CNB Newsletter
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CLINICAL NEUROSCIENCE BERN

Dear CNB members,

With the CNB Newsletter, we intend to inform you about upcoming CNB events, ongoing projects and give insights into the research topics of selected CNB members. In this edition we look back on the Brainweek 2021 and are looking forward to the Annual Meeting 2021.
We are pleased to introduce the research group of PD Dr. Anke Salmen and PD Dr. Robert Hoepner, as well as the research group of Prof. Dr. phil. nat. Sonja Kleinlogel.
Please also note that we are updating and upgrading the CNB-Website, so please feel free to contact Ms. Noémi Allet (noemi.allet@artorg.unibe.ch) if you want to make changes on your research group-site (e.g. add photos, videos, members etc.).

We hope you enjoy reading the May 2021 edition.

Prof. Dr. Sebastian Walther
President CNB

① 23th Brainweek Bern

Monday, 15th of March 2021 – Thursday, 18 th of March 2021

Monday, 15th of March 2021, 18:15
"Do men and women learn differently?"
Prof. Dr. Elsbeth Stern (behavioral scientist)
Moderation: Prof. Dr. med. Roland Wiest
Through Prof. Dr. Stern's lecture we learned much about differences between the sexes. Interestingly, education seems to benefit specific gender stereotypes but there are ways to enhance fairness in children's education. On the topic of gender Nonbinary many exciting questions came up and Prof. Stern informed how to support people psychologically. Her exciting lecture and the following discussion encouraged further thinking and raised interest in the topic.

Tuesday, 16th of March 2021, 18:15
"Anxiety disorders - in times of the pandemic"
Prof. Dr. med. Katharina Stegmayer (Physician, University Psychiatric Services Bern, UPD)
Moderation: Prof. Dr. med. Sebastian Walther
In Prof. Dr. med. Stegmayer's lecture we learned how fears arise and why they might also be useful. Furthermore, in the informative and exciting lecture Prof. Stegmayer elaborated on the role of epigenetics and that psychotherapy aims at confronting feara. In addition to this psychotherapy, sports, such as yoga or jogging, but also sufficient sleep are beneficial. Both the moderator Sebastian Walther and Katharina Stegmayer received numerous questions and provided multiple tips and points of contact for those affected or their relatives.

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Wednesday, 17th of March 2021, 18:15
"Introduction to the Rosetta Space Mission"
Prof. em. Dr. Kathrin Altwegg (Astrophysicist, University of Bern)
Moderation: Prof. Dr. med. vet. Daniela Schweizer
Mrs. Altwegg took us along on the Rosetta mission and explained how data and samples from the comet were collected. It was a very exciting and informative lecture, even for non-physicists. The Q & A session was very lively, Mrs. Altwegg answered not only physical but also very personal questions, e.g. whether one can believe in God as an astrophysicist and how it was for her to work together with theologians and philosophers. She said: "We physicists ask how, but philosophers and theologians ask why. I can explain to you as a physicist how the earth came into being, but you will not find the answer to the why in physics, but in philosophy and theology. These fields are not mutually exclusive, they complement each other."
Afterwards, a feature film was shown, telling the story of three women who changed the world.

Thursday, 18th of March 2021, 18:15
Panel discussion "Life after a stroke"
Input presentation: PD Dr. med. Dr. phil. Arseny Sokolov
Panel discussion: Prof. Dr. med. Urs Fischer, Dr. phil. Martina Studer, Prof. Dr. med. René Müri
Moderation: Prof. Dr. Tobias Nef

On Thursday 60 spectators watched the exciting input lecture on the topic of cerebral stroke and its consequences. Afterwards, a very lively discussion took place, with many options to ask questions and receive valuable answers by the experts. The audience was very diverse, with questions coming from affected people and relatives, but also from students and medical professionals.

The next Brainweek Bern will take place from the 14th to the 17th of March 2022. The program and further informations will be published on the Brainweek homepage: www.brainweekbern.ch. You also find the programs and impressions from past events on that site.

