IPT Science Day 2025

Official Booklet

21st August 2025

University of Zurich[UZH]

ETH zürich

Contents

1. Preface

Welcome to the 4th edition of the IPT Science Day. This event is brought to you by the IPT Student Committee, which is made up of PhD and master's students from various IPT labs.

After the challenges of the pandemic, we realized that many new members hadn't had the chance to really connect. The IPT Science Day is our way of addressing that. It is a space for everyone to share their research and to learn about what's happening in other labs. We hope it helps in building connections, fostering collaboration, and just getting to know each other better.

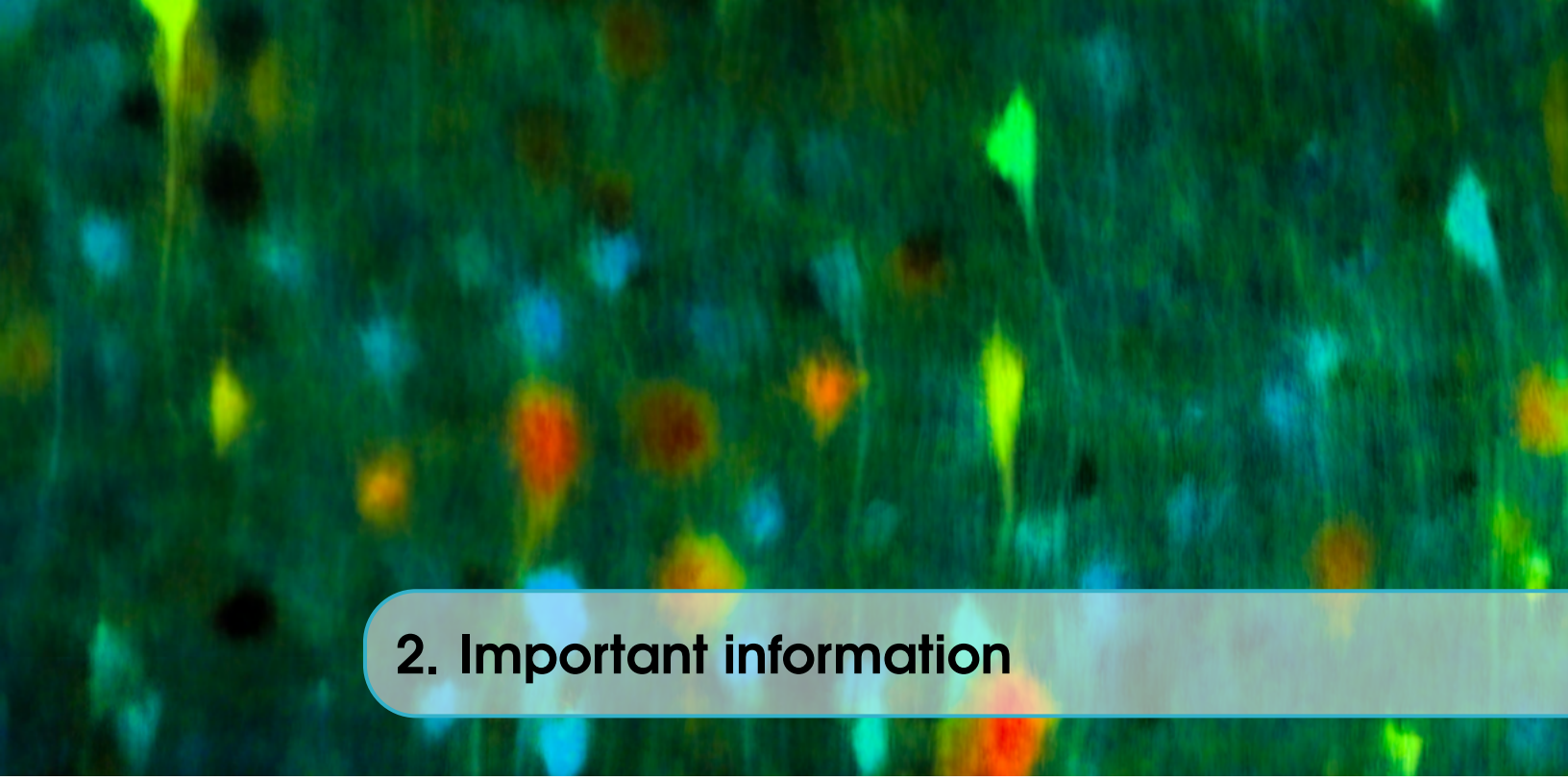
This booklet will help you navigate the day's program. It is also a handy reference to revisit the work of other IPT members. We hope you find it useful and that the IPT Science Day becomes a regular event we all look forward to.

If you have questions or suggestions, feel free to talk to any of the committee members.

With this, we wish you a great IPT SCIENCE DAY!

Your IPT Student Committee:
Marta Mazurkiewicz, Saphira Müller, Manuel Zinnenlauf, Viktor Beilmann, Hanna Preuss, Cristian Ciobanu, Annika Canziani, Sara Ferreira, Patricia Sonderegger and Rachele D'Angelo.

Special thanks to Lukas Glandorf.



2. Important information

Dear participant of the IPT Science Day, please read the information below carefully and do not hesitate to contact us with further questions!

We will host a diverse program with talks by members of the different labs. Please be aware that this is an environment of trust and please do not share unpublished information with non-attendees!

TEC - *Trust, Exchange and Collaborate*. We encourage you to interact with your fellow researchers as much as possible to build an environment where we can get to know each other, trust each other, and exchange who we are and what we are experts in. This exchange will provide the first potential collaborations, and hopefully, you will keep in contact to be able to ask for help (if needed) quickly.

What to expect

Introduction by Prof. Dr. Bruno Weber, presentations by 8 PhDs/Postdocs, and a special talk by Prof. Daniel Erlacher
There are 8 distinct groups within the IPT, each focusing on their unique area of research. This diversity contributes to the rich scientific environment at IPT, though it can sometimes be a challenge to get a comprehensive view. To help with this, several groups will share presentations. These might cover the broader goals of the group or delve deeper into a specific project. It is a chance for you to learn more and ask any questions you might have about their research.
We are also pleased to have Prof. Erlacher from the University of Bern join us for a special talk.

Poster display session for scientific exchange
We are hosting a poster session featuring 18 posters. While presenters will be stationed at their posters for the majority of the session, they might occasionally step away to view other posters. If you find a poster unattended, just circle back after a short while. This session is a great opportunity to get a glimpse of the diverse research at IPT and for presenters to discuss their work. We encourage active engagement, so do not hesitate to strike up conversations and ask questions!

Apéro
Beyond the scientific discussions and exchange, there will be ample opportunities for you to interact with fellow PhD students and Postdocs from various labs. We have scheduled regular breaks and will conclude with a BBQ. We encourage you to strike up conversations, especially with those you might not interact with often.

3. Program

Time	Activity	Details	Location
12:30 - 12:45	Introduction Speech	IPT Student Committee + Prof. Bruno Weber	Y03 G85
12:45 - 13:45	External Speaker	Prof. Daniel Erlacher	Y03 G85
13:45 - 14:15	Break		
14:15 - 15:20	Short Talk Competition	5 Minute Talks	Y03 G85
15:20 - 15:45	Break		
15:45 - 16:45	Poster Session	Poster Number 1-19	Lichthof
16:45 - 17:00	Break		
17:00 - 17:30	Closing remarks and Best Talk Award	IPT Student Committee	Y03 G85
17:30 - open	Barbecue		outside Mensa

Talks

Kim Marquart (Schwank group)
"High-Throughput Directed Evolution of PAM-specific SpCas9 Variants"

Andrin Abegg (Tyagarajan group)
"Sexually dimorphic control of contextual memory specificity through inhibitory postsynaptic remodeling in hippocampal engram neurons"

Matteo Ranucci (Zeilhofer group)
"Serotonin and GABA co-transmission from descending inhibitory terminals from the Rostral Ventromedial Medulla to the dorsal horns of the spinal cord"

Peter Kulcsar (Schwank group)
"Rescue of MC4R related obesity by in vivo base- and prime-editing in mice"

Henri Zanker (Saab group)
"Monitoring Neuronal and Axonal Health In Vivo Using Two-Photon FLIM"

András Tálas (Schwank group)
"In vivo rescue of a urea cycle disorder via RNA-LNP-mediated prime editing"

Patricia Sonderegger (Landolt group)
"The role of the LC-NA System in Experimental Sleep Fragmentation"

Sasha Melkonyan (Schwank group)
"Large gene insertion therapy for Huntington's disease"

Posters

Nima Makham (Razansky group, #1)
"Micro-Robotic Therapeutics Driven by Acoustic Field Response"

Eva Remlova (Razansky group, #2)
"Deep Tissue Optoacoustic Monitoring of Photothermal Treatments in the NIR-II Assisted with Silica-coated Gold Nanorods"

Cristian Ciobanu (Razansky group, #3)
"Predicting stroke in a flash: Listening to carotid artery plaques with optoacoustic imaging"

Ladina Hösli (Weber group, #4)
"Rapid High-Pressure Freezing Workflow for Improved Brain Tissue Preservation"

Felipe Velasquez (Weber group, #5)
"Quantitative microscopy techniques for in vivo brain imaging"

Henri Zanker (Saab group, #6)
"Monitoring Neuronal and Axonal Health In Vivo Using Two-Photon FLIM"

Zainab Faik (Saab group, #7)
"Distinct Metabolic Specializations in White Matter Oligodendrocytes, Astrocytes, and Axons"

Urvashi Dalvi (Saab group, #8)
"The relationship between mitochondrial ROS in oligodendrocytes and axonal health"

Marta Mazurkiewicz (Zeilhofer group, #9)
"The role of oligodendrocytes in Western diet-induced pain"

Rachel Meister (Weber group, #10)
"Effects of a ketogenic diet on neuronal and astrocytic metabolism in the mouse brain: a two-photon FLIM study"

Posters (cont.)

Nicola Schmid (Weber group, #11)
"Studying Astrocyte-Neuron Interaction In Vivo via Specific Astrocyte Depletion"

Viktor Beilmann (Weber group, #12)
"Overactivation of prefrontal astrocytes alters local neuronal activity and impairs cognition via acting on the kynurenine pathway"

Anna Lasne (Weber group, #13)
"Microglial contribution to the regeneration of aquaporin-4-antibody mediated astrocytopathy-driven neuroinflammation"

Hanna Preuss (Weber group, #14)
"The Growing Network: Constructing an Atlas of Brain Vascular Development"

Annika Canziani (Patriarchi group, #15)
"Naturalistic Memory Allocation via Neuromodulation"

Rachele D'Angelo (Landolt group, #16)
"5G RF-EMF and sleep"

Yanik Weber (Schwank group, #17)
"Continuous Evolution of RNA Editors to Enhance A-to-I and C-to-U Editing"

Priscilla Wang (Schwank group, #18)
"Directed Evolution of Novel RNA-binding DNA Nucleases"

Michael Rappleye (Patriarchi group, #19)
"A high-throughput platform for identification of GPCR activating single domain antibodies"

Prof. David Erlacher

Daniel Erlacher is a group leader and lecturer at the Institute of Sport Science at the University of Bern, Switzerland. His research is focused on motor learning in lucid dreams, sleep in elite sports, and sleep-related regeneration processes.

Daniel Erlacher received his Ph.D. in Sport Sciences at Heidelberg University, Germany and continued his scientific career as a Postdoc there before moving to Bern. He carried out research all over the world, including Stanford University, USA and Tokyo Gakugei University, Japan, among others. Daniel is a recipient of multiple investigator awards.

4. Confidentiality

It is an important goal that the event participants can safely exchange their scientific results between different labs and institutions. Consequently, all developments shall be kept strictly confidential by all participants of the IPT Science Day and shall not be disclosed to persons outside of the IPT Science Day, provided that the results are not published by the authors/originators. Furthermore, no participant in the event shall use any scientific results to the detriment of the host institutions. In particular, no participant shall impair a host institution's right to seek the protection of intellectual property contained in such results by premature publication or other premature disclosure of results.

