKLION
CRETE - GREECE
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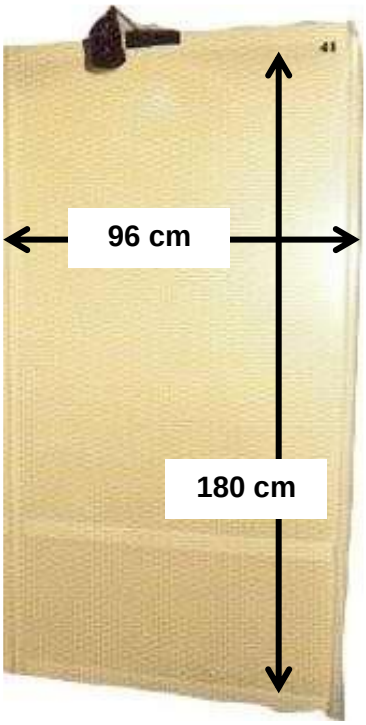
FODELE BEACH
HOTEL PLAN

POSTER PRESENTATION



✓ Each author will have a board space of (HxW) 180 cm x 96 cm (5ft 10in x 3ft 2in), on which to mount the poster. The poster should be designed to summarize current research in graphic forms. Presentations should be self-explanatory so that the author is free to supplement and discuss particular points. For easy identification, provide a poster heading, listing its title and author(s), identical to that on the official program.

✓ The poster board **(PORTRAIT ORIENTATION)** is double-sided with one presentation on each side. You will find your number on the poster board. The boards will be arranged in numerical order outside the conference hall.

✓ Poster materials may be mounted on thin poster paper or cardboard and attached to the poster board with the material provided by the organizers.

✓ **DO NOT USE PUSH-PINS OR GLUE** (materials for attaching illustrations will be available at the help desk inside the poster room).

✓ **DO NOT PAINT OR WRITE ON THE BOARD**

✓ Do not mount your poster on heavy or thick backing, as it may be difficult to fasten to the board. If you require assistance with mounting or removing your poster, there will be assistants inside the room.

✓ Each author is responsible for assembly and removal of his/her own presentation.

✓ Please remove your poster promptly. Materials left on the poster boards after the removal deadline will be taken down. The organizers or the hotel staff has no responsibility for materials that may be lost or damaged.

✓ The poster sessions have a designated time in which the poster presenters are requested to be available at their poster to discuss their research with the meeting attendees.

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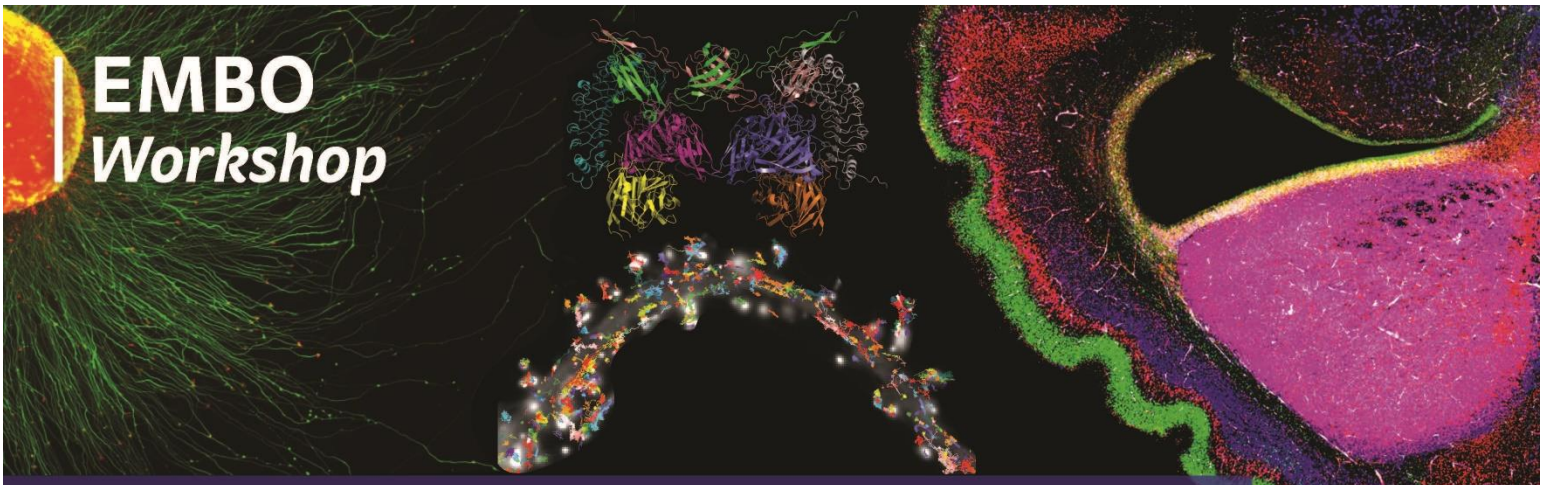

EMBO Workshop

Molecular neurobiology

08 – 12 May 2018 | Crete, Greece

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Application and Abstract submission deadline
31 January 2018

Registration fee single/shared room:

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Academic.....984/837 EUR
Industry.....1437/1287 EUR

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