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② Selected Research Groups

PD Dr. med. Anke Salmen

PD Dr. med. Robert Hoepner

Translational Neuroimmunology and Data Science
Dept. of Neurology and DBMR, Inselspital, Bern
University Hospital, University of Bern

Our research is dedicated to the investigation of neuroimmunological disorders of the central nervous system (CNS) combining clinical and translational neuroscience. Our group focuses on the investigation of CNS inflammatory and demyelinating conditions, Multiple Sclerosis (MS) being the most common, but antibody-driven CNS autoimmunity such as Neuromyelitis optica spectrum disorders (NMOSD) representing an equally important research field. Further, new disease entities have recently been characterized by specific antibodies such as Anti-NMDA- and other autoimmune encephalitides and lastly also GFAP-astrocytopathy, highlighting the need for a well-structured cohort including clinical and paraclinical phenotype description.
The overarching goal is the optimized treatment of our patients via a better understanding of the diseases, involved pathomechanisms and discovery of novel treatment strategies, but also a better understanding of adverse effects and treatment or prevention thereof.
To this end, we conduct direct patient-related research based on prospective and retrospective studies of our neuroimmunological patient cohort, but also using novel approaches such as available open source databases, e.g. the FDA Adverse Event Reporting System (FAERS). These data sources and settings require a deep understanding of advantages and potential pitfalls of the used resources.

With these approaches, we investigate adverse effects, safety and efficacy of MS immunotherapies, potential predictors of treatment effects and disease course, modifiers of the disease course, e.g. vitamin D, and of course current topics such as the COVID pandemic in relation to MS. In addition, we clinically and preclinically investigate one of the "novel" disease entities – MOG-IgG-associated disorders (MOG-AD) – in particular.
Based within the ZEN, our group conducts basic translational research with the focus of different model systems of antibody-mediated CNS disorders and visual outcomes in these models in a close collaboration with the Ophthalmology, Prof. Volker Enzmann, novel potential treatment options and the optimization of treatment, especially the investigation of steroid resistance in MS relapse treatment.
The first translational project that we would like to describe in more detail thus covers experimental models of antibody-driven CNS autoimmunity with a focus on visual outcomes. With advancements in autoantibody detection methods and the identification of antibodies of pathogenic relevance, a better differentiation of MS from autoantibody-mediated demyelinating CNS syndromes such as NMOSD and MOG-AD has become possible. Still, the distinct features of their immunopathology are insufficiently understood.
With visual impairment representing a major symptom of MS, NMOSD and MOG-EM severely affecting the patient's daily living and quality of life, the better understanding of its pathophysiology is crucial. Moreover, the anterior visual system serves as a very suitable model to assess pathophysiological features of demyelinating CNS disorders as it is an easily accessible neuronal structure, known to be involved in different entities. This structure can be measured on a functional and structural level in a standardized way, not only in the human disease, but also in animal models. In particular, neuronal degeneration is possibly reflected in retinal degeneration with axonal and ganglion cell loss and measureable via optical coherence tomography (OCT). In a murine experimental model system mimicking MOG-AD, we successfully demonstrated a positive treatment effect of a novel monoclonal antibody directed against the neonatal Fc receptor (FcRn) on both spinal cord and visual disease

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manifestations (manuscript in preparation, data presented at EAN 2019, funded by UCB Pharma). This treatment approach is currently being transferred into a clinical phase 3 study.

The second project focuses on the understanding of steroid signaling in people with neuroimmunological diseases. Glucocorticosteroids (GC) are the mainstay of relapse treatment, however, approximately one third of our patients do not fully recover, leading to an increased disability. We have recently demonstrated that vitamin D deficiency contributes to GC resistance, as it is associated with a downregulation of the GC receptor. Findings were consistent in a mouse model of MS and in human T cells, thus providing a possible target for increasing the efficacy of GC therapy in neuroimmunological diseases. An interplay between vitamin D and GC and their respective receptors has been demonstrated which is currently further investigated, taking advantage of mouse models with T cell specific functional depletion of these receptors.

As a last example, we investigate sex differences in neuroimmunological diseases again combining clinical data, such as a slightly decreased efficacy of sphingosine-1 phosphate (S1P-) inhibitors in young female MS patients, and basic science. We will model different hormonal and S1P situations in the mouse model to study sex differences in more depth aiming to understand how we could improve respective treatments, but also to tackle unmet needs in the field of sex differences in human medicine.