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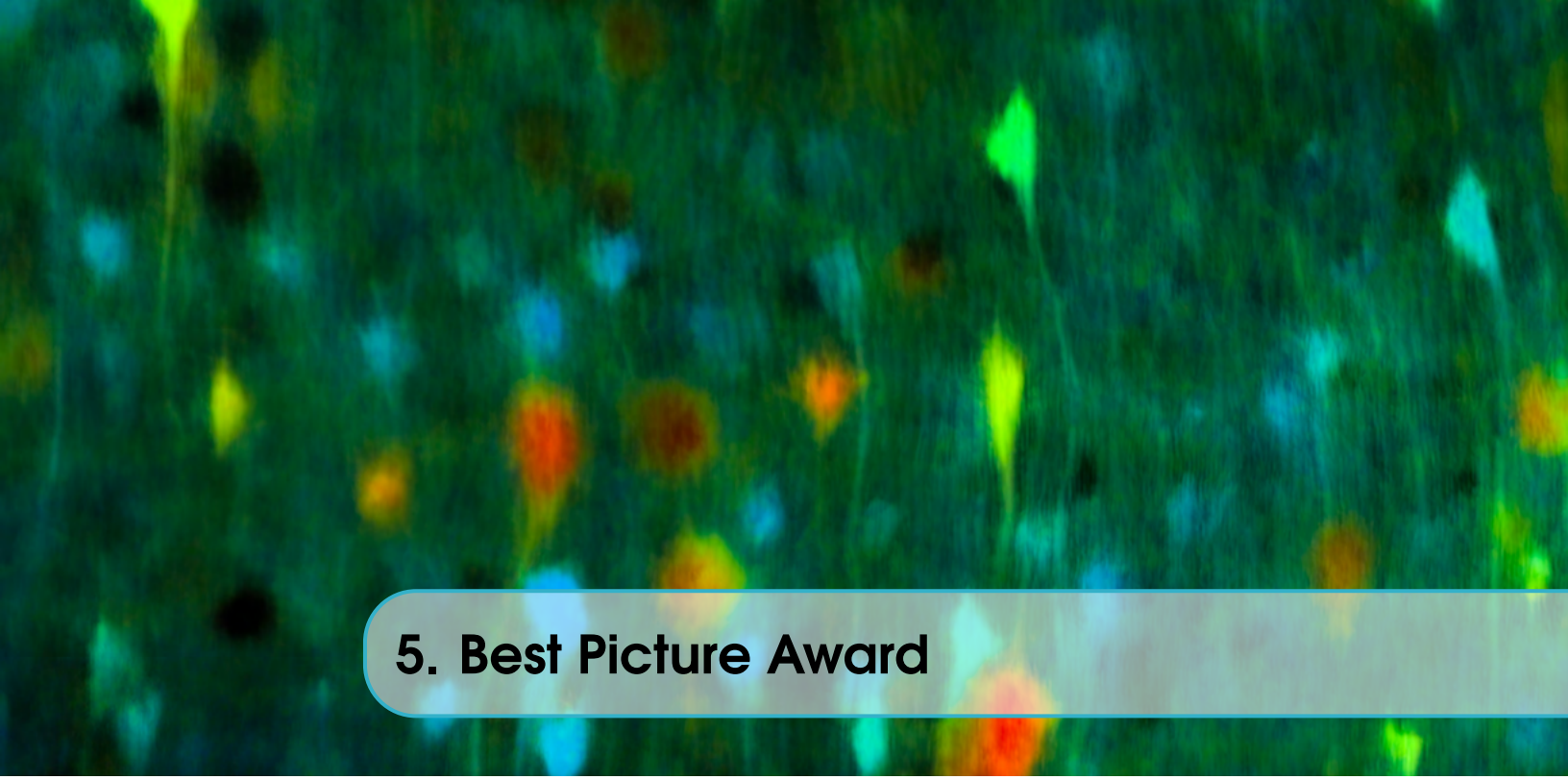


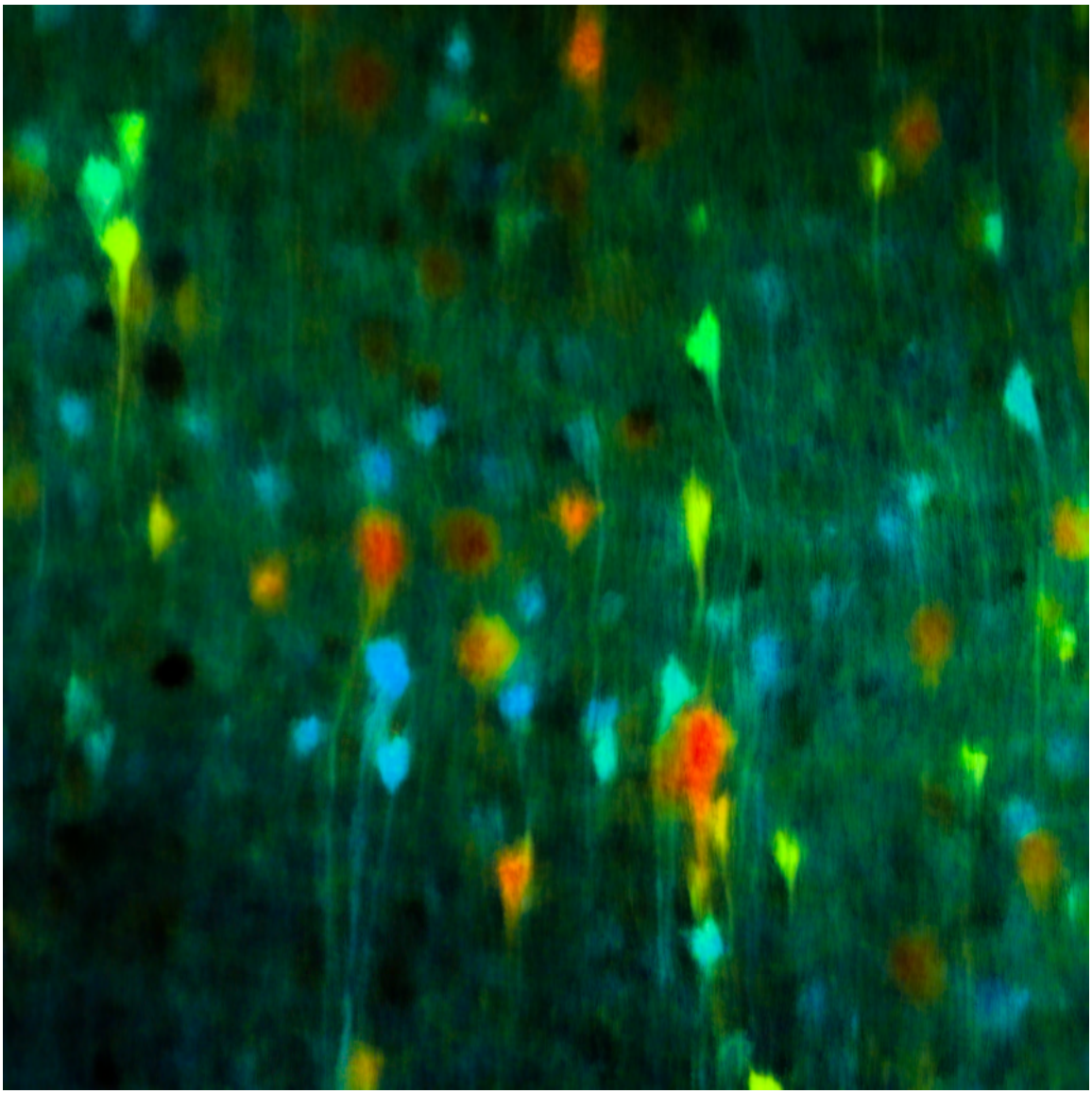
5. Best Picture Award

This year's Science Day features a Best Picture Award. IPT members were invited to showcase their most beautiful scientific images. The winning image, selected through a vote by the IPT Student Committee, is featured prominently on the title page and in each chapter heading. It is described as:

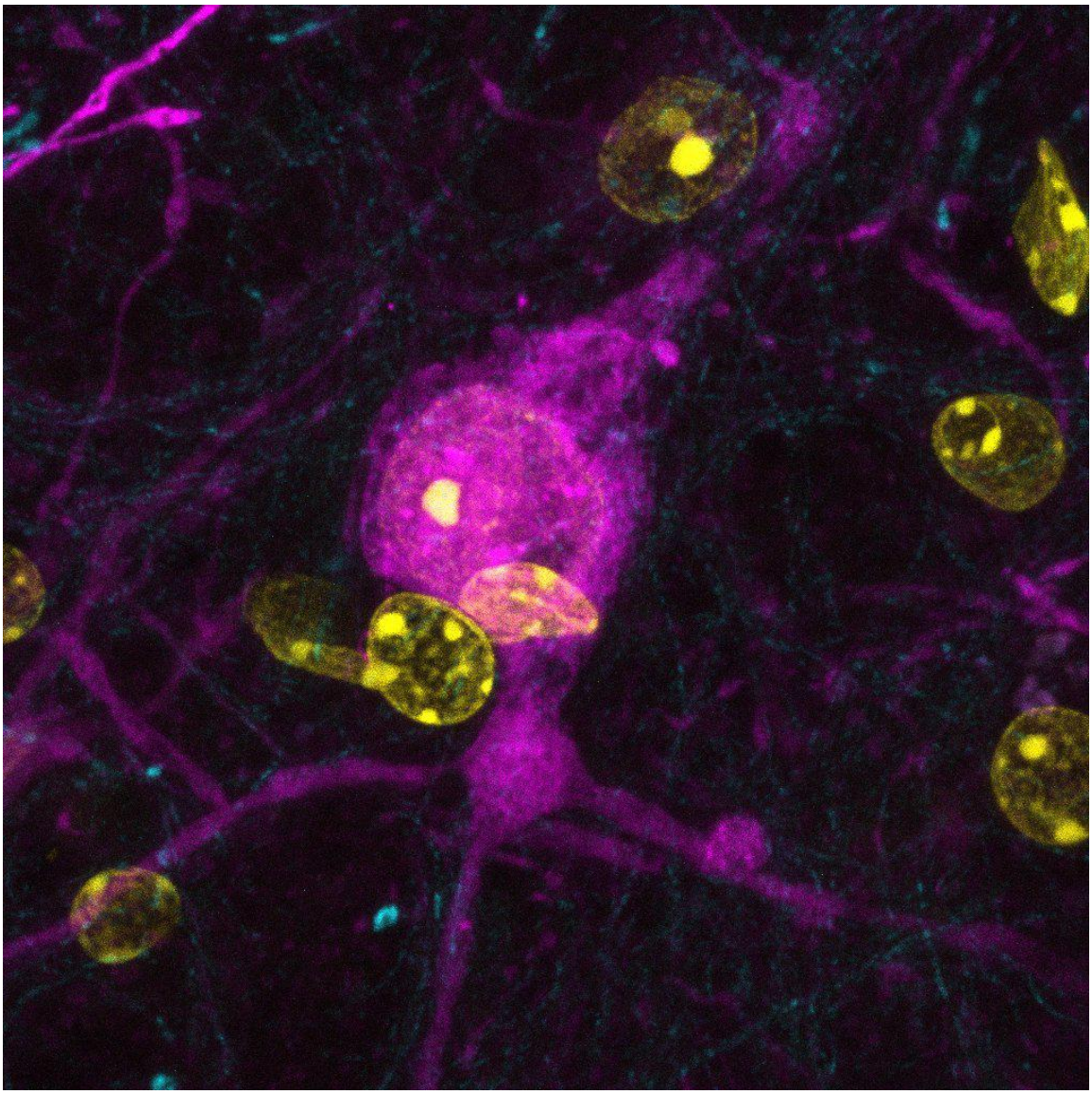
ATP levels in acute slice neurons analysed with our new algorithm for pile-up corrected FLIM.

Congratulations to Rachel Meister from the Weber Lab!

