CNB Newsletter 4/2018

UNIVERSITÄT BERN

CLINICAL NEUROSCIENCE BERN

Dear CNB members,

With the CNB Newsletter, we would like to inform you about upcoming CNB events and ongoing projects. This edition includes an interview with the first candidate of the newly established PhD track in Clinical Sciences as well as a review of the past Brainweek Bern.

We are also pleased to introduce the research groups of Prof. Smita Saxena and Prof. Pascal Escher.

We hope you enjoy reading the April 2018 edition.

Prof. Dr. Sebastian Walther
Vice-President CNB

① PhD in Health Sciences (Clinical Sciences)

Interview with PhD candidate Johannes Kaesmacher

Johannes Kaesmacher is the first candidate officially enrolled in the new PhD program in Clinical Sciences, which was recently established by the Graduate School for Health Sciences in collaboration with the CNB. His project will be affiliated with the Department of Neurology (Thesis advisor: U. Fischer) and the Institute of Diagnostic and Interventional Neuroradiology (Co-referee: J. Gralla) and addresses contemporary endovascular stroke treatment. We met Johannes for a short interview and he shared his first experiences and further expectations with us.

Where do you see the benefits of the new program compared to a conventional MD PhD?

Johannes Kaesmacher: In a conventional MD PhD program, the propaedeutic studies are usually entered parallel to the Medical Master studies and the thesis is conducted right after the final medical examination. While I agree that this is a valid and reasonable concept for life sciences, I think that a doctoral program in clinical research should mainly be offered to medical doctors who already have engaged in clinical work more consistently. When conducting clinical research, I think it is necessary to fully understand unresolved clinical questions and clinical dilemmas, which need to be assessed in future trials. Moreover, I support the concept of the PhD in Clinical Sciences as it allows doctors, who found interest in clinical research at a later stage in their career (e.g. during their first years after the board exam), to still enter the track of medical academia.

What is the topic of your research project and how does it link to your tasks in the clinic?

My research centers on the value of intravenous thrombolysis in the current era of thrombectomy. Several randomized controlled studies have consistently shown

that mechanical thrombectomy improves the outcome of acute ischemic stroke patients when added to best medical care. However, whether intravenous thrombolysis with tissue-type plasminogen activator prior to the start of mechanical thrombectomy adds additional benefit is still uncertain. Due to the design of mentioned trials, evaluating intravenous thrombolysis plus mechanical thrombectomy versus intravenous thrombolysis only, the additional effect of intravenous thrombolysis before mechanical thrombectomy could not be elucidated. To account for the lack of evidence regarding this important clinical question, a randomized controlled trial, organized in Bern, is currently taking place. I think that the research topic harbors close connection to clinical practice as the outcome of this trial is likely to directly affect current clinical practice and will have a major impact on the organization of acute stroke patient care. In my clinical practice, I got involved in stroke imaging and treatment decisions on a regular basis. Indications for medical or interventional treatment are highly reliant on exact imaging interpretation and the importance of imaging will most likely continue to grow in the imminent era of personalized medicine.

How do you plan to cope with the double burden: Involvement in the clinic and in research?
I share the opinion that profound research training is time-consuming. Therefore, I have tried to split the protected research time to large clusters of 100% research time (12 months each). This time allows me to have enough time for establishing research protocols for prospective studies or to get involved in the initiation phase of a large multi-center randomized controlled trial. As the maintenance of such project is usually less time consuming, I think these tasks may also be handled during periods of full engagement in daily clinical routine.

What are you especially looking forward to?
I am particularly looking forward to the CAS Clinical Research Course (https://www.cas-clinicalresearch.ch/). This course covers a broad area of epidemiological and statistical training. It ranges from the basic of epidemiological concepts and study designs to applied Bayesian Statistics in medical research and training regarding the conduct of meta-analysis and systematic literature reviews. Moreover, development and validation of prognostic models and the assessment of its quality will be covered. I hope that participation in this course will allow me to formulate adequate research hypothesis in the near future, to choose appropriate study designs and to draw reasonable conclusions from the results of such studies, respectively.

