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CNB Newsletter 12 / 2022

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 17th Annual Meeting and are looking forward to the Brainweek 2023.
We are pleased to introduce the new members of the Executive Committee Prof. Dr. med. Mirjam Heldner and Prof. Dr. med. Philippe Schucht as well as the new research group of Tatiana Bremova-Ertl, MD, PhD.
Also note that we are updating and upgrading the CNB-Website, so please feel free to contact Ms. Alessia Carlucci (alessia.carlucci@unibe.ch) if you want to make changes on your research group-site (e.g. add photos, videos, members etc.).

Please send an updated list with all your Group-Members (name, position, contact-information) so that we can update the website.

We hope you enjoy reading the December 2022 edition.

Prof. Dr. Sebastian Walther
President CNB

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17th CNB Annual Meeting

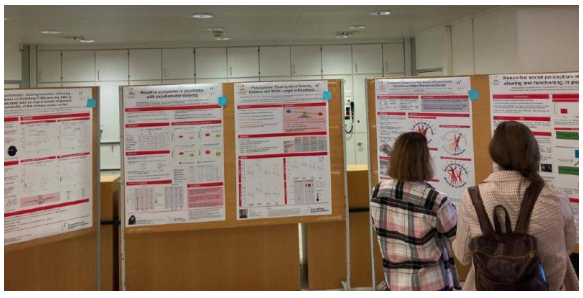
Friday, 9th of September, 9.00-17.15

This Year's Annual Meeting was held at the Inselspital, in the auditorium Ettore Rossi. The Welcome Address, held by the CNB president Sebastian Walther, was followed by the first Key-note Speaker Inti Zlobec, she introduced us to digital pathology. Prof. Zlobec gave exciting insights to computational approaches in pathology using machine learning and advanced image analysis. Her talk triggered a very active discussion. Afterwards, the four selected abstracts were presented by young investigators: Matthias Ertl, Kristina Berve, Kaizhen Li, and Mandy Müller.

The Key-note number 2 "Precision neurooncology" was held by Wolfgang Wick. He focused in his keynote lecture on genetic alterations in brain tumors that allow designing specific treatments for carriers of distinct genetic profiles. Much of this work includes disentangling the mechanism of tumor progression. Here, the application of genetically informed precision medicine improves the survival rates of patients.
The Poster-Session enjoyed lively discussion and a broad range of topics.

It was a fantastic showcase of the local neuroscience research in Bern. Finally, three poster awards were given:

- Chiffi Gabriele (Category: Basic research animal)
  Title: " Tick-borne encephalitis affects sleep-wake behavior and locomotion in infant rats"
- Wunderlin Marina (Category: Basic research human)
  Title: "Responsiveness to auditory stimulation during slow wave sleep predicts long-lasting increases in memory performance in older adults"
- Schumacher Rahel (Category: Clinical Research)
  Title: "Modality-modulated difficulties in flexible attention allocation after stroke".



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In the Afternoon the Parallel Symposia took place. Three symposia informed on “Non-invasive Brain Stimulation and Cognition”, gave us a look into “Neuro-Vision – overlapping topics of Ophthalmology & Neurology” and talked about “Artificial Intelligence for Brain Tumor Radiotherapy”. Furthermore, the afternoon was concluded by two parallel workshops. One on “resting states of the brain” expanding on the use of functional MRI and EEG data, while the other workshop focused on “risk prediction in genetics”.

In the Group Leader Meeting three new group leaders were welcomed (Dr. Ertl, Dr. Scheidegger, and Dr. Heldner). Group leaders further discussed the next annual meeting and brain week as well as the inclusion of further new members. Please consider updating your information on the CNB website (www.neuroscience.unibe.ch)

Thank you all again for a great Annual Meeting, with lots of Talks, Interactions and Posters.

We’re looking forward to next Year!

The next Annual Meeting will take place on the 8th of September 2023. The program and further information will be published on our website (www.neuroscience.unibe.ch) and sent out via mail. If you like to participate as a speaker, help organize or have some ideas for the next Annual Meeting please reach out to any member of the Executive Committee. We are looking forward to your inputs, ideas and help.

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New member of the Executive Committee

Prof. Dr. med. Mirjam Heldner

Associated Professor for Neurology and Stroke, at the Faculty of Medicine, at the University of Bern (Switzerland) and Deputy Head of the Neurovascular Outpatients Clinics, at the Department of Neurology, at the University Hospital of Bern (Switzerland).