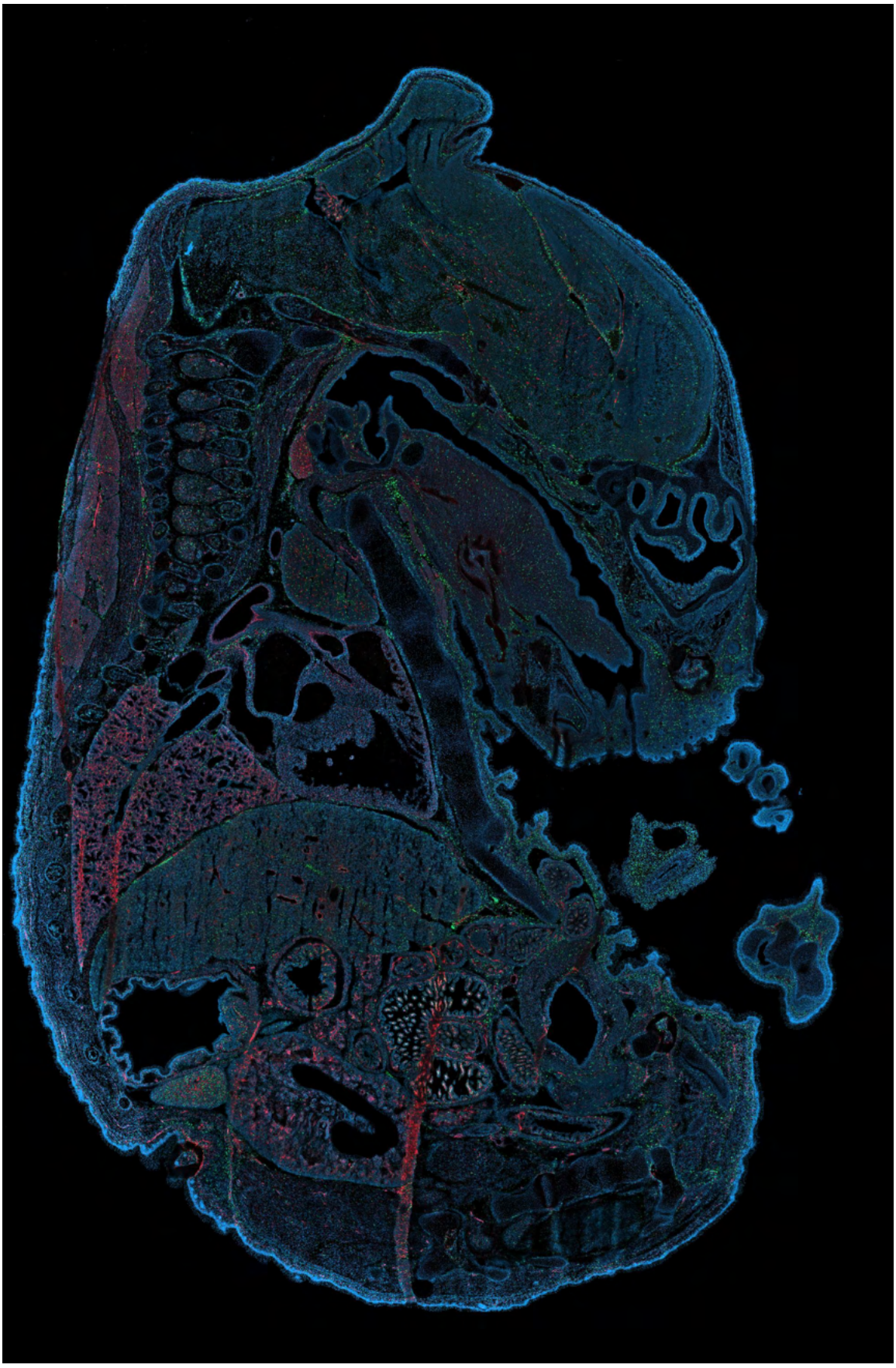
While we have highlighted a winner, we believe every submission deserves recognition. Thus, we have included all entries in the subsequent pages for you to appreciate and perhaps pick your own favorite. The entries are displayed without any specific ranking. A heartfelt *Thank You* to everyone who contributed!



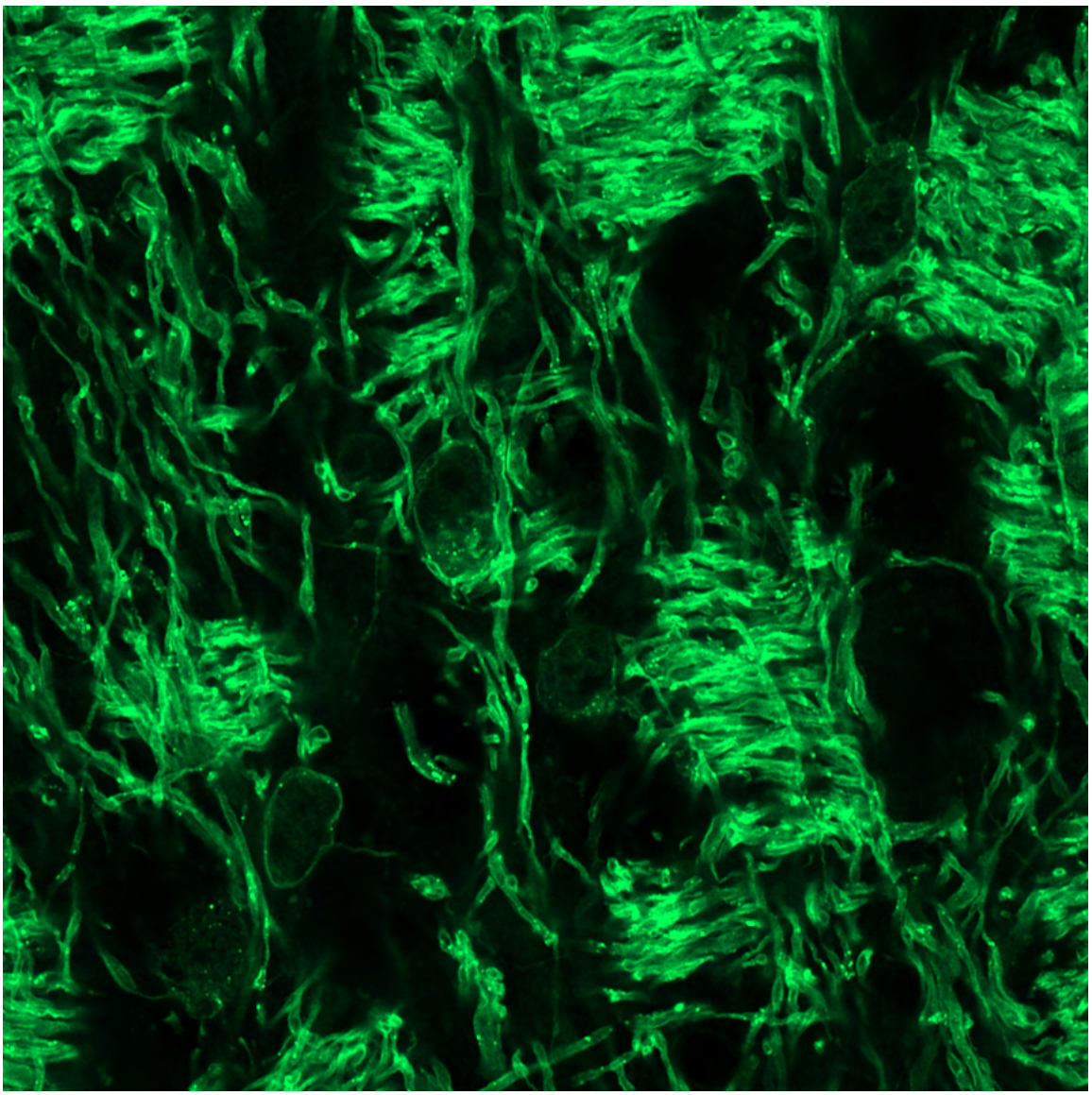
- Rachel Meister



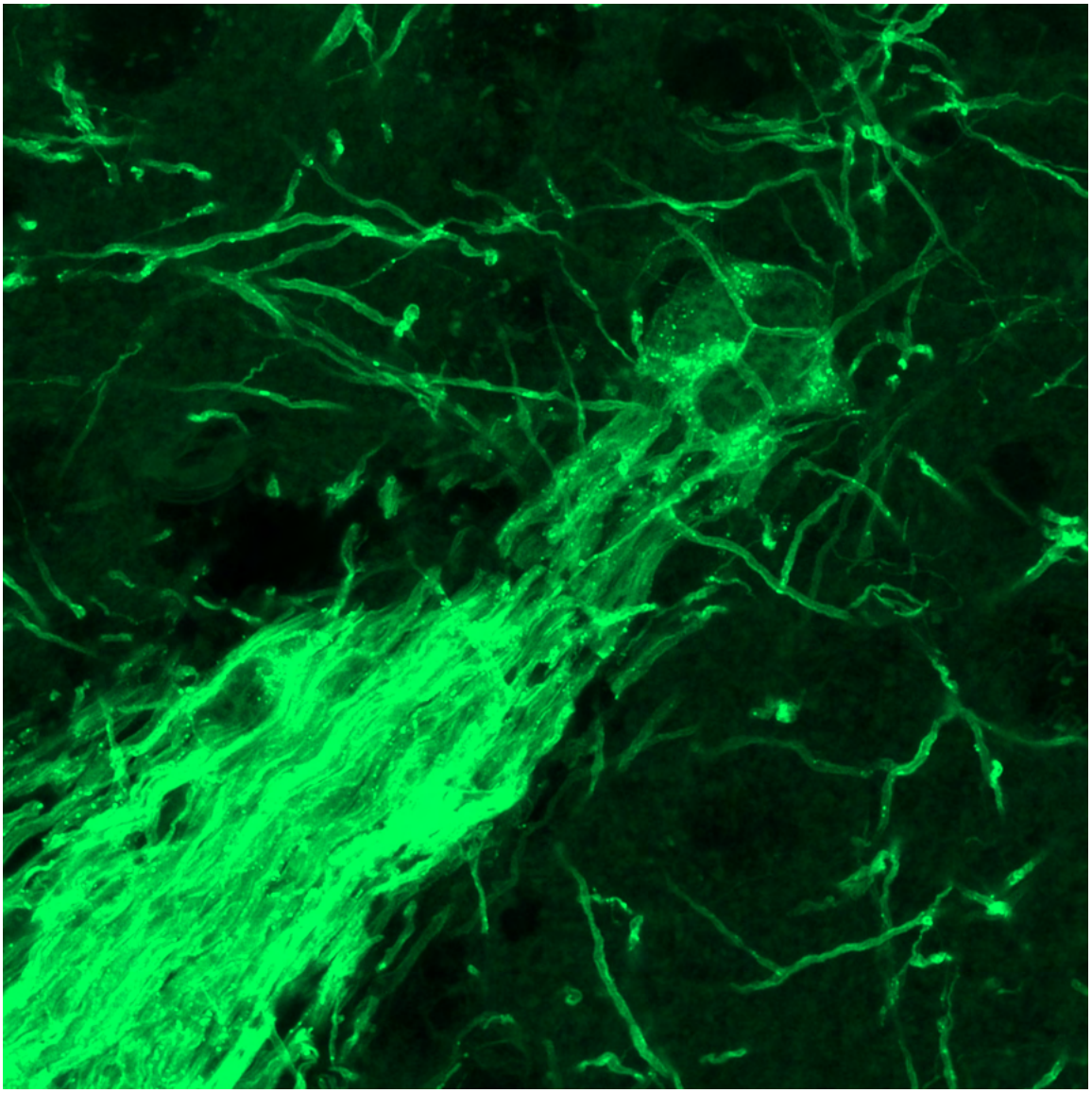
- Annika Canziani



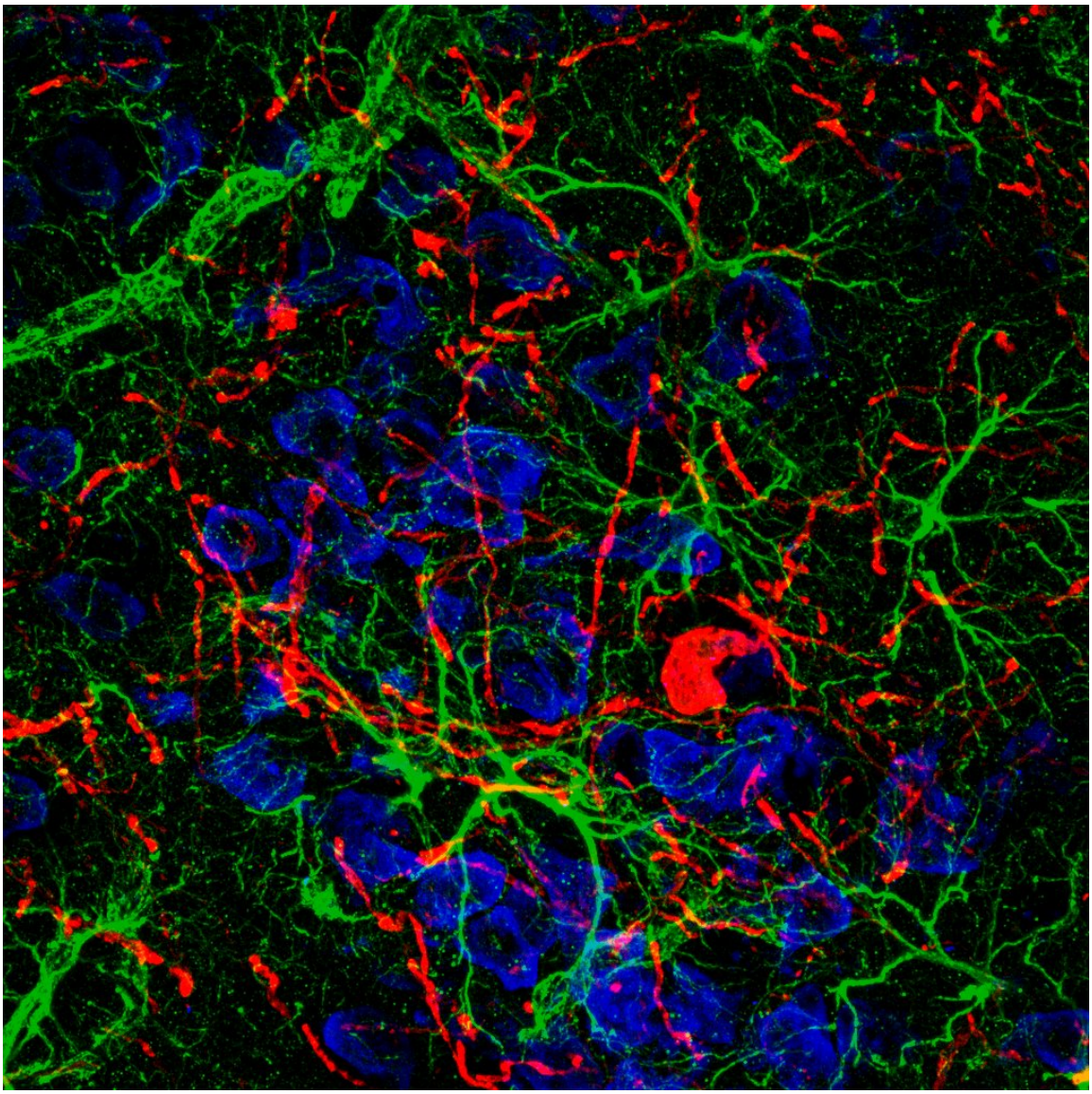
- Hanna Preuss



- Sevasti Gaspari



- Sevasti Gaspari



- Viktor Beilmann

6. Abstracts

On the following pages the abstracts of the participants are collected. They will give you a brief idea of everybody's project and expertise.