If you have any further questions regarding the application process or want to learn from his experiences in the program so far, please contact Johannes Kaesmacher by email:

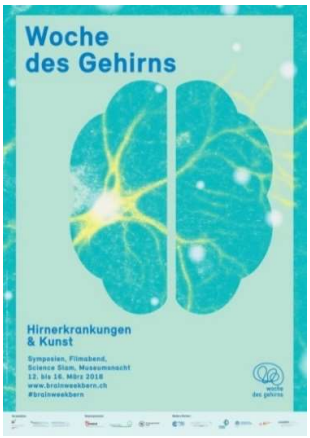
johannes.kaesmacher@insel.ch

② Review: Brainweek Bern 2018

We are looking back on another successful Brainweek with various events relating to the overall topic *Hirnerkrankungen & Kunst*. Evening symposia on sleep, brain injuries and cerebralparesis took place. Further, we realized a movie night on schizophrenia, the CNB Science Slam and contributed to Friday's Museumsnacht in the Psychiatrie-Museum Bern. We are pleased that all evenings were very well-frequented and are especially happy that the second edition of the CNB Science Slam was of great success. We again recorded a high number of participants and a lot of networking and (scientific-) exchange took place during this evening. Thank you all for attending!
A special thank goes to all presenters for their creative, well-prepared and entertaining contributions. It was a pleasure to watch your performances.
In the end, most votes were obtained for the contribution of Giuseppe Zito from the Neuoimaging Cluster. Congratulations!

We would further like to congratulate Prof. Sebastian Walther and his team for being awarded the Hirnliga Forschungspreis 2018 (CHF 20'000) for their work on nonverbal communication in Schizophrenia. The award ceremony took place during the symposia *Sleep in Art and Science* of this year's Brainweek.
Please find below some impressions of the evenings.

The next Brainweek Bern will take place from the 11th to the 15th of March 2019. The preliminary program and further information as well as all programs of past events can be found on the Brainweek homepage: www.brainweekbern.ch



Giuseppe Zito - Winner of CNB Science Slam 2018
CNB Science Slam, 14. March 2018

Award Ceremony Forschungspreis 2018 Hirnliga
Symposium Sleep in Art and Science, 12. March 2018


Networking @
CNB Science Slam, 14. March 2018

Symposium Sleep in Art and Science, 12. March 2018


Symposium Brain injuries, 13. March 2018


Symposium Cerebralparesis, 15. March 2018


Movie Night on Schizophrenia, 14. March 2018


Museumsnacht Psychiatrie-Museum Bern, 16. March 2018

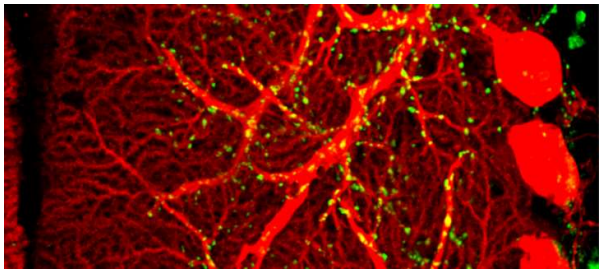
③ Selected Research Groups

Prof. Dr. Smita Saxena

Neurodegenerative Disease Laboratory
Center for Experimental Neurology
Dept. of Neurology, Inselspital

Neurodegenerative diseases (NDs) are debilitating conditions that stem from the selective dysfunction and loss of neurons. In NDs such as Parkinson's disease (PD), Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS) and Spinocerebellar ataxia type 1 (SCA1), vulnerable neuronal populations are lost in specific regions of the CNS. A commonality among NDs is that symptoms typically manifest in the fifth or sixth decade of life. There is presently no cure or therapeutic intervention that can reverse or halt the progression of NDs. In select cases of NDs, such as ALS, current therapy acts to prolong life for a brief period (<6 months). A major hindrance to the development of therapies for NDs is that the pathomechanisms underlying these diseases are not well understood. A common finding in NDs, is that neuronal dysfunction and pathology often significantly precedes overt clinical symptoms.

Research efforts in our lab are primarily focused on understanding pathomechanisms that drive neurodegeneration from circuits to molecular and cellular pathology. In particular, we are interested in examining how changes in cerebellar circuitry modulate or initiate degeneration in SCA1, a fatal cerebellar ND that results in progressive ataxia, dysarthria and the degeneration of cerebellar neurons. Employing conditional mouse models, proteomics, transcriptomics, pharmacogenetics, connectomics, in vivo calcium imaging, and behavioral readouts, we are deciphering how early alteration in the cerebellar circuitry governs disease onset and progression. Another major area of research is in generating human iPSC-derived *in vitro* models of ALS, a fatal motor neuron disease that results in paralysis and death typically within 4-5 years of disease onset. Finding efficacious therapy for ALS, most cases of which are sporadic and genetically heterogeneous, has been hampered by the lack of relevant pre-clinical models. Our aim is to derive human motor neurons from skin fibroblasts of both familial and sporadic ALS as well as control patients using cellular reprogramming. This undertaking will provide us with a relevant ALS platform to screen small molecule compound library and identify molecules that are able to reduce cellular and axonal-stress and protect motor neurons from degeneration.