Training and research areas:
After studying medicine and obtaining her doctorate in Bern, she completed her specialist training at the University Clinic for Neurology in Bern (Switzerland). Here she specialized in the field of vascular neurology. Her main clinical and scientific interest is the prediction of vessel occlusions, acute therapy, cerebral venous sinus thrombosis, cause and secondary prevention of cerebral infarctions and atherosclerosis. Her research stay at the University of Oxford/UK (2016/2017) deepened the latter foci. She is leading the research group prevention and atherosclerosis at the Bernese Stroke Centre.

Awards:
She has received several awards as first, last or co-author (e.g., by WSO, ESO, Paul Dudley White International Scholar Award, EJoN Award, Peter Huber Award, Day of Bernese Clinical Research Award, SFCNS Award).

Professional:
She is as member of different professional associations (e.g., WSO, WSO Board of Directors, ESO Fellow, ESO Board of Directors, ESO education committee, ESO WISE steering group). She is a member of the evaluation committee of grants for trainees and equality for protected research time and member of the executive committee of clinical neuroscience at the University of Bern. She is mentoring CWIN (Connecting Women In Neurosciences) at the University of Bern. She is co-organiser of the ESO-ESO-department-to-department visits at the Stroke Center Bern. She is part of the faculty of the ESO-ESMINT-ESNR Stroke Winter School and of the MAS Stroke Medicine, at the University of Bern.

Publications:
To date, she has published around 150 publications, of which the majority are original contributions in international high-ranking journals.

Special interests:
Her current priorities are the implementation of the ESO European Stroke Action Plan, the promotion of junior strokologists – especially those from middle- and low-income countries, from Eastern Europe and gender equality and equity.

Prof. Dr. med. Mirjam Heldner introduces her research group:
I am leading the research group prevention and atherosclerosis at the Bernese Stroke Centre.

The team is dedicated to providing high quality and clinically relevant research to decipher pathophysiology, diagnosis and prognoses of cerebrovascular diseases and ultimately to inform treatment decisions, develop guidelines and improve patient outcomes. We are a young and/or experienced, diverse and flexible multidisciplinary team who work collaboratively to ensure that the various knowledge and talents in the team are combined to the best effect. We value intensive, open cooperation and communication with academic and industrial partners around the globe. This enables us to profit from local knowledge and cultural diversity to foster an international point of view regarding the next scientific frontiers of cerebrovascular diseases.

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Stroke is the second leading cause of death and the third leading cause of disability worldwide. The majority of the burden of stroke (60–70%) as well as of atherosclerosis across all countries in the world is associated with elevated systolic blood pressure (the single most important risk factor for stroke) and unhealthy lifestyle risk factors, such as smoking, obesity, low physical activity, and poor diet (e.g., excessive salt, sugar, and alcohol intake and low fruit and vegetable consumption). Her research group is working on several projects which address those vascular risk factors and diseases.

Our vision is to reduce the burden of stroke and this vision drives our efforts to improve stroke care. I would like to conclude this summary of my research group with the quotation from Hippocrates: prevention is better than cure.

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Recent Publications:

- "Management of Cerebral Venous Thrombosis Due to Adenoviral COVID-19." Annals of neurology, 2022 Oct;92(4): 562-573. doi: 10.1002/ana.26431. Epub 2022 Jul 4. https://pubmed.ncbi.nlm.nih.gov/35689346/.

- "Association of diabetes mellitus and admission glucose levels with outcome after endovascular therapy in acute ischaemic stroke in anterior circulation." European journal of neurology. 2022 Oct; 29 (10): 2996-3008. doi: 10.1111/ene.15456. Epub 2022 Jul 1. https://pubmed.ncbi.nlm.nih.gov/35719010/.

- "Post-SARS-CoV-2-vaccination cerebral venous sinus thrombosis: an analysis of cases notified to the European Medicines Agency." European journal of neurology. 2021 Nov;28(11):3656-3662. doi: 10.1111/ene.15029. Epub 2021 Aug 4. https://pubmed.ncbi.nlm.nih.gov/34293217/.

- "Frequency of Thrombocytopenia and Platelet Factor 4/Heparin Antibodies in Patients with Cerebral Venous Sinus Thrombosis Prior to the COVID-19 Pandemic." JAMA. 2021 Jul 27 ; 326(4):332-338. doi: 10.1001/jama.2021.9889. https://pubmed.ncbi.nlm.nih.gov/34213527/.