Our clinical, research and study team luckily consists of highly enthusiastic colleagues from different backgrounds, being clinicians, nurses, study coordinators (with a background in biology and pharmacy) and basic researchers offering a broad basis of expertise. We therefore would like to take this opportunity to thank the whole team in the clinics, lab and study department. In addition to these valued colleagues, we also thank all our internal (Neuroradiology, IDSC, Ophthalmology, Psychiatry) and external partners (Swiss MS registry, German competence network MS, other international collaborators and labs).

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Recent publications:

- Diem L, Friedli C, Chan A, Salmen A, Hoepner R. Vaccine Hesitancy in Patients With Multiple Sclerosis - Preparing for the SARS-CoV-2 Vaccination Challenge. Neurol Neuroimmunol Neuroinflamm 2021;8:e991 doi:10.1212/NXI.0000000000000991

- Ostkamp P, Salmen A, Pignolet B, Görlich D, Andlauer TFM, Schulte-Mecklenbeck A, Gonzalez-Escamilla G, Bucciarelli F, Gennero I, Breuer J, Antony G, Schneider-Hohendorf T, Mykicki N, Bayas A, Then Bergh F, Bittner S, Hartung HP, Friese MA, Linker RA, Luessi F, Lehmann-Horn K, Mühlau M, Paul F, Stangel M, Tackenberg B, Tumani H, Warnke C, Weber F, Wildemann B, Zettl UK, Ziemann U, Müller-Myhsok B, Kümpfel T, Klotz L, Meuth SG, Zipp F, Hemmer B, Hohlfeld R, Brassat D, Gold R, Gross CC, Lukas C, Groppa S, Loser K, Wiendl H, Schwab N, and on behalf of the German Competence Network Multiple Sclerosis (KKNMS) and the BIONAT Network. Sunlight exposure exerts immunomodulatory effects to reduce multiple sclerosis severity. PNAS 2021 Vol. 118 No. 1 e2018457118; doi:10.1073/pnas.2018457118

- Veselaj K, Kamber N, Briner M, Friedli C, Diem L, Guse K, Miclea A, Wiest R, Wagner F, Grabe H, Abegg M, Horn MP, Bigi S, Chan A, Hoepner R and Salmen A. Evaluation of diagnostic criteria and red flags of myelin oligodendrocyte glycoprotein encephalomyelitis in a clinical routine cohort. CNS Neurosci Ther. 2020;00:1–13. doi: 10.1111/cns.13461

- Bagnoud M, Briner M, Remlinger J, Meli I, Schuetz S, Pistor M, Salmen A, Chan A, Hoepner R. c-Jun N-Terminal Kinase as a Therapeutic Target in Experimental Autoimmune Encephalomyelitis Cells 2020, 9, 2154; doi:10.3390/cells9102154

- Vicini R, Brügger D, Abegg M, Salmen A, Grabe HM. Differences in morphology and visual function of myelin oligodendrocyte glycoprotein antibody and multiple sclerosis associated optic neuritis. J Neurol 2020 (online first), doi:10.1007/s00415-020-10097-x

- Abrahamyan S, Eberspächer B, Hoshi MM, Aly L, Luessi F, Groppa S, Klotz L, Meuth SG, Schroeder C, Grüter T, Tackenberg B, Paul F, Then-Bergh F, Kümpfel T, Weber F, Stangel M, Bayas A, Wildemann B, Heesen C, Zettl U, Warnke C, Antony G, Hessler N, Wiendl H, Bittner S, Hemmer B, Gold R, Salmen A and Ruprecht K. Complete Epstein-Barr Virus Seropositivity in a Large Cohort of Patients With Early Multiple Sclerosis. J Neurol Neurosurg Psychiatry 2020, doi: 10.1136/jnnp-2020-322941

- Gasperi C, Salmen A, Antony G, Bayas A, Heesen C, Kümpfel T, Linker RA, Paul F, Stangel M, Tackenberg B, Bergh FT, Warnke C, Weber F, Wiendl H, Wildemann B, Zettl UK, Ziemann U, Zipp F, Tumani H, Gold R, Hemmer B; German Competence Network of Multiple Sclerosis. Association of Intrathecal Immunoglobulin G Synthesis With Disability Worsening in Multiple Sclerosis. JAMA Neurol. 2019 Apr 29. doi:10.1001/jamaneurol.2019.0905.