Confocal image showing Purkinje neurons (red) and excitatory climbing fiber inputs (green) onto Purkinje cell dendrites.

Representative publications:

- Ruegsegger C., Stucki, D., Steiner, S., Angliker, N., Radecke, J., Keller E., Zuber B., Rüegg, M.A., Saxena S. (2016). Impaired mTORC1-Dependent Expression of Homer-3 Influences SCA1 Pathophysiology. Neuron, 89(1):129-146.
- Ruegsegger C., Maharjan N., Goswami A., Filézac de L'Etang A., Weis J., Troost D., Heller M., Gut H., Saxena S. (2016).Aberrant association of misfolded SOD1 with Na(+)/K(+)ATPase-α3 impairs its activity and contributes to motor neuron vulnerability in ALS. Acta Neuropathol., 131(3):427-51.
- Filézac de L'Etang A., Maharjan N., Cordeiro Braña, M., Ruegsegger C., Rehmann R., Goswami A., Roos A., Troost D., Schneider B.L., Weis J., Saxena S. (2015). Marinesco-Sjögren syndrome protein SIL1 regulates motor neuron subtype-selective ER stress in ALS. Nature neuroscience, 18(2):227-238.

For more information, please contact:

Prof. Dr. Smita Saxena
smita.saxena@dbmr.unibe.ch
Freiburgstrasse 14, 3010 Bern
+41 31 632 13 47

Prof. Dr. Pascal Escher

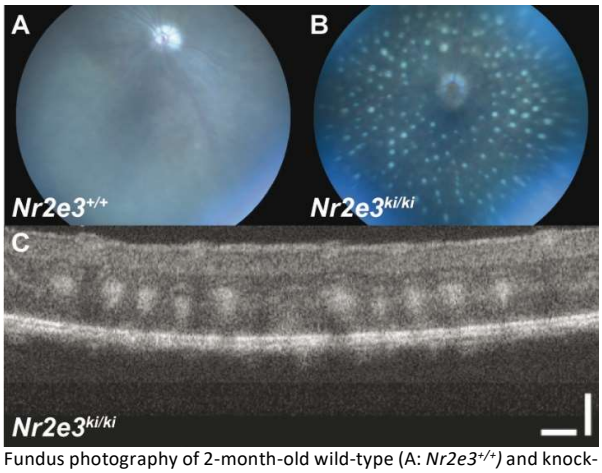
Ophthalmogenetics Group
Universitätsklinik für Augenheilkunde,
Inselspital

The vertebrate retina is a model system for neuronal development. Vertebrate retinal histogenesis is characterized by an evolutionarily-conserved sequential birth of retinal cell classes with a substantial temporal overlap in the time windows for the generation of the different retinal neurons and glial cell from the initial pool of retinal progenitor cells. A central question in retinal development is therefore to understand what drives a retinal progenitor cell, unrestricted in cell fate, to undergo mitosis, and then the post-mitotic precursor cells to undergo terminal differentiation towards a specific cell fate.

Photoreceptors are the sensory neurons of the retina, capable to transform light into nerve impulses. There are two kinds of photoreceptors, bright light- and color-sensitive cones and dim light-sensitive rods. In the mouse retina, cone photoreceptors sensitive to blue light ('blue cones') are the first photoreceptors to be differentiated during embryonic development. Rod precursors are generated over an extended period of time, starting at embryonic day 13 in the central retina, peaking around birth and ongoing until postnatal day 6. We study the transcriptional network regulating development, terminal differentiation and maintenance of cone and rod photoreceptors. Whereas members of the homeobox-containing transcription factor family are essential for initial ocular and retinal development (Pax6, Otx2, Crx), several members of the nuclear hormone receptor family are involved in the terminal differentiation of photoreceptors. Nuclear receptors are a large family of ligand-activated transcription factors, acting as molecular switches in development, metabolism, homeostasis, etc. For instance, the photoreceptor-specific nuclear receptor NR2E3 is necessary to specify proper rod precursor development and to suppress cone-specific gene expression in rods. Specifically, in the absence of NR2E3, early-born rod precursor cells are committed to 'blue' cone cell fate resulting in an about 2-fold increase in 'blue' cones, and the rods are non-functional hybrid photoreceptors, expressing both rod- and cone-specific genes. In human, recessive mutations in *NR2E3* cause enhanced S-cone sensitivity syndrome (ESCS) also called Goldmann-Favre syndrome: 'blue' cones hyperproliferate forming whorls and rosettes in the outer retina, whereas the rods express both rod- and cone-specific genes and are therefore non-functional. Consequently, patients show a pathognomonic increase in sensitivity to blue light and are night blind. We also identified a unique dominant *NR2E3* mutation causing a more severe retinal degeneration called *retinitis pigmentosa*, affecting first rods, and, later in life, cone photoreceptors.