- "Treatment and Outcome in Stroke Patients with Acute M2 Occlusion and Minor Neurological Deficits." Stroke. 2021;52:802–810. 2021 Jan 26. https://www.ahajournals.org/doi/10.1161/STROKEAHA.120.031672.

- "Symptomatic and asymptomatic intracranial atherosclerotic stenosis: 3 years' prospective study." Journal of Neurology volume 267, pages1687–1698 (2020). 25 February 2020. https://link.springer.com/article/10.1007/s00415-020-09750-2.

- "Prediction of cerebral venous thrombosis with a new clinical score and D-dimer levels." Neurology. June 23, 2020. https://doi.org/10.1212/WNL.0000000000009998.

- "Long-Term Prognosis of Patients With Transient Ischemic Attack or Stroke and Symptomatic Vascular Disease in Multiple Arterial Beds." Stroke. 2021;52:802–810. 26 January 2021. https://www.ahajournals.org/doi/10.1161/STROKEAHA.120.031672?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed.

- "National Institutes of Health Stroke Scale Score and Vessel Occlusion in 2152 Patients With Acute Ischemic Stroke." Stroke. 2013;44:1153–1157. 7 March 2013. https://www.ahajournals.org/doi/10.1161/STROKEAHA.111.000604?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed.

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New member of the Executive Committee

Prof. Dr. med. Philippe Schucht

Deputy Head of Neurosurgery
HORAO Research group,
Translational Research Lab,
Department of Neurosurgery,
Inselspital Bern.

The project HORAO follows a multidisciplinary approach combining clinical neurosurgery, neuroradiology/AI, bio photonics, optical engineering and neuropathology to develop a new type of surgical microscope based on Mueller Polarimetry.

Surgery for brain tumors has made great progress over the last decades. Two major challenges remain and have significant importance for patients` survival and quality of life. For one, even with the current high-performance microscopes the differentiation between tumorous and healthy tissue remains very difficult. This inadequacy to identify tumor borders is a significant risk factor for both poorer survival if tumor remains in-situ and neurological deficits if too much tissue is removed. In addition, we are yet not able to visualize and identify specific fibre tracts of the brain during surgery.

The ability to see fibre tracts non-invasively and in real-time during surgery would not only provide information on the neurological function in sight – derived from the orientation of the fibres – but also identify tumor tissue due to the absence of fibres. In search of an innovative approach to visualize fiber tracts, we explored new ways of kick-starting scientific projects and obtaining novel ideas. The HORAO project started with a crowdfunding challenge followed by a crowdsourcing global competition. Ultimately, the competition led to a collaboration with the Laboratoire de physique des interfaces et couches minces at the Ecole Polytéchnique of Paris. The new conjoint research team successfully tested a solution based on Mueller Polarimetrie in a series of experiments and was awarded a research prize by an industry leader in medical technology, as well as a 4-year SINERGIA Grant by the Swiss National Science Foundation.

Today, the HORAO consortium consist of four partners: The LPICM in Paris oversees prototyping and construction of next generation technical solutions based on Mueller Polarimetry. Neurosurgery provides clinical aspects and tests solutions in their Translational Research Lab. Neuropathology provides cross-correlation with standard genetics and advanced molecular genetics, and specialists of artificial intelligence at Neuroradiology`s SCAN Lab use machine-learning for post-processing of polarimetric data.

The ultimate goal of our consortium is the full integration of polarimetry-based real-time tractography and tumor identification into the microsurgical work-flow.

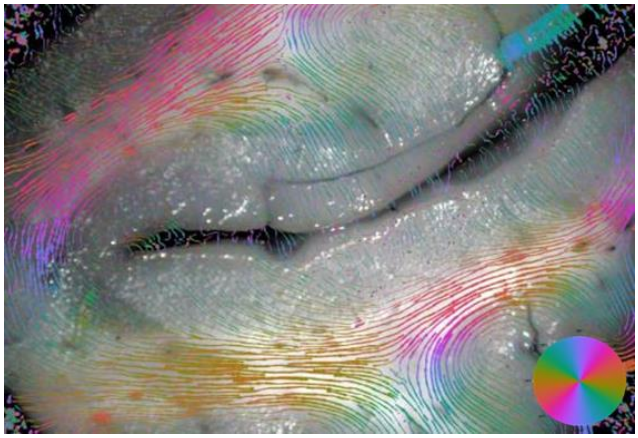

Fig.: Identification of fibre tracts using Mueller polarimetry in reflection configuration, color-coded for spatial orientation.