Furthermore, you will find a small intro to each of the groups and what the labs' main research focuses are (Arand, Landolt, Patriarchi, Razansky, Saab, Schwank, Tyagarajan, Weber and Zeilhofer groups). You can find this information at the start of the respective sections.

Abstracts - Arand group

The Arand Lab*

The department focuses on the metabolism of xenobiotic and endogenous bioactive substances with particular emphasis on the enzyme family of epoxide hydrolases. These enzymes have been originally recognized for their crucial role in xenobiotic metabolism. Indeed, they catalyze the turnover of potentially carcinogenicmetabolites into less active products. In addition, they interfere with a range of physiological processes such as inflammation, pain, angiogenesis and vascular dynamics by controlling the levels of a specific class of endogenous signaling molecules. By applying a broad spectrumof methods (e.g. electrophysiology,mass spectrometry, behavioral physiology, immunohistochemistry, protein biochemistry) the group examines how the epoxide hydrolases fulfill their double role.

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Year joined IPT
2023

Andreas Stäuble*
Post-Doc in the Arand Lab

Folate receptor α positive lipid nanoparticles as a vector for braintargeted gene therapy

Our goal is to develop a gene therapy that can pass the blood cerebrospinal fluid brain barrier. For this purpose, we equip lipid nanoparticles (LNPs) with folate receptor α (FRα). Therefore, we mimic endogenous FRα positive exosomes that transport folate to the brain. These exosomes can pass the ependymal cell layer between CSF and brain and deliver folate to their cerebral target cells. Exosomes and LNPs have the same diameter of approximately 100nm. LNPs are mechanically produced synthetic particles that encapuslate oligonucleotides and can be loaded with receptors. By mimicking FRα positive exosomes, we enable our FRα positive LNP to cross the ependymal cell layer.

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Year joined IPT
2020

Manuel Zinnenlauf*
PhD in the Arand Lab

Protein protein interaction of xenobiotic metabolizing enzymes

Metabolism of foreign compounds, such as toxins or pharmaceutical drugs, is often a prerequisite for their efficient excretion from our organism. The majority of the enzymes involved in this metabolism reside anchored with a single hydrophobic domain in the membrane of the endoplasmic reticulum. In addition to their detoxification functions, these enzymes often play an additional role in the turnover of endogenous signaling molecules and thus are potential contributors to cellular signaling. The kinetic interplay between different isoenzymes is not yet well understood. Elucidating the physical interaction between these membrane bound isoenzymes could substantially enhance our understanding on their regulatory, functional and kinetic interplay. In my project, were screening a library of these enzymes using a FACS-FRET approach in order to gain a novel understanding on how protein-protein interactions affect the kinetics of these enzymes.

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Abstracts - Landolt group

The Landolt Lab*

Imaging molecular markers of plasticity and sleep in humans

Our research combines and integrates methods of specific pharmacology, neurophysiology, human genetics, molecular brain imaging and neurocognitive testing, to investigate the roles for neuro-modulators, receptors and transporters in regulating sleep-associated brain functions in health and disease.

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Year joined IPT
2023

Rachele Maria D'Angelo*
PhD in the Landolt Lab

5G RF-EMF and sleep

5G technology raised concerns about its potential health impacts, particularly on sleep and brain health. Despite public concerns, no experimental studies have tested the effects of 5G radio-frequency electromagnetic fields (RF-EMF) on sleep in humans, and no causal biological mechanism has been identified. Our previous research revealed that a 30-minute pre-sleep exposure to 5G RF-EMF at 3.6 GHz affected sleep EEG patterns in a genotype-dependent manner linked to the CACNA1C gene. This gene encodes a key subunit of the L-type voltage-gated Cav1.2 channels, which regulate brain functions crucial for neuronal plasticity, learning, memory, and sleep quality. Given these findings, our main hypothesis is that the effects of 5G RF-EMF on sleep electrophysiology could be mediated by the Cav1.2 channels in the brain. My PhD project aims to determine whether pharmacologically blocking these channels can attenuate or prevent these effects, with a focus on sleep spindle frequency and memory performance.

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Year joined IPT
2022

Marta Ratajczak*
PhD in the Landolt Lab

Overnight emotion reset of hyperaroused tension by application of low doses of sublingual dexmedetomidine

Sleep is a fundamental physiological process. Consolidated, uninterrupted sleep supports healthy brain function and maintains both physical and mental health. Disturbingly, insomnia is the most common sleep disorder, characterized by difficulty initiating sleep, maintaining sleep continuity, or experiencing poor sleep quality. Severe sleep fragmentation can lead to increased overnight emotional distress and amygdala hyperactivation. In particular, restless rapid eye movement (REM) sleep has been suggested to disrupt emotional adaptation. Importantly, sound REM sleep is the only state during which the Locus Coeruleus (LC) is silenced, allowing the brain a 'rest' from noradrenaline (NA) exposure. Our team has developed orodispersible tablets (ODTs) for sublingual administration of the selective alpha-2 adrenoreceptor agonist dexmedetomidine (DMTN), which attenuates LC activity. We hypothesize that DMTN consolidates fragmented sleep and could represent an innovative, fast-acting pharmacological intervention to prevent and resolve chronic hyperarousal, a common feature of stress-related insomnia. The focus of our approach is to elucidate the role of restless REM sleep in LC silencing during sleep.prt of my PhD project, I am investigating how ODT-DMTN promotes physiological sleep patterns and enhances the restorative benefits of undisturbed REM sleep.

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Year joined IPT
2022

Laura Schnider*
PhD in the Landolt Lab

Targeting memory consolidation in depression via pharmacological slow-wave sleep promotion

Insomnia and daytime sleepiness are common clinical features in major depressive disorder (MDD), however, targeted sleep treatments are limited. Sodium oxybate (SOX), a GHB/GABAB receptor agonist approved for narcolepsy, enhances slow-wave sleep (SWS) and reduces next-day sleepiness, making it a promising candidate for improving sleep in MDD. In my current project, I examine the effects of a single nocturnal dose of SOX in individuals with MDD, compared to trazodone - one of the most frequently prescribed off-label medications for sleep disturbances in MDD - and placebo. While our previous research has shown that SOX strongly enhances deep sleep, this study focuses on whether improved sleep also leads to cognitive benefits. Since memory consolidation is thought to be sleep dependent, enhancing sleep quality may improve patients' ability to learn and remember therapeutic content—an essential process for the success of psychotherapy in MDD.

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Year joined IPT
2023

Patricia Sonderegger*
PhD in the Landolt Lab

The role of the LC-NA System in Experimental Sleep Fragmentation

My research investigates how stress affects sleep, with a particular focus on the brain mechanisms underlying sleep-wake regulation. We examine the role of the locus coeruleus–noradrenaline (LC-NA) system, a key driver of arousal, in mediating stress-related sleep disturbances. In an experimental model, healthy young adults are exposed to auditory stimuli during non-rapid eye movement (NREM) sleep to transiently induce hyperarousal. We test whether low-dose dexmedetomidine—a selective α2-adrenergic agonist that dampens noradrenergic activity—can counteract this hyperarousal. We hypothesize that attenuating LC-NA tone will reduce sleep fragmentation and promote deeper, more consolidated sleep. This research aims to advance our understanding of stress-related insomnia and inform the development of targeted pharmacological interventions.

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Abstracts - Patriarchi group

The Patriarchi Lab*

The Patriarchi Lab develops new molecular tools to illuminate the hidden language of chemical transmission in the brain.
Our brain has a language of its own. At the core of its complex functions is chemical communication occurring between and among neurons and astrocytes, which use an alphabet composed of a myriad secreted signaling molecules, including neurotransmitters, neuropeptides, hormones etc. Understanding the chemical language of the brain is a goal of fundamental importance, as many of these signaling molecules or the cellular receptors that relay their signals, are involved in diseases of the nervous system and are potential targets of pharmaceuticals that could restore physiological brain functions. Towards this goal, an important first step is to decipher the associations between animal behavior, neural activity, and the precise spatial and temporal dynamics of these secreted molecules.

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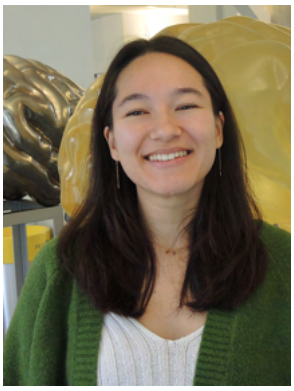

Year joined IPT
2024

Annika Canziani*
PhD in the Patriarchi Lab

Naturalistic Memory Allocation via Neuromodulation

Norepinephrine (NE) is a neuromodulator released by the locus coeruleus (LC) to mediate many physiological functions such as wakefulness, attention and acute stress. Intuitively, memories of stressful experiences are more intense than those of a mundane afternoon. Is it possible that the NE released during such an experience has a role in this phenomenon? Memories are thought to be stored in engrams – a sparse population of neurons, which is active during the encoding stage of the experience and undergo a long-term physical or chemical change. Evidence for the involvement of NE in learning and memory exists, but how it interacts with engrams is not well studied. To understand the role of NE in memory engrams, both fiber photometry and the miniaturized two-photon microscope (Mini-2P) will be used to record NE dynamics during contextual fear conditioning. The two techniques will provide complementary data in terms of their spatio-temporal resolution but the Mini-2P's images will be especially interesting, since there is only limited knowledge about the pattern of NE release.

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Year joined IPT
2025

Anna Durner*
Master Student in the Patriarchi Lab

Development of a genetically encoded biosensor based on the human orexin type 1 receptor (OX1R)

The neuropeptide orexin (hypocretin) regulates arousal, motivation, and reward via two GPCRs: OX1R and OX2R. While a biosensor for OX2R (OxLight1) exists, no equivalent tool is available for OX1R. Here, we report the development of a cpVenus-based fluorescent biosensor for human OX1R, enabling real-time visualization of receptor activation in living cells. The sensor was designed by inserting circularly permuted Venus into the third intracellular loop (ICL3) of OX1R, guided by Ballesteros–Weinstein numbering and design strategies from OxLight1 and dLight. Four variants (SG1, SG2, DG1, DG2) were generated using different ICL3 insertion points and ICL2 modifications. Constructs were assembled by Gibson Assembly, sequence-verified, and tested in HEK293T cells by confocal live-cell imaging after stimulation with orexin A. SG2, featuring TM5/TM6-derived flanking residues, showed the best response with a $\Delta F/F$ of ~330% (vs. ~620% for OxLight1). Variants with short linkers or ICL2 mutations showed lower responses. The best-performing construct was subcloned into an attB-compatible vector for stable cell line generation. Additionally, a site-directed mutagenesis screen targeting the ICL3 segment (LSSLI–DQL) was initiated to further enhance the dynamic range.

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Year joined IPT
2025

Tommaso Fava*
research assistant in the Patriarchi Lab

TrkB-cpGFP sensor development

TrkB, the receptor for brain-derived neurotrophic factor (BDNF), is a key regulator of neuronal survival, differentiation, and synaptic plasticity. Ligand binding triggers conformational changes across its extracellular and transmembrane domains, leading to receptor activation and downstream signaling. We propose to develop a genetically encoded fluorescent indicator by fusing circularly permuted GFP (cpGFP) to the C-terminus of a kinase-dead, truncated TrkB. This design exploits conformational changes occurring near the transmembrane region to modulate cpGFP fluorescence via structural rearrangement of its β-barrel. The resulting sensor will report TrkB activation in real time and in live cells, independently of kinase activity. This tool will enable direct visualization of receptor engagement and may support applications in neurobiology, receptor pharmacology, and high-throughput screening.