To understand the molecular mechanisms underlying the high variability in clinical phenotypes observed in recessive and dominant *NR2E3*-linked retinal degenerations, we resort to structural and functional analyses in vitro and in cellular models, and generated several genetically modified mouse models. We identified so far absence of NR2E3 protein, absence of binding of NR2E3 to DNA sequences regulating photoreceptor-specific gene expression, impaired dimerization of the NR2E3 protein and a trans-repressing effect of NR2E3 towards CRX as potential disease mechanisms in *NR2E3*-linked retinal degenerations.

Additionally, the Ophthalmogenetics group contributes to the molecular diagnostic of rare eye diseases.



Fundus photography of 2-month-old wild-type (A: *Nr2e3*$^{+/+}$) and knock-in mice harboring a patient-specific *NR2E3* mutation (B: *Nr2e3*$^{ki/ki}$). The white spots visible by fundus photography colocalize with the rosettes and whorls located in the outer retina of *Nr2e3*$^{ki/ki}$ mice, as imaged by optical coherence tomography (C).

Selected recent publications:

- Olivares AM, Han Y, Soto D, Flattery K, Marini J, Molemma N, Haider A, Escher P, DeAngelis MM and Haider NB. The nuclear hormone receptor gene Nr2c1 (Tr2) is a critical regulator of early retina cell patterning, Dev. Biol., 429:343-355, 2017.
- Boulling A and Escher P. Coupling ex vivo electroporation of mouse retinas and luciferase

reporter assays to assess rod-specific promoter activity, Exp. Eye Res., 148:79-82, 2016.
- Escher P, Vaclavik V, Munier FL and Tran HV. Presence of a triple concentric autofluorescence ring in NR2E3-p.G56R-linked autosomal dominant retinitis pigmentosa (ADRP), Invest. Ophthalmol. Vis. Sci., 57:2001-2002, 2016.
- von Alpen D, Tran HV, Guex N, Venturini G, Munier FL, Schorderet DF, Haider NB and Escher P. Differential dimerization of variants linked to enhanced S-cone sensitivity syndrome (ESCS) located in the NR2E3 ligand-binding domain, Hum. Mutat., 36:599-610, 2015.

For more information, please contact:

Prof. Dr. Pascal Escher
pascal.escher@dbmr.unibe.ch
Freiburgstrasse 14, 3010 Bern
+41 31 632 67 33

④ Open calls

HORIZON 2020: Systems approaches for the discovery of combinatorial therapies for complex disorders

First-Stage Submission Deadline: 2 October 2018

Link to Horizon 2020

Scope:
- Should aim to understand at systems level the pathophysiology of a disorder in groups of patients responding well or poorly to particular therapies
- Further develop combinatorial therapies tailored to the needs of individuals or stratified patient groups.
- Focusing on already available and/or authorized therapeutic interventions or currently in late stages of developments
- Integrate multidimensional and longitudinal patient data using systems approaches

Expected impact:
- New concepts of combinatorial therapies for complex disorders tailored to the needs of individuals or stratified patient groups
- Improved efficacy and take-up in the clinical setting
- Enable the development of personalized medicine
- Increased research & innovation opportunities in this industry intensive field, particularly for SMEs

Eligibility: ≥3 partner from 3 different EU Member States/Associated Countries

Duration: Typically 3-5 years

Budget: EUR 4 - 6 million

⑤ Upcoming events

25. May 2018	CNB Annual Meeting 2018 "Big Data and Big Models in Clinical Neuroscience"
11. - 15. March 2019	Brainweek Bern 2019

CNB Annual Meeting 2018

The next CNB Annual Meeting will take place on the 25th of May 2018 in the Auditorium Ettore Rossi.

The overall topic is *Big Data and Big Models in Clinical Neuroscience*. We are delighted that Prof. Viktor Jirsa (Aix Marseille Université) and Prof. Bjoern Menze (Technische Universität München) accepted to give a key note.

You are kindly asked to register and submit abstracts (free contribution) on www.conftool.com/cnbam2018.

Deadline is the 22nd of April 2018.

Further information can be found on the CNB homepage (www.neuroscience.unibe.ch).

For any inquiries, please contact:

Romina Theiler
romina.theiler@insel.ch
+41 31 632 55 94