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Recent publications

- "Natural history of meningiomas: a serial volumetric analysis of 240 tumors." Journal of neurosurgery, 137(6), S. 1639-1649. American Association of Neurological Surgeons 10.3171/2022.3.JNS212626.

- "Safe surgery for glioblastoma: Recent advances and modern challenges." Neuro-Oncology, 9(5), S. 364-379. Oxford University Press 10.1093/nop/npac019

- "Integrated longitudinal analysis of adult grade 4 diffuse gliomas with long-term relapse interval revealed upregulation of TGF-β signaling in recurrent tumors." (Im Druck). Neuro-Oncology Oxford University Press 10.1093/neuonc/noac220

- "Space-expanding flap in decompressive hemicraniectomy for stroke." (Im Druck). Journal of neurosurgery, S. 1-8. American Association of Neurological Surgeons 10.3171/2022.5.JNS22381

- "SLOW: A novel spectral editing method for whole-brain MRSI at ultra high magnetic field." Magnetic resonance in medicine, 88(1), S. 53-70. Wiley-Liss 10.1002/mrm.29220

- "Next generation sequencing in adult patients with glioblastoma in Switzerland: a multi-centre decision analysis." Journal of neuro-oncology, 158(3), S. 359-367. Springer 10.1007/s11060-022-04022-7

- "Quantitative Analysis of the MGMT Methylation Status of Glioblastomas in Light of the 2021 WHO Classification. "Cancers, 14(13), S. 3149. MDPI AG 10.3390/cancers14133149

- "Global comparison of awake and asleep mapping procedures in glioma surgery: An international multicenter survey." Neuro-Oncology, 9(2), S. 123-132. Oxford University Press 10.1093/nop/npac005

- "Management of postoperative internal carotid artery intimal flap after carotid endarterectomy: a cohort study and systematic review." Journal of neurosurgery, 136(3), S. 647-654. American Association of Neurological Surgeons 10.3171/2021.2.JNS2167

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New research group

Rare Neurodegenerative Diseases

Tatiana Bremova-Ertl, MD, PhD
Deputy senior doctor

Balance clinic, Centre of rare diseases, University hospital of Neurology

My research group focuses on diagnostics and treatment of rare neurodegenerative diseases. The overall goal is to improve the clinical management and the quality of life of affected patients and their families, through both translation and back-translational approach. My specific aims are: First, to establish new surrogate parameters and biomarkers for future clinical trials in these rare neurodegenerative conditions. Second, to find new diagnostic methods to gather and follow-up these biomarkers. Third, to conduct the clinical trials on safety and efficacy of potentially neuroprotective substances.

Rare diseases are often neglected in clinical practice, due to their phenotyping heterogeneity, and complexity. Establishing sensitive and specific biomarkers in these rare disorders leads to earlier diagnosis / recognition of the condition, and (if available) avoids delays in access to disease-modifying treatments.

Ocular motor function in rare neurodegenerative metabolic diseases

One representative of such a rare metabolic disease is Niemann-Pick type C (NPC) disease. It is an autosomal recessive lysosomal storage disease affecting an estimated 1:100,000 people. The disease presents with a number of focal neurological deficits, the most frequent being cerebellar ataxia, gaze palsy, dystonia, seizures, cognitive decline, and enlarged spleen and liver. Thanks to the multinational, worldwide collaboration, we were able to show that vertical supranuclear saccade, not a gaze palsy, is the hallmark of the M. Niemann-Pick type C (NPC) disease in the largest cohort of patients with this severe rare metabolic, neurodegenerative disease examined so far (Bremova-Ertl et al. 2021).

Further, using OCT, we demonstrated retinal degeneration in patients with NPC1 and significant correlation between retinal neuroaxonal degeneration with clinical measurements, being a potential biomarker in this neurodegenerative IEM (Havla et al., 2020). In another metabolic rare disease, the so-called neuronopathic Gaucher disease, caused by the lack of the glucocerebrosidase enzyme (GBA), my collaborators and I were able to show that these patients also feature unique patterns of the impairment of the vestibulo-ocular reflex that was preserved over time (Fig 1 Bremova-Ertl et al. 2018). Given this intra-individual consistency, vestibulo-ocular reflex can be further investigated as a promising biomarker to follow-up these patients in the clinical routine.