- Hoepner R, Bagnoud M, Pistor M, Salmen A, Briner M, Synn H, Schrewe L, Guse K, Ahmadi F, Demir S, Laverick L, Gresle M, Worley P, Reichardt HM, Butzkueven H, Gold R, Metz I, Lühder F, Chan A. Vitamin D increases glucocorticoid efficacy via inhibition of mTORC1 in experimental models of multiple sclerosis. Acta Neuropathol. 2019 Apr 27. doi: 10.1007/s00401-019-02018-8.

- Miclea A, Salmen A, Zoehner GC, Panos CI, Briner M, Chan A, Evangelopoulos EM, Hoepner R. Age-dependent variation of female preponderance across different phenotypes of multiple sclerosis: a retrospective cross-sectional study. CNS Neurosci Ther. 2018; DOI: 10.1111/cns.13083.

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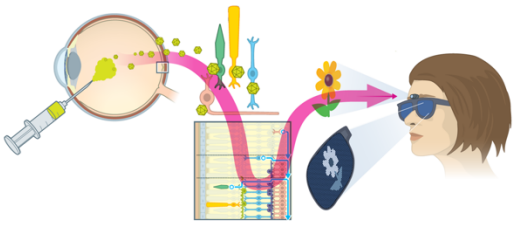
Prof. Dr. phil. nat. Sonja Kleinlogel

Translational Optogenetics
Institute of Physiology,
University of Bern

Optogenetics introduces light-sensitive proteins genetically into target cells to render them light controllable. The optogenetics technology uses engineered, non-pathogenic viruses as taxicabs for the optogenes. What sounds like science fiction has developed into a powerful state-of-the-art technique to analyze neuronal circuits, to precisely manipulate cellular activity by light and to restore lost function in pathologies. The Kleinlogel lab pursues the goal to take optogenetics to the next level, by engineering new powerful designer optogenetic tools as new optophamacologics. Our interests are highly interdisciplinary, strongly goal-oriented and focused on functional restoration using state-of-the-art genetic, molecular and cell biology techniques, including optogenetics, protein engineering, CRISPR/Cas gene editing and viral engineering combined with functional evaluation at the retinal and cortical levels by patch-clamp and extracellular electrophysiology (multi-electrode arrays, ERG and laminar probes) as well as with behavioral paradigms in mice.
We develop and apply novel optogenetic tools (including viral taxicabs and promoters) to decipher functional involvement of receptors and cells, equally in health and in pathologies. We work with cell lines, primary cells, ex vivo tissues (including human donor tissue) and mice (including own transgenic lines). Due to our translational interests, we closely collaborate with the Eye Clinic at the Inselspital and the DBMR though the regenerative neuroscience cluster and collaborations with Prof. Adamantidi's group (joint Velux grant).

The lab's recent focus lay on the retina and the restoration of vision, with dedicated translational research to move lab discoveries into a clinical optogenetic gene therapy. We have pioneered OptoGPCR optogenetic tool engineering and application, which are light-sensitive G-protein coupled receptors that make formidable pharmacological targets and allow hijacking of specific intracellular signaling pathways by light throughout the body. We are now part of an ERC Synergy consortium with colleagues from the Paul Scherrer Institute (G. Schertler), the University of Manchester (R. Lucas) and the Charité Berlin (P. Hegemann) to further develop and apply OptoGPCRs, highlighting their topicality. Our first OptoGPCR, Opto-mGluR6 was over the last years developed into a highly effective gene therapy to target the first interneurons of the retina, the bipolar cells, supplemented by synthetic cell-specific promoters and synthetic adeno-associated viral capsids engineered in our lab. As a whole, the designer cell-targeted gene therapy restores excellent visual capabilities in blind mice by restoring intricate signaling in the remaining retinal neuronal network. Arctos Medical (www.arctosmedical.com), a Spin-off company from the University of Bern, which I co-founded together with Walter Inäbnit (former CEO Haag-Streit Holding) and my husband Michiel van Wyk in 2012 under a grant from the Commission for Innovation and Technology (now InnoSuisse) currently develops the Opto-mGluR6 gene therapy with the ambitious goal to enter clinical trials in 2022 to treat blind patients and hopefully restore useful vision.