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Year joined IPT
2024

Ralph Gradisch*
Post-Doc in the Patriarchi Lab

Expanding the toolbox of genetically-encoded sensors to study monoaminergic neurotransmitters

In recent years, substantial progress in the development of an optogenetic toolbox of sensors allowed us to monitor ligand-induced conformational activation of neurotransmitter receptors, such as the dopamine, serotonin (5-HT), or norepinephrine receptors, with high spatiotemporal resolution. The ability to directly study receptor activation with light is greatly enhancing our understanding of their function and regulation in vitro, using high-throughput assays, and in vivo, in living animals' brains by applying advanced imaging techniques. Similar to already existing GPCR-based sensors, the introduction of a circularly permutated green fluorescent protein (cpGFP) into the human serotonin transporter (SERT) resulted in a fully functional genetically-encoded fluorescent indicator. It permits direct optical recordings of SERT function by coupling conformational changes in SERT upon 5-HT binding, transport, and/or efflux with changes in the fluorescence intensity (brightness). In contrast to gold standard radioligand assays used to characterize transporter pharmacology, this indicator provides insights into transporter dynamics in real-time, compounds' binding- and off-kinetics, as well as the differentiation of substrates from inhibitors. Finally, this sensor will hopefully complete our understanding of synaptic transmission by complementing existing GPCR-based 5-HT sensors to monitor the dynamics of serotonin reuptake in freely behaving mice.

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Year joined IPT
2025

Katja Osman*
PhD in the Patriarchi Lab

Development of a light-activatable MC4R agonistic nanobody

The melanocortin-4 receptor (MC4R) is a G protein–coupled receptor and a key switch in the leptin-melanocortin molecular axis, regulating energy homeostasis, appetite and satiety. Dysfunction of the MC4R is a major contributor to hyperphagia and obesity. Current tools to study the pathways of the individual receptor subtypes often lack specificity, limiting mechanistic insight. Molecules with high specificity for MC4R are therefore essential to unravel its precise molecular function. pN162, a recently developed nanobody with high affinity for the orthosteric binding pocket of MC4R, offers a promising approach to receptor-specific targeting. Using pN162 as a foundation, our goal is to enable precise spatiotemporal control of receptor activation, by fusing a light-oxygen-voltage (LOV) domain to pN162, creating a light-switchable variant. This design allows blue light–dependent conformational changes in the LOV domain to modulate the nanobody's binding, enabling MC4R activation only upon illumination. This approach offers a novel optogenetic tool to better understand MC4R signaling dynamics with high resolution.

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Year joined IPT
2023

Michael Rappleye*
Post-Doc in the Patriarchi Lab

A high-throughput platform for identification of GPCR activating single domain antibodies

Single domain antibodies (SdAb) have revolutionized molecular biology, structural biology, and therapeutics with their binding capabilities, low molecular weight, thermostability, and ease of expression. SdAb's long CDR3 makes them uniquely suited for binding the orthosteric binding pockets of G-protein Coupled Receptors (GPCRs), the largest class of mammalian receptors. SdAb's that bind and activate GPCRs at the orthosteric site have significant promise as therapeutics and structural biology aids. Despite GPCR extracellular accessibility, identifying GPCR-activating SdAb's remains challenging. We hypothesized that cell surface tethered SdAb could activate GPCR-based fluorescent indicators, enabling the identification of GPCR activating SdAb with sensor fluorescence. SdAb library variants were co-expressed with GPCR-based fluorescent sensors in a landing pad cell line, strictly linking phenotype to genotype. We then used FACS to enrich for SdAb-mediated GPCR activation. Naïve libraries of SdAb were pre-enriched against purified target receptor using yeast, phage, or ribosome display before input into the tethered screening system. Starting from pools of 104-5 SdAbs, we have enriched for receptor fluorescence. During enrichment we observe a decrease in UMI barcode diversity, signaling fluorescence-based enrichment for specific SdAb's. Further development of the platform will push the ability to rapidly identify SdAb-GPCR activators.

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Year joined IPT
2021

Valentin Rohner*
PhD in the Patriarchi Lab

Next-Generation GPCR-Based Indicators for In Vivo imaging of Spatiotemporal Norepinephrine Dynamics

Norepinephrine (NE) is a monoamine neuromodulator involved in many neurophysiological functions. Genetically encoded fluorescent indicators based on GPCRs allow precise tracking of NE release in vivo. These indicators are made by inserting a circularly permuted fluorescent protein (cpFP) into the third intracellular loop of a GPCR, translating receptor activation into fluorescence changes. The ligand specificity of the GPCR scaffold remains largely intact, and different GPCR subtypes and cpFPs can be used to fine-tune properties. Our lab recently engineered an improved multicolor family of NE indicators based on the α1a adrenergic receptor using combinatorial mutagenesis and screening. The new variants, nLightG2 and nLightR2, show 2.4× and 4× greater dynamic range than their predecessors. Their NE EC50 values closely match those of the human receptor homolog. These new tools enable improved detection of endogenous NE release ex vivo and in vivo via two-photon imaging and fiber photometry during optogenetic or behavioral stimulation. Furthermore, they are compatible with red or green fluorescent calcium indicators for multiplexed imaging. Notably, nLightG2 enabled visualization of rapid, localized NE transients in the mouse visual cortex in response to a looming stimulus. We expect that nLightG2/R2 will be useful to the scientific community, enabling new discoveries and serving as a base for better understanding NE physiology and pathophysiology.

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Year joined IPT
2023

Vittorio Sandri*
PhD in the Patriarchi Lab

Engineering Near-Infrared GPCR-Based Indicators for Neurotransmitter Imaging

The development of genetically encoded GPCR-based indicators has represented a breakthrough in the field of neuroimaging, enabling the study of pharmacological events in a spatiotemporal manner. Driven by the need to monitor neurotransmitter homeostasis in vivo, efforts in this field have led to the development of various tools based on widely studied neuromodulatory receptors. However, current state-of-the-art indicators rely solely on the use of green and red circularly permuted fluorescent proteins, which present limitations such as high autofluorescence and poor tissue penetration. The use of near-infrared (NIR) fluorescent proteins addresses these issues by offering lower autofluorescence and reduced absorption and scattering at the employed excitation and emission wavelengths. This project aims to implement microscopy- and FACS-based high-throughput screening platforms to engineer NIR and IR norepinephrine indicators. The ultimate goal is to establish a robust strategy for developing a new class of fluorescent imaging tools.

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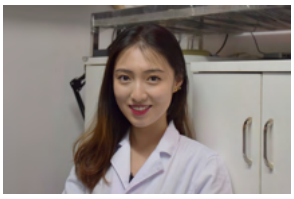

Year joined IPT
2025

Jiachen Song*
Post-Doc in the Patriarchi Lab

The Role of the Noradrenergic LC-mPFC Pathway in Observational Rank Learning

In most animal societies, social rank is a fundamental feature. Social rank is typically stable after being established and has profound consequences for health, survival, reproductive success, and multiple behaviors. While establishing rank through direct physical encounters is effective, it is also energetically costly and inherently risky. It is likely that animals also apply sociocognitive competence to shape their social interactions. Indeed, a number of species rely on observational learning and transitive inference to determine which individuals in a social group are more dominant than others. However, the underlying neural mechanisms that enable this complex cognitive process are poorly understood. While the medial prefrontal cortex (mPFC) is a known hub for encoding social rank, and the neuromodulator norepinephrine (NE) is critical for modulating its activity during social cognition. How the brain learns about social rank without direct experience remains fundamentally unknown. This project will address this gap by combining a novel behavioral paradigm with state-of-the-art biosensors to test the central hypothesis that norepinephrine (NE) release in the medial prefrontal cortex (mPFC) provides the critical signal for translating observed social interactions into an internal representation of rank.

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Abstracts - Razansky group

The Razansky Lab*

Daniel Razansky works at the interface of engineering, biology and medicine to devise novel tools for high performance functional and molecular imaging.
The focus is on methods that can broadly impact pre-clinical research and clinical practice by delivering information presently not attainable with existing state-of-the-art imaging modalities. In particular, new imaging paradigms based on optoacoustics, ultrasonography, fluorescence microscopy, magnetic resonance imaging and their synergistic combinations are developed to enable multi-scale observations with unprecedented spatiotemporal resolution and deep penetration into living intact organisms. The group contributes to the creation of these new technologies in several diverse ways, from the establishment of solid theoretical background, inverse methods, and instrumentation to the development of in vivo small animal imaging methodologies and smart contrast enhancement approaches. Biomedical applications range from preclinical studies into neurodegeneration, functional neuroimaging, cancer and metabolic research to cardiovascular diagnostics and dermatologic applications in human subjects.

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Year joined IPT
2024

Yi Chen*
Post-Doc in the Razansky Lab

Decoding Paradoxical BOLD Responses to Transcranial Ultrasound Stimulation with Concurrent Optoacoustic Magnetic Resonance Imaging

Transcranial ultrasound stimulation (TUS) can affect neural activity with high spatial precision, advancing non-invasive neuromodulation towards targeted treatment of brain disorders. The ability to directly monitor TUS responses is crucial for ensuring optimal outcomes. While blood-oxygenation level dependent (BOLD) functional magnetic resonance imaging is currently the only modality suitable for studying TUS effects in both human and non-human primate brains, the underlying physiology and mechanisms of action remain largely unknown because of the highly convoluted nature of the BOLD signal. To address this, we developed a fully hybridized system for concurrent optoacoustic and magnetic resonance imaging of TUS (OMRITUS) with holographic stimulation capabilities to comprehensively characterize the evoked hemodynamic changes in murine brains. Our findings reveal paradoxical negative BOLD signals in the activated cortical regions, coupled with positive total hemoglobin changes monitored with optoacoustic tomography. Multi-spectral readings further demonstrated a stronger increase in deoxygenated hemoglobin compared to oxygenated hemoglobin, suggesting a potential molecular basis for the negative BOLD responses. OMRITUS enables the study of complex TUS-hemodynamic interactions, paving the way for enhanced optimization of precision neuromodulatory interventions.

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Year joined IPT
2023

Cristian Ciobanu*
PhD in the Razansky Lab

Predicting stroke in a flash: Listening to carotid artery plaques with optoacoustic imaging

Patients suffering from atherosclerosis often develop lipid-rich plaques in their carotid arteries, which may rupture and cause strokes. Identifying vulnerable plaques is key to stroke prevention. Optoacoustic imaging, which uses light to generate ultrasound signals from molecules like lipids, shows promise for non-invasive plaque assessment. However, imaging deep structures such as the carotid artery presents unique challenges. In this research, we aim to address several technical hurdles to improve image quality and lipid quantification. In vivo ultrasound and optoacoustic images of carotid plaques were collected from patients. Corrections for speed of sound variations and system response were made using phantom measurements. A deformable registration method was developed to compensate for vessel motion, enabling frame averaging and noise reduction. To improve accuracy in lipid quantification, we are developing simulation-based and physics-informed machine learning models to correct for the complex wavelength-dependent attenuation of light, which prohibits accurate quantification with conventional methods. Once optimized, we will analyze lipid signals in plaques and correlate them with stroke outcomes in a patient cohort. Radiomics and other machine learning methods will be used to identify imaging features that best predict plaque vulnerability.

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Year joined IPT
2019

Hector Estrada*
Senior Scientist in the Razansky Lab

Imaging ultrasound neuromodulation in mice

Transcranial ultrasound neuromodulation is a promising technique with potential to help us treat and better understand the brain. Current methods of transcranial ultrasound delivery and functional brain imaging in humans cannot provide a detailed account of the brain activity under ultrasonic stimulation. In order to know how ultrasound affects the neurons in a living brain, we combined the optical tools developed to image calcium dynamics in mice with precise ultrasound delivery (FLUS). Using a fluoro-thermal tag, we are able to visualize in real time the position and relative intensity of the ultrasound focus. We hope the FLUS system and our methods can help clarify how ultrasound waves can be exploited in brain therapy and neuroscience.

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Year joined IPT
2021

Irmak Gezginer*
PhD in the Razansky Lab

Concurrent optoacoustic tomography and magnetic resonance imaging of functional brain activity in mice

Optoacoustic tomography (OAT) enables non-invasive, multiparametric characterization of cerebral hemodynamics across the entire mouse brain, providing unique functional information not attainable through other imaging modalities. However, validating the specificity and accuracy of transient biological signals captured by OAT in vivo remains challenging. To overcome this limitation and maximize the potential of OAT, we developed a hybrid magnetic resonance and optoacoustic tomography (MROT) system, which allows simultaneous acquisition of OAT and MRI data. The concurrently collected bimodal data facilitates precise anatomical coregistration and accurate brain parcellation, significantly enhancing interpretability and integration of multimodal findings. We demonstrate comprehensive multiparametric brain-wide responses obtained simultaneously during various experimental paradigms, including different breathing gas conditions, sensory stimulation, and resting-state acquisitions. This integrated approach enables robust cross-validation between modalities and provides deeper insight into the complex dynamics underlying neurovascular and neurometabolic coupling, thus offering novel capabilities for investigating brain function and associated disorders.