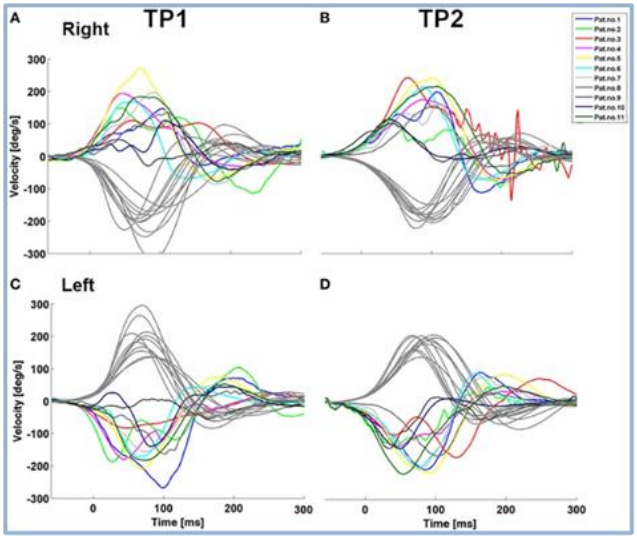

Fig. 1 Longitudinal development of the vestibulo-ocular reflex (VOR) in individual patients with neuronopathic Gaucher disease. Note the variety of patterns of a VOR impairment, which remains stable over time. The stained curves indicate the eye movement with every curve representing a mean of 10 ± 5 HIT of a particular patient. Grey depicts the head movement. From Bremova-Ertl et al., 2018

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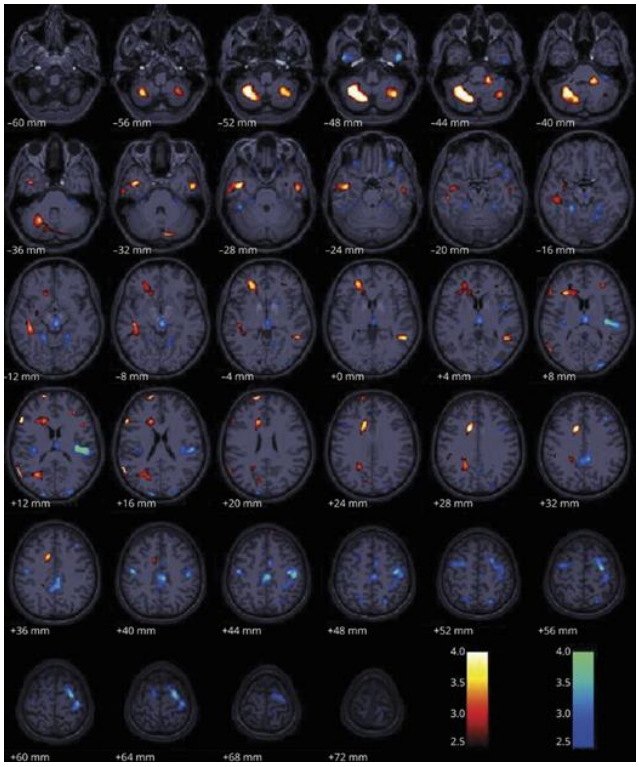
Clinical, ocular motor, and imaging profile of Niemann-Pick type C heterozygosity

One of my most relevant work is the work on the clinically healthy carriers of a single mutation in NPC1 gene having a carrier frequency of 1:200 in the general population. The healthy carriers may be at risk for late-onset neurodegeneration (Schneider et al., 2019; Bremova-Ertl et al., 2020). NPC heterozygotes seem to recapitulate some characteristic features of symptomatic NPC disease, and feature signs of neurodegeneration. PET imaging revealed significantly decreased glucose metabolic rates in 50% of participants (**Fig 2**).