Currently we are investigating the quality of optogenetically restored vision at the cortical level and are highly interested in functional changes within retinal neurons to ultimately optimize the artificial vision restoration approach. We are also very keen to learn more about signal processing in the human retina. Further, we are studying the plasticity of the cortex during degeneration and following restoration and how this plasticity could be influenced to ultimately achieve higher quality of restored vision. We are also venturing out of the retina with designer OptoGPCRs to, for example, target heart and brain in collaborative efforts to understand and manipulate beta-adrenergic signaling in the failing heart or in the framework of chronic pain. At the engineering end we are aiming for complete bidirectional light control of OptoGPCRs and shifting activation wavelengths to the far red for deeper tissue penetration and improved orthogonal activation during imaging or multiplexed optogenetic approaches.

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Selected publications:

- van Wyk M, Pielecka-Fortuna J, Löwel S, Kleinlogel S. Restoring the ON Switch in Blind Retinas: Opto-mGluR6, a Next-Generation, Cell-Tailored Optogenetic Tool. PLoS Biol. 2015 May 7;13(5):e1002143. doi: 10.1371/journal.pbio.1002143. PMID: 25950461; PMCID: PMC4423780.

- van Wyk M, Kralik J, Stocker N, Kleinlogel S. Bipolar cell targeted optogenetic gene therapy restores virtually normal retinal signaling, spatial acuity and contrast vision in blind mice. submitted.

- Kleinlogel S, Vogl C, Jeschke M, Neef J, Moser T. Emerging approaches for restoration of hearing and vision. Physiol Rev. 100(4), 1467-1525 (2020).

- Hulliger EC, Hostettler SM, Kleinlogel S. Empowering Retinal Gene Therapy with a Specific Promoter for Human Rod and Cone ON-Bipolar Cells. Mol Ther Methods Clin Dev. 2020 Mar 13;17:505-519. doi: 10.1016/j.omtm.2020.03.003. PMID: 32258214; PMCID: PMC7114634.

- David A, Hulliger E, van Wyk M, Odenthal M, Buening H, Kleinlogel S. Evolution of recombinant adeno-associated viral vectors with favorable retinal penetration properties. Hum Gene Ther 29(12), A25 (2018).

- van Wyk M, Hulliger EC, Girod L, Ebneter A, Kleinlogel S. Present Molecular Limitations of ON-Bipolar-Cell Targeted Gene Therapy. Front Neurosci. 11:161 (2017).

- Kleinlogel S. Optogenetics for Vision Recovery: From Traditional to Designer Optogenetic Tools. In K. Appasani (ed.) Optogenetics: From Neuronal Function to Mapping and Disease Biology. Cambridge: Cambridge University Press. pp.327-355. (2017).

- Kleinlogel S. Optogenetic user's guide to Opto-GPCRs. Front Biosci (Landmark Ed). 21:794-805 (2016).

- Streit J, Kleinlogel S. Dynamic all-optical drug screening on cardiac voltage-gated ion channels. Sci Rep. 8(1):1153 (2018).

- Perny M, Muri L, Dawson H, Kleinlogel S. Chronic activation of the D156A point mutant of Channelrhodopsin-2 signals apoptotic cell death: the good and the bad. Cell Death Dis. 7(11):e2447 (2016).

- Kleinlogel S, Terpitz U, Legrum B, Gökbuget D, Boyden ES, Bamann C, Wood PG, Bamberg E. A gene-fusion strategy for stoichiometric and co-localized expression of light-gated membrane proteins. Nat Methods 8(12):1083-8 (2011).

- Kleinlogel S, Feldbauer K, Dempski RE, Fotis H, Wood PG, Bamann C, Bamberg E. Ultra light-sensitive and fast neuronal activation with the Ca^{2+}-permeable channelrhodopsin CatCh. Nat Neurosci. 4:513-8 (2011).

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③ Upcoming events

29. October 2021	Annual Meeting
14th-17th March 2022	Brainweek Bern

For any inquiries, please contact:

Noémi Allet

noemi.allet@artorg.unibe.ch