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Year joined IPT
2020

Lukas Glandorf*
Post-Doc in the Razansky Lab

Quantitative Mapping of Cerebrovascular Network Dynamics in Stroke Using Optical Coherence Microscopy

Understanding how microvascular blood flow adapts under pathological stress is critical in stroke research. However, current imaging tools either offer high resolution over small fields-of-view or cover large areas without capillary detail. To bridge this gap, we developed a quantitative, in vivo imaging platform based on extended-focus optical coherence microscopy, tailored for mesoscale cerebrovascular mapping. Using Bessel beam illumination and Doppler processing, we achieve volumetric imaging of brain vasculature with micrometer resolution and extract total flow velocities and directions across thousands of vessels. We further introduce network-based analysis tools including artery-vein separation and flow topology classification. Applying this to a mouse stroke model, we observed widespread capillary stalling in the penumbra and quantified how vascular topology impacts stall susceptibility. Notably, certain flow configurations were more prone to ischemia-induced failure, yet their distribution remained robust post-stroke. These insights highlight the importance of topological resilience in vascular networks and offer a powerful framework to study cerebrovascular function and its breakdown in disease.

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Year joined IPT
2024

Tian Jin*
Post-Doc in the Razansky Lab

Coordinated Two-Photon Fluorescence and Optoacoustic Microscopy of Neural, Vascular, and Cellular Dynamics in the Mouse Brain

Imaging techniques capable of visualizing the nervous and vascular systems are essential for uncovering the fundamental mechanisms underlying brain functions. To enable visualization of both systems at the microscale with a streamlined imaging setup, we developed dual-modal two-photon fluorescence optoacoustic microscopy (TPOAM) for imaging neuronal calcium activity concurrently with label-free hemodynamic detection. TPOAM achieves sub-micron lateral resolution and real-time multi-plane imaging capability with temporal resolution down to 100 ms enabled by a rapid spiral scanning strategy. We use TPOAM to offer a comprehensive platform for studying neural, vascular, and cellular dynamics in the brain. In addition, we are also working on the development of miniaturized TPOAM systems, as well as fully optical detection schemes for TPOAM.

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Year joined IPT
2021

Xiang Liu*
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Handheld embedded laser-diode illumination optoacoustic system for real-time 3D angiography of deep tissues

The clinical adoption of optoacoustic imaging is currently being impeded by the bulky design and high cost of traditional systems based on solid-state lasers. We introduce a cost-effective, high-performance Handheld Embedded Laser-diode Illumination Optoacoustic System (HELIOS) based on a spherical array probe incorporating a compact illumination source located in close proximity to the imaged object. High performance drivers have been designed to produce 1.8 mJ energy pulses at 915 nm wavelength, sufficient for rendering entire ~1 cm3 image volumes with high spatial and temporal resolution. The fast imaging performance is further facilitated by high-speed acquisition electronics capable of simultaneous sampling of all the 256 transducer channels at 400 Hz pulse repetition frequency of the laser diodes. HELIOS attains image quality and performance metrics on par with those achieved with solid state laser sources. We demonstrate volumetric angiography of human fingers and palm in a freehand mode and perform large-scale volumetric compounding of vascular structures from the time-lapse 3D data. This advancement represents a major leap toward translation of optoacoustics into point-of-care and resource-limited settings.

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Year joined IPT
2023

Nima Mahkam*
PhD in the Razansky Lab

Micro-Robotic Therapeutics Driven by Acoustic Field Response

Focused ultrasound enables wireless actuation of agents deep within tissue. We introduce microparticles that exhibit two coupled FUS responses: acoustophoretic trapping for guided transport in confined geometries, and controllable thermal transduction for on-site therapy. In spatially structured fields, the particles self-assemble at pressure nodes, are stably trapped in small vessels, and can be translated under physiologic flow without invasive mechanical contact. By tuning burst length, duty cycle, and acoustic intensity, we switch reversibly between manipulation and heating, producing rapid, localized temperature rises suitable for hyperthermia or ablation while sparing surrounding regions. We detail particle architecture, field configurations for stable trapping under flow, and control schemes that enable robust confinement, transport, reversible release, and repeatable thermal dosing. Temperature rise and lesion size scale with drive parameters, enabling predictable, on-demand energy deposition. This capability supports catheter-free interventions in deep sites. Together, these results establish a microrobotic therapeutic approach in which a single, remote acoustic field provides precision positioning and tunable heat to treat tissue on demand.

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Year joined IPT
2023

Eva Remlova*
PhD in the Razansky Lab

Deep Tissue Optoacoustic Monitoring of Photothermal Treatments in the NIR-II Assisted with Silica-coated Gold Nanorods

Gold nanoparticles (AuNPs) absorbing light in the near-infrared (NIR) range offer unparalleled benefits for both optoacoustic (OA) imaging and photothermal therapy (PTT), stemming from their ability to transform optical energy into heat. These unique theranostic capabilities are further complemented with the high sensitivity of OA signals to temperature variations. However, AuNP typically experience rapid photodegradation when exposed to high laser intensities, which hinders their efficient monitoring with OA. To address this critical limitation, we capitalize on the enhanced photostability of silica-coated gold AuNRs featuring an absorption peak in the second NIR window (NIR-II, 1064 nm). Their comprehensive evaluation under exposure to nanosecond-pulsed and continuous-wave (CW) radiation revealed that the synthesized AuNRs are photostable under laser energy densities required for efficient therapy under OA imaging guidance, which was confirmed with electron microscopy images. Real-time volumetric OA mapping of PTT-induced temperature variations was verified using simultaneous thermal camera readings, whilst post mortem experiments in mice corroborated the viability of this theranostic approach in deep biological tissues.

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Year joined IPT
2022

Shruti Sundar*
PhD in the Razansky Lab

Discerning Amyloid-β and Tau Pathologies with Learning-Based Quantum Sensing

Neurodegenerative diseases such as Alzheimer's disease (AD) are characterized by early, subtle microstructural changes that are challenging to detect with conventional imaging. We present a label-free quantum sensing method using a polarization-entangled photon source to distinguish between different AD and healthy mouse model brain tissue. By analyzing entanglement decoherence induced by tissue scattering, we extract two physical observables: linear entropy and tangle, as sensitive indicators of structural differences. These observables follow a theoretical Werner state model, allowing physical interpretation of their variation. These observables were used as input features to train a support vector machine (SVM) classifier, which achieved accurate separation between AD and healthy samples across cortical and hippocampal regions, including in unseen test data. Interestingly, entanglement was more preserved in AD samples, suggesting differential scattering behavior. The results were validated against immunohistochemical techniques and a commercial confocal microscope, confirming disease pathology. These findings suggest that quantum sensing could serve as a potential tool for distinguishing biological samples, with applications in the field of neurodegenerative disorders.

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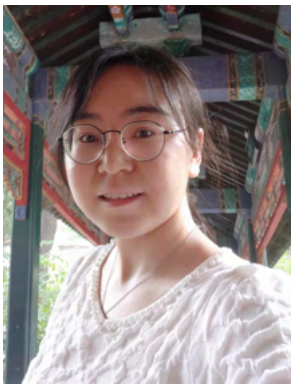

Year joined IPT
2021

Lin Tang*
PhD in the Razansky Lab

Integrating nanotechnology with noninvasive optical imaging to illuminate tissue structure and function

Optical imaging techniques based on fluorescent and absorption-based (optoacoustic) contrast have become indispensable tools in biology and medicine owing to their rich functional andmolecular contrast. However, the resolution and imaging depth of intravital optical imaging is commonly challenged by light diffusion and strong background signals generated by living tissues. We are developing contrast agents with strong spectral signatures in the second near-infrared (NIR-II) window to boost the sensitivity, contrast and penetration depth of optoacoustic and fluorescence imaging. For localization-based angiographic applications, biocompatible cell-sized particles have been developed that exhibit high fluorescence brightness and deformable shape for free circulation. Furthermore strongly absorbing nanoparticles are devised for superior optoacoustic efficacy in the second near-infrared window.

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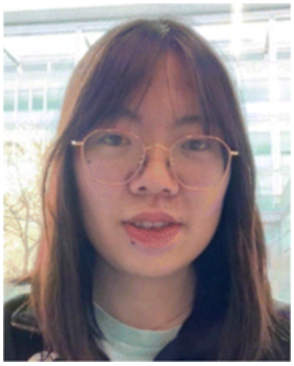

Year joined IPT
2019

Quanyu Zhou*
Post-Doc in the Razansky Lab

Needle beam two-photon microscopy for simultaneous multiplane neural and vascular imaging

Comprehensive understanding of brain functions necessitates high-speed imaging of neuronal and vascular dynamics across extensive volumes. Functional neuroimaging investigations with two-photon microscopy are commonly hindered by its limited depth of field which restricts imaging rates across multiple planes. We introduce needle-shaped beam two-photon microscopy (NB-2PM), a versatile platform for high-throughput neurovascular imaging at sub-cellular resolution across multiple depths. It employs customized diffractive optical elements to enable generating single- or multiplane needle beams with up to 10 times elongated depth of field relative to Rayleigh lengths and engineered axial energy distribution to effectively offset light attenuation with depth. The proposed method was applied to snapshot volumetric vascular imaging and multi-plane neurovascular dynamic recordings of resting state and stimulus-evoked activity in mice. NB-2PM can seamlessly be integrated into existing microscopy systems, thus providing a scalable platform for gaining comprehensive insights into the functional architecture of murine brain.

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Abstracts - Saab group

The Saab Lab*

We are interested in understanding how glial cells and neurons interact to maintain normal brain function and long-term cellular homeostasis. The mechanisms by which glial cells are involved in regulating neuronal functions and metabolism are still poorly understood. Current working models suggest that both myelinating oligodendrocytes and astrocytes, which form a pan-glial syncytium by gap-junction coupling, are highly glycolytic and supply neuronal compartments with energy substrates to fuel energy demands and to support long-termintegrity. We are particularly interested in how myelinated axons are maintained by glial support functions. Very little is known about the cellular mechanisms underlying axon-glial interactions and metabolic cooperation. How do myelinating oligodendrocytes sense neuronal activity and how are these signals translated into maintaining neuronal functions? How are these cellular interactions perturbed during inflammation, normal aging and upon neurological pathologies? And could perturbations in axon-glial communication and deficits in glial metabolic support impact the etiology and pathogenesis of neurodegenerative diseases? To address these questions we combine molecular genetics, electrophysiology, in vivo and ex vivo two-photon imaging, histology, electron microscopy and behavioral studies in mice to investigate cellular mechanisms regulating intercellular communication, energy homeostasis and cellular integrity.

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Year joined IPT
2020

Urvashi Dalvi*
PhD in the Saab Lab

The relationship between mitochondrial ROS in oligodendrocytes and axonal health

Oligodendrocytes (OLs) myelinate axons to enable rapid electrical conduction and provide metabolic support essential for long-term neuronal integrity. Dysregulated OL function contributes to axonal degeneration in aging and neurological disorders, yet the intrinsic molecular alterations within OLs that influence axonal health remain poorly defined. Mitochondrial reactive oxygen species (mROS) modulate cellular pathways in a context-dependent manner and accumulate in neurodegeneration, but their impact on OL biology and axonal integrity is unclear. To elucidate the role of OL mROS, we generated OL-mCat mice with mitochondrially targeted expression of catalase specifically in OLs. We confirmed localization of HA-tagged catalase to mitochondria of mature OLs in white-matter tracts. Electrophysiological recordings from optic nerves revealed a striking ability of myelinated axons from OL-mCat mice to sustain prolonged axonal activity in an age-dependent manner. Additionally, aged OL-mCat mice showed reduced axonal damage and improved sensorimotor function. In a model of experimental autoimmune encephalomyelitis, OL-specific mROS quenching attenuated axonal pathology and clinical severity. These findings demonstrate that oligodendroglial ROS critically regulate axonal function and suggest that targeted mROS reduction in OLs may confer neuroprotection in aging and neuroinflammatory disease.