Fixation 2. Voxelwise brain 18FDG-PET analysis in Niemann-Pick type C (NPC) heterozygotes, across all participants (n = 16) Red: Decreased metabolic rates. Blue: Increased metabolic rates ($p < 0.01$; $k > 20$ voxels, n = 23 healthy controls, global mean scaling, 8 mm Gaussian). Decreased metabolic rates are most prominent in the left parietal cortex, followed by left anterior cingulate cortex, bilateral cerebellum, and right temporal and left temporal gyri. Increased brain metabolism was detected in midbrain and tegmentum right insula, followed by bilateral postcentral region, left insula, and posterior cingulate cortex. From Bremova-Ertl et al., 2020

The NeurOphthalmoscope: Early diagnosis of brain diseases

The eyes are a promising biomarker, as they are easy to examine, and provide a convenient access to study the brain health. Thus, in the frame of the InnoSuisse project consortium "The NeurOphthalmoscope: Early diagnosis of brain diseases", we thrive to develop a cutting-edge Virtual Reality Tool NeurOphthalmoscope or "NEOS" (Fig 1) that will enable a high-quality, multimodal, time-saving, patient- and user-friendly, neuro-ophthalmological and neuro-otological examination. In the sense of the medical entrepreneurship to improve the standard-of-care, I collaborate with industry, including the start-up company machineMD, CSEM (Centre Suisse d'Electronique et de Microtechnique), and Helbling Technik Bern AG.

Fig. 3 Experimental VR set-up. The device is multi-functional (8 examinations in one device), mobile, suitable for bedside testing, and patient-friendly, generating objective, reproducible and quantifiable results. The examination is time-efficient and well tolerated. The optical stimuli are presented. Real-time registration of eye movements on notebook. Source: Private source, machineMD

To depict the NEOS usefulness in the real-life setting, I present a case of the 60 year-old woman having a concussion after a bicycle accident. One day after the accident she developed a salt waste syndrome and spent 5 days in the intensive care unit. She complained about difficulties when changing visual focus. Her insurance was not willing to pay for examinations because repeated MRI examinations were

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read as normal. NEOS shows a horizontal saccadic paresis that is the horizontal fast eye movements are slowed, while vertical fast eye movements are spared. This clearly points to a structural damage in the parapontine reticular formation (PPRF). So, NEOS does reveal an objective functional loss.

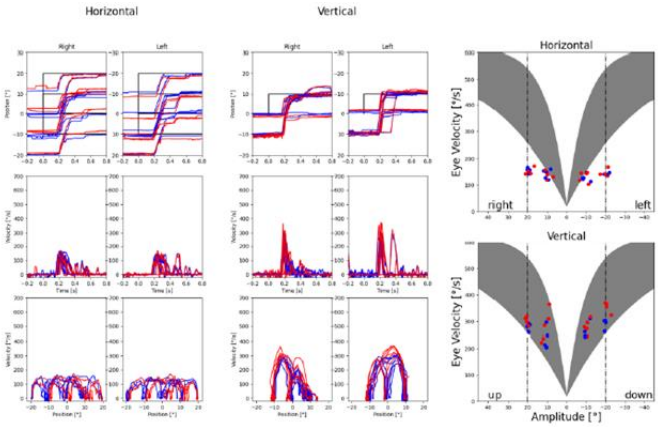

Fig. 4 Main sequence of horizontal and vertical saccades in response to stimuli. Note the decreased saccadic velocities to the right and to the left. Source: machineMD

A Longitudinal Study of Neurological Functions, Associated Brain Connectivity, and Metabolic Markers in Young Patients with Classic Galactosemia GALIGMA

One of our current projects focuses on yet another rare metabolic disease classical galactosemia (CG), characterised by the inability to metabolize galactose. Due to the high galactose content in mammalian milk, newborns with this disorder present with acute intoxication syndrome, which can become life threatening. Thus, in Switzerland, it is part of the neonatal screening. Upon diagnosis, a galactose-restricted diet is immediately introduced and recommended for life. Despite this early intervention, individuals with CG commonly develop long-term complications particularly in the brain. To date, a comprehensive understanding of the onset and the development of CNS-related symptoms in CG is still lacking. Together with the Department of Pediatrics, namely Dr. Matthias Gautschi, Division Metabolism, and Prof. Regula Everts-Brekenfeld, Division Neuropsychology, and the Ph.D. candidate Anja Maria Vossenkaul we aim to characterize the neuropsychological, neurological, and metabolic phenotypes in children and adult population suffering classical galactosemia.

Multinational, randomized, placebo-controlled, double-blinded, cross-over Phase III clinical trial to assess safety and efficacy of Acetyl-L-Leucine (IB1001) versus Placebo for the treatment of NPC.