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Year joined IPT
2022

Zainab Faik*
PhD in the Saab Lab

Distinct Metabolic Specializations in White Matter Oligodendrocytes, Astrocytes, and Axons

Axonal integrity is crucial for brain function. However, the mechanisms by which oligodendrocytes and astrocytes support axonal health in white matter, especially their metabolic interactions and energy sources, remain poorly understood. In this study, we used two-photon imaging of the optic nerve alongside compound action potential (CAP) recordings to monitor both cellular ATP homeostasis and axonal spiking activity. We developed novel adeno-associated virus (AAV) delivery strategies to express the FRET-based ATP sensor Ateam1.03 specifically in optic nerve oligodendrocytes or astrocytes. Our findings revealed distinct metabolic capacities in glial cells and axons. Both oligodendrocytes and astrocytes were able to maintain some ATP levels in the absence of glucose, while axonal conduction ceased entirely. Oligodendrocytes were more efficient in switching to lipid metabolism during aglycemia compared to astrocytes, which required more time to initiate this pathway. We also identified differences in the ability of axons and glial cells to metabolize other substrates for ATP production. Our findings suggest that both oligodendrocytes and astrocytes can metabolize fatty acids or other substrates during hypoglycemia, potentially allowing the precious glucose to be delivered to axons to support critical antioxidant functions.

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Year joined IPT
2021

Henri Zanker*
PhD in the Saab Lab

Monitoring Neuronal and Axonal Health In Vivo Using Two-Photon FLIM

Glial cells play a pivotal role in supporting neuronal and axonal function, particularly by regulating metabolic processes. Dysfunction of oligodendrocytes (OL) and myelin, as seen in multiple sclerosis, has been linked to axonal degeneration. However, when and how neurons and axons suffer upon OL dysfunction remains unclear, particularly during demyelination. Here, we established in vivo FLIM of biosensors in cortical neurons and subcortical white matter axons to monitor neuronal and axonal health. Using the FRET-based ATP sensor ATeam, we demonstrate that FLIM can detect ATP deficits in degenerating neurons and axons in vivo. By combining ATP imaging with two-photon chemical ablation (2Phatal), we tracked the temporal dynamics of energy failure in neurons undergoing apoptosis. Furthermore, using transcortical window implantations, we imaged axonal projections in the corpus callosum in vivo. Using Rbp4-Cre mice we expressed ATeam specifically in layer 5 neurons and monitored their callosal axons over several weeks while inducing demyelination with cuprizone. This approach revealed ATP deficits in callosal axons forming swellings before disappearing, indicating that a subset of axons degenerates due to OL dysfunction or demyelination. Taken together, in vivo 2P-FLIM enables the monitoring of metabolic shifts in degenerating neurons and axons, which could offer critical insights into cellular processes involved in the pathophysiology of neurodegenerative diseases.

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Abstracts - Schwank group

The Schwank Lab*

Our main goal is the clinical translation of genome editing tools. We engineer novel CRISPR-based genome editing variants, develop vehicles and approaches for their in vivo delivery, and conduct CRISPR screens to unravel the genetic components of complex diseases such as cancer.

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Year joined IPT
2025

Miriam Ader*
Master Student in the Schwank Lab

Characterization and translation of RNA base editor variants identified with OrthoRep-mediated directed evolution

RNA base editors act transiently on the transcriptome, minimizing off-target efects while maintaining protein functionality and bypassing DNA-repair machinery and protospacer adjacent motif requirements. The REPAIR system, using a catalytically impaired type VI Cas nuclease (dCas13b) and ADAR2, enables A-to-I RNA editing. Enhanced by protein engineering and directed evolution, ADAR2 also mediates C-to-U conversions, resulting in the RESCUE tool. Editing efficiency highly depends on the sequence context. OrthoRep allows the continuous evolution of RESCUE and REPAIR editors, selecting variants with sequence specificity. This parallel evolution process led to the identifcation of multiple variants that will further be characterized.

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Year joined IPT
2025

Julia Ege*
Master Student in the Schwank Lab

Multiplexed cloning of chimeric spCas9 proteinss

In my Master's thesis, I aim to expand the targeting range of Streptococcus pyogenes Cas9 (SpCas9) by establishing a cloning strategy that enables the multiplexed assembly of multiple chimeric Cas9 variants simultaneously. To broaden PAM (Protospacer Adjacent Motif) recognition, I aim to create chimeric Cas9 proteins where I exchange the spcas9 PAM-interacting domain (PID) with numerous orthologous domains.

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Year joined IPT
2025

David Erne*
Master Student in the Schwank Lab

Conjugation of antibodies to lipid nanoparticles for the production of CAR-T cell therapies directly in patients

The aim of this work is to develop mRNA-loaded LNPs that specifically bind to and deliver CD3+ T cells. Binding elements (Fab fragments, nanobodies and DARPins) are coupled to LNPs and then tested in vitro and in vivo for their functionality with regard to the coupling of the binding elements to the LNPs and the effectiveness of mRNA delivery to the T cells. To do this, LNPs are linked with different binding formats, and then the coupling of the LNPs to CD3+ T cells is tested and transferred to the mouse model. The coupling of the targeting moieties to the LNP is mediated by click chemistry and/or maleimide.

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Year joined IPT
2024

Silvan Estermann*
Technician in the Schwank Lab

Enhancing therapeutic protein expression from circular RNA via selection of Internal Ribosomal Entry Sites

mRNA based therapeutics have gotten an up-draft since the development of the first approved mRNA-based vaccines during the recent pandemic. However, for less-transient applications such as gene addition, linear mRNA lacks the necessary stability for prolonged expression. Circular RNA (circRNA) shows higher stability and prolonged protein expression due to its inherent resistance to exoribonucleases. However, circRNA needs to be translated through a cap-independent mechanism, as they lack a 5' end and therefore a cap structure. For circRNA, ribosome recruitment is mediated through binding sites formed by the tertiary structure of the RNA itself, termed Internal Ribosomal Entry Sites (IRESes). As ribosomal recruitment through IRESes is generally less efficient than for a traditional 5' cap, I aim to develop a novel and accessible platform for the selection of highly expressing IRESes in cells of interest. With this, I aim to enhance protein translation and therefore therapeutic potential of circRNA.

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Year joined IPT
2023

Sara Ferreira*
PhD in the Schwank Lab

Towards in vivo generation of CAR T cell therapies

Chimeric Antigen Receptor (CAR) T cell therapies have become increasingly relevant due to their success against hematologic malignancies. Nevertheless, they still face several limitations. Traditionally, CAR T cells are generated ex-vivo resorting to viral vectors and transferred to patients following lymphodepletion. This approach poses high costs and manufacturing complexity, preventing scalability and widespread application. Here, we propose to develop a different production approach. Our goal is to enable in-patient generation of transient CAR cells by resorting to Lipid Nano Particle (LNP) delivery of CAR coding mRNA, bypassing the need for ex-vivo engineering. This approach dramatically reduces costs, as well as the logistical complexities of personalized manufacturing. Moreover, transient CAR expression achieved with mRNA, without random lentiviral integration, presents a significantly improved safety profile whilst eliminating the need for lymphodepletion. By resorting to in vivo imaging system and LNPs carrying luciferase mRNA, we intend to decipher the ideal composition of a splenotropic LNP. We will further optimize delivery and expression, and access CAR cell efficacy with a syngeneic mouse tumor model. By eliminating the reliance on specialized manufacturing facilities, this in vivo CAR cell engineering platform holds the potential to transform CAR T cell therapies.

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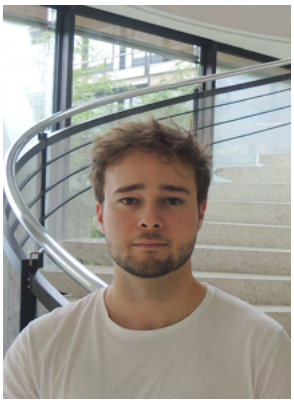

Year joined IPT
2024

Charles Guillain*
Master Student in the Schwank Lab

Evolving the Bxb1 Integrase Using Phage-Assisted Continuous Evolution (PACE)

My project aims to harness the power of directed evolution, specifically Phage-Assisted Continuous Evolution (PACE), to engineer the integrase Bxb1 for enhanced efficiency and precision in integrating DNA payloads within the mammalian genome. By evolving the Bxb1 integrase, I seek to improve its ability to target and insert large DNA constructs into specific chromosomal sites without the need for pre-installed recognition sequences. The project focuses on optimizing the integrase's performance through iterative cycles of mutation and selection, ultimately developing a versatile tool for site-specific genome editing. This approach has the potential to significantly advance therapeutic gene integration by enabling the precise insertion of large genetic constructs into clinically relevant loci with high efficiency and specificity, thereby overcoming current limitations in targeted genome engineering.

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Year joined IPT
2023

Peter Kulcsar*
Post-Doc in the Schwank Lab

Rescue of MC4R related obesity by in vivo base- and prime-editing in mice

Obesity poses a significant public health challenge. Monogenic obesity, a severe subtype, arises from disruptions within the leptin-melanocortin system, often attributed to mutations in the melanocortin 4 receptor (MC4R) gene. Loss-of-function mutations in MC4R are associated with early-onset obesity in both humans and mice. Developing new treatment methods for these patients is crucial, as lifestyle interventions are often insufficient and MC4R agonists show strong side effects and are not applicable in patients with homozygous loss-of-function mutations. In this study, we employed both base and prime editing to restore MC4R function in a knockout mouse model. Following in vitro screening of multiple base and prime editing strategies using a reporter cell line, the most effective editors were selected for in vivo application. Treated mice exhibited a significant reduction in body weight reaching wild-type levels, alongside normalized glucose tolerance and key metabolic biomarkers. Notably, application of the base editing strategy was also effective in older mice that had already developed obesity, resulting in complete phenotypic rescue. Although base- and prime editing has been previously applied in neurons, its therapeutic application in the central nervous system (CNS) remains largely unexplored. This study provides a proof-of-concept for the correction of monogenic obesity via precise genome editing in the hypothalamus and expands the toolkit for in vivo CNS editing.

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Year joined IPT
2020

Kim Fabiano Marquart*
Post-Doc in the Schwank Lab

High-Throughput Directed Evolution of PAM-specific SpCas9 Variants

The broad utility of CRISPR-Cas systems continues to drive innovation in genome editing technologies. However, engineering proteins for precise and efficient editing remains a significant bottleneck, particularly when aiming for high specificity and applicability. In this work, we present a novel framework for evolving and functionally validating genome editors that are tailored to specific PAM-sequence contexts. By integrating continuous directed protein evolution with scalable cellular assays and ML, we demonstrate a streamlined approach for generating new genome editing tools. This platform enables targeted improvement in the SpCas9 variants without compromising general applicability, offering a promising route to next-generation, ultra-specific CRISPR-based technologies. Our findings support the utility of combining empirical evolution with data-driven methods to accelerate the development of customized genome engineering solutions.

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Year joined IPT
2023

Sasha Melkonyan*
RA in the Schwank Lab

Large gene insertion therapy for Huntington's disease

Huntington's disease (HD) is a severe, inherited neurodegenerative disorder. Despite over a hundred clinical trials in the past two decades, no approved disease-modifying therapies currently exist.Identification of expanded CAG repeats in the HTT gene as the causative mutation has spurred the development of therapeutic strategies focused on reducing HTT expression. However, no clinically relevant strategy for allele-specific knockdown of HTT with broad applicability across the entire patient population has been demonstrated to date. We propose a novel approach for the functional inactivation of the pathogenic HTT exon 1 through the endogenous insertion of a therapeutic exon 1 copy. This strategy preserves endogenous expression levels of the wild-type huntingtin while ensuring selective degradation of the protein fragment derived from the pathogenic exon 1.

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Year joined IPT
2023

Saphira Müller*
PhD in the Schwank Lab

Towards targeted large DNA insertions into the genome – Understanding R2 Retrotransposon mechanisms

My project aims to investigate the mechanism and enhance the efficiency of R2 retrotransposon integration into the genome. Retrotransposons are transposable elements that facilitate gene movement across species, driving genetic diversity and evolution. They are categorized into DNA transposons and retrotransposons, with R2 elements uniquely integrating into the 28S ribosomal DNA (rDNA) locus, which exists in multiple copies in vertebrates. R2s naturally insert large DNA sequences from an RNA template into the 28S locus via target-primed reverse transcription (TPRT), yet the host factors that mediate this process remain unknown. To uncover these cofactors, we will perform a genome-wide CRISPRi screen in two human cell lines—K562 (leukemia) and hTERT-RPE1 (retinal pigment epithelium). Cells will be challenged with an R2 integration reporter that couples successful large-fragment insertion to fluorescence activation. Deep sequencing of sgRNA representation will identify candidate host factors that enhance or impair R2 integration. Top hits will be arrayed and characterized to illuminate key steps of the TPRT mechanism, with a focus on second-strand synthesis, which remains largely unexplored. Further applications will include testing R2 integration in vivo in mice. Ultimately, this work will establish a novel platform for precise, large-cargo genome insertion, expanding the toolkit for gene-therapy applications beyond current viral and transposon systems.