Acetyl-DL-leucine (ADLL) has been used for more than 6 decades in France to treat acute vertiginous episodes. The clinical experience has shown that it is a well-tolerated drug without serious adverse events. In 2015, my pilot case-series study in patients with NPC indicated the possible positive symptomatic effects on cerebellar ataxia, but also other modalities of this rare debilitating disease. The further basic research studies, and clinical trials demonstrated the positive effects of acetyl-L-leucine (ALL) in lysosomal storage disorders, suggesting not only symptomatic, but also disease-modifying effects (Fig 4, Kaya E et al., 2020).

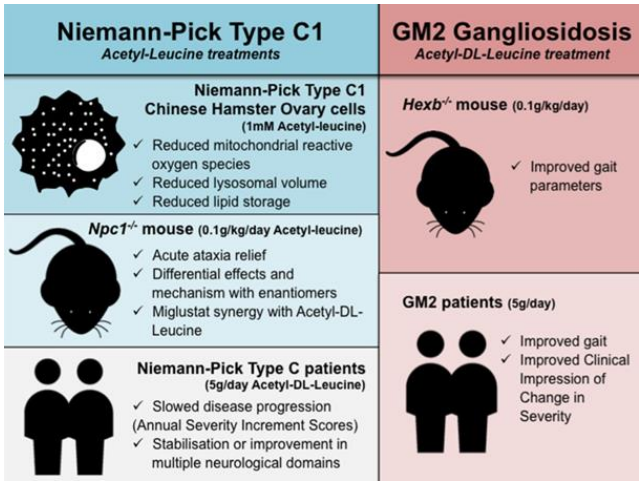

Fig. 4 Illustration of the effects of Acetyl-Leucine on Niemann-Pick Type C1 vs. GM2 Gangliosidosis. From Kaya E., et al., 2020.

I am the principal investigator of the only study site in Switzerland for the multinational, randomized, placebo-controlled, double-blinded, cross-over Phase III study that will assess the safety and efficacy of ALL (IB1001) versus Placebo for the treatment of children >4 years of age and adults with NPC (NCT05163288) . The development of this re-purposed drug for lysosomal storage diseases is a model example of the translational and back-translational research enabled by the close cooperation with the lab of Prof. Frances Platt, University of Oxford.

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I believe that the active interaction of all relevant stakeholders, i.e. patient communities, medical specialists and industrial partners is the key to improve the quality of life of patients with rare neurodegenerative diseases.

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Recent publications

- "Efficacy and Safety of N-Acetyl-L-Leucine in Children and Adults With GM2 Gangliosidoses." Neurology. 2022 Dec 1;10.1212/WNL.0000000000201660.
- "Efficacy and safety of N-acetyl-L-leucine in Niemann-Pick disease type C." Journal of Neurology. 2022 Mar ;269(3):1651-1662.
- "Effects of Acetyl-DL-Leucine on Ataxia and Downbeat-Nystagmus in Six Patients With Ataxia Telangiectasia." Journal of Neurology. 2022 Jan;37(1):20-27. doi: 10.1177/08830738211028394. Epub 2021 Oct 7.
- "A cross-sectional, prospective ocular motor study in 72 patients with Niemann-Pick disease type C." 2021 Sep;28(9):3040-3050. doi: 10.1111/ene.14955. Epub 2021 Jul 12.
- "Acetylation turns leucine into a drug by membrane transporter switching." Scientific reports. 2021 Aug 4;11(1):15812. doi: 10.1038/s41598-021-95255-5.
- "Do heterozygous mutations of Niemann-Pick type C predispose to late-onset neurodegeneration: a review of the literature." Journal of Neurology. 2021 Jun;268(6):2055-2064. doi: 10.1007/s00415-019-09621-5. Epub 2019 Nov 7.
- "Loss of NPC1 enhances phagocytic uptake and impairs lipid trafficking in microglia." Nature Communications. 2021 Feb 24;12(1):1158. doi: 10.1038/s41467-021-21428-5.
- "Acetyl-leucine slows disease progression in lysosomal storage disorders." Brain communications. 2020 Dec 20;3(1):fcaa148. doi: 10.1093/braincomms/fcaa148. eCollection 2021.

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③ Upcoming events

13th – 16th March 2023	Brainweek Bern
15th March 2023	Researchers' Night
8th September 2023	18th CNB Annual Meeting

For any inquiries, please contact:

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