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Year joined IPT
2025

Maria Repson*
Technician in the Schwank Lab

Phage-assisted continuous evolution of genome editing tools

As a Research Technician, I work together with Kim Marquart and Lukas Schmidheini, both in the lab and through their start-up Nerai, toward the shared goal of developing better, more precise and powerful genome editing tools. I support the ongoing research and help move these technologies closer to real-world applications.

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Year joined IPT
2025

Laura Schäfer*
Master Student in the Schwank Lab

Enhancing Template-Jumping Prime Editing Efficiency for Large DNA Insertions

We aim to improve the efficiency of template-jumping prime editors (TJ-PEs) for precise insertion of large DNA sequences without inducing double-strand breaks. By incorporating the PE3b strategy, we seek to optimize the performance of pegRNA-driven insertions. In a second phase, we will adapt a selection scheme using the OrthoRep system, a yeast-based directed evolution platform, to evolve TJ-PE variants and improve their integration capabilities. These engineered editors are expected to exhibit higher insertion efficiency, offering a more reliable and scalable platform for precise genome editing with broad therapeutic potential.

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Year joined IPT
2025

Céline Schönenberger*
Master Student in the Schwank Lab

Enhancing CAR Therapy for Solid Tumors via RNA Co-Delivery

Chimeric antigen receptor (CAR)-based immunotherapies have demonstrated remarkable success in treating hematologic malignancies. However, translating this success to solid tumors remains challenging due to physical barriers, heterogeneous antigen expression, and potent immunosuppressive signals within the tumor microenvironment. This project focuses on enhancing CAR therapies not just by optimizing receptor design, but by enhancing the ability of primary immune cells to overcome exhaustion and suppression within solid tumors. To evaluate different CAR constructs an mRNA-based transfection approach is being optimized to achieve robust CAR expression in murine primary macrophages and T cells, transient expression suitable for in vitro functional studies. Alongside this, the inhibitory receptor SIRPα, a key mediator of the "don't eat me" signal, will be silenced using siRNA to help further improve the cells' tumor-clearing potential. The efficiency of our dual-RNA approach will be assessed by measuring HER2 tumor cell phagocytosis and killing in functional assays that compare CAR expression alone, SIRPα knockdown alone, and their combination. This approach couples targeted recognition with checkpoint inhibition to amplify anti-tumor immunity.

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Year joined IPT
2024

Kostas Stiklioraitis*
PhD in the Schwank Lab

Assessing The Interplay Between Chromatin And Gene Editing Outcomes

New generation genome editing tools, such as prime editors, offer superior versatility compared to traditional CRISPR-Cas endonucleases by allowing all 12 possible base conversions as well as short deletions and insertions. Recent studies from our and other labs have demonstrated that in addition to the target DNA sequence context, locus-specific chromatin features can strongly influence editing rates. In this project, we aim to systematically assess how native epigenetic marks affect prime editing efficiencies across diverse cellular contexts with the intention of building 'cell-type aware' predictive models. Additionally, we aim to develop and validate strategies for modulating local chromatin states. We hypothesize that these platforms could be used to both expand the breadth of editable sites within the human genome by improving the accessibility of heterochromatic DNA, and to reduce editing at known off-target sites.

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Year joined IPT
2025

Fabian Stähli*
Master Student in the Schwank Lab

Circularization of Modified RNA for Therapeutic Applications

In the years preceding the pandemic, the idea of mRNA-based medicines was generally met with skepticism due to the immunogenic nature and inherent instability of RNA. These widespread concerns were proven wrong by the broad application of state-of-the-art synthetic mRNA in the COVID-19 vaccines. mRNA is largely immunoquiescent owing to the incorporation of modified nucleosides and high purity. The translational efficacy of synthetic mRNA is high, which makes it perfectly suitable for therapeutics. However, the half-life of such synthetic mRNA is in the range of a few hours, which is ideal for vaccines but unsuitable for gene addition therapies. Circular RNA can overcome this problem by increasing resistance to exonuclease-mediated degradation. This Master thesis aims to identify potent self-splicing ribozymes that enable circularization of modified RNA, thereby reducing its susceptibility to degradation.

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Year joined IPT
2025

Daniel Teixeira*
Master Student in the Schwank Lab

Benchmarking various large-insertion genome editing tools

As a Master's student in Biomedicine, I joined the Schwank Lab for my thesis project, working closely with Eleonora and Saphira. My research focuses on benchmarking various large-insertion genome editing tools, with a key aspect dedicated to analyzing and comparing their off-target effects. By systematically evaluating these tools, this project aims to provide insights into their efficiency and specificity, contributing to the advancement of precise genome engineering techniques.

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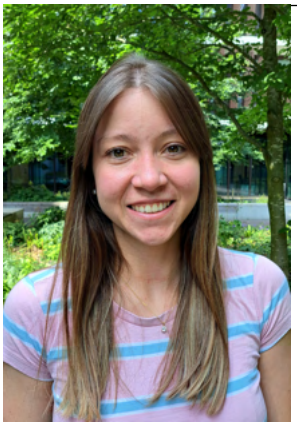

Year joined IPT
2023

Elina Villiger*
PhD in the Schwank Lab

Gene Editing Rescues MC4R Function and Reverses Genetic Obesity in Mice

Obesity presents a major public health issue, with monogenic obesity - often caused by mutations in the melanocortin 4 receptor (MC4R) gene - representing a severe, early-onset form. These loss-of-function mutations disrupt the leptin-melanocortin system, rendering lifestyle interventions ineffective. Current pharmacological treatments are limited, particularly for patients with homozygous MC4R mutations. To date, monogenic obesity has not been targeted using genome editing. In this study, we applied base and prime editing to restore MC4R function in a knockout mouse model. After screening multiple base editing strategies in vitro, we selected the most effective for in vivo use. Treated mice showed a marked reduction in body weight, normalization of glucose tolerance, and improved metabolic markers. Importantly, even obese adult mice responded to treatment with full phenotypic rescue. Due to low in vivo efficiency of prime editing, we optimized pegRNA design, editing strategies, and dosing regimens. While most led to partial rescue, neonatal delivery of the top-performing prime editor achieved substantial weight reduction. Though base and prime editing have been used in neurons, their therapeutic use in the CNS remains largely untapped. Our work offers proof-of-concept for genome editing–based correction of monogenic obesity in the hypothalamus, expanding the potential of CNS-targeted therapies.

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Year joined IPT
2022

Priscilla Wang*
PhD in the Schwank Lab

Directed Evolution of Novel RNA-binding DNA Nucleases

Originally evolved as a prokaryotic immune system against invading bacteriophages and other mobile genetic elements, clustered regularly interspaced short palindromic repeats (CRISPR) systems and their associated (Cas) nucleases have revolutionized the fields of biology and medicine. Despite their widespread use as gene-editing tools, there are two major limitations to their use in the clinic. First, delivery vectors (ie. AAV) have limited packaging limits. Second, positioning of CRISPR-Cas complexes is controlled by a protospacer adjacent motif (PAM), or a transposon-associated motif (TAM) for transposon-derived nucleases (ie. TnpB, IscB) thought to be evolutionary ancestors of Cas nucleases. Therefore, long and complex PAMs and TAMs greatly restrict the availability of genomic sites targetable for gene editing. We may address these limitations by using directed evolution and protein engineering to improve the activity and relax the PAM/TAM preference of recently discovered miniature nucleases. We can improve these nucleases by applying a directed evolution method called phage-assisted continuous evolution (PACE) using an evolution logic that links DNA-binding activity at relaxed PAMs/TAMs to M13 phage propagation.

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Year joined IPT
2020

Yanik Weber*
PhD in the Schwank Lab

Continuous Evolution of RNA Editors to Enhance A-to-I and C-to-U Editing

Programmable A-to-I and C-to-U RNA editors enable transient transcript recoding but often exhibit limited catalytic activity. Here, we coupled the yeast continuous directed evolution platform OrthoRep—whose error-prone polymerase exclusively replicates editor genes—to selectable phenotypes that either restore auxotrophy or repress toxin expression via precise RNA editing. By adjusting paired edits, crRNA spacer length and target-mRNA abundance, we fine-tune evolutionary pressure. In proof-of- principle experiments, we rapidly enriched the ADAR2 E488Q gain- of-function mutation and discovered additional variants (e.g., D420R) that boost on-target editing. This generalizable pipeline accelerates optimization of RNA-modifying effectors for research and therapeutic applications, providing a rapid, scalable route for the directed evolution of high-activity RNA editors.

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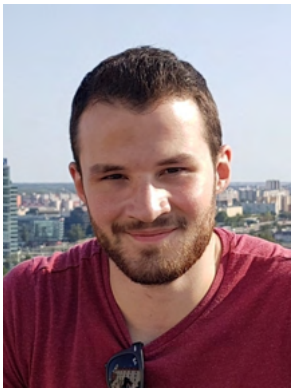

Year joined IPT
2020

Andrin Abegg*
PhD in the Tyagarajan/Karayannis Lab

Sexually dimorphic control of contextual memory specificity through inhibitory postsynaptic remodeling in hippocampal engram neurons

Hippocampus-dependent episodic memory encoding and consolidation in neuronal ensembles -or engrams- require dynamic and engram-specific plasticity of excitatory connectivity. Although excitatory cells comprise the bulk of hippocampal neurons, around 15% of the neuronal population is inhibitory. While an increasing interest in inhibitory signaling has led to the discovery of its importance for controlling episodic memory encoding and consolidation, its contribution to the function of individual engram neurons is largely unknown. In this project, we study the inhibitory synaptic plasticity of hippocampal engram neurons and its function in memory specificity. We employ the Fos-TRAP2 system to label and manipulate contextual fear memory engrams in mice. We demonstrate that engram neurons in the dentate gyrus display a potentiation of perisomatic inhibitory input lasting at least one week after initial memory encoding. This inhibitory plasticity involves both GABA- and glycine receptors in a sexually dimorphic manner. We use Cre-dependent RNA interference and deletion in combination with the Fos-TRAP2 system to disrupt inhibitory signaling specifically in engram neurons. By targeting GABA-A receptors, glycine receptors, and the scaffold protein Gephyrin independently, we demonstrate that male and female mice have different requirements for the engram-specific accumulation of inhibitory postsynaptic proteins to maintain contextual memory specificity.

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Abstracts - Weber group

The Weber Lab*

Our group uses a wide range of imaging tools to study the cell-to-cell communication pathways involved in energy metabolism and information processing in cerebral cortex. Furthermore, we are working on dissecting the interaction of neurons and astrocytes with the vascular system, which is responsible for maintaining adequate delivery of oxygen and energy substrates to the brain. As well as studying these systems, the development of imaging systems for in vivo research is an additional research focus of the group.

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Year joined IPT
2014 and 2024

Ladina Hösli*
Scientist in the Weber Lab

Rapid High-Pressure Freezing Workflow for Improved Brain Tissue Preservation

Although chemical fixation is standard for EM sample preparation, it introduces artifacts such as osmotic imbalances, shrinkage, and structural distortion, that compromise ultrastructural quantification of volume fractions and delicate cellular interfaces. High-pressure freezing (HPF) circumvents these issues by rapidly fixing tissue in a near-native state, enabling precise volume EM analyses. Importantly, cessation of blood flow and energy supply lead to immediate ultrastructural changes, ionic shifts, cell swelling and molecular alterations, which underscores the importance of rapid tissue processing. Here, we present an optimized HPF workflow that shortens tissue handling to just about 50 seconds from animal sacrifice to freezing. By sandwiching brain tissue directly between copper carriers and redesigning the HPF middle plate, we eliminate mechanical handling artifacts and reduce post-mortem degradation. This rapid fixation preserves cellular architecture, yielding more reproducible, quantitative EM data. Overall, our streamlined approach supports fine-scale preservation of brain tissue nano-architecture, establishing a robust platform for accurate volume EM investigations.

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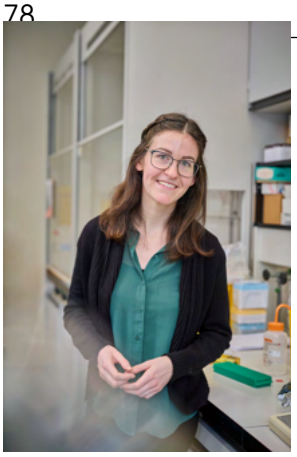

Year joined IPT
2020

Rachel Meister*
PhD in the Weber Lab

Effects of a ketogenic diet on neuronal and astrocytic metabolism in the mouse brain: a two-photon FLIM study

Ketogenic diets (KDs) protect against epileptic seizures and have been shown to be beneficial in a wide range of furthers diseases, from metabolic to neurodegenerative and even psychiatric. The high fat intake leads to increased production of blood ketones, notably BHB, which serve as alternative energy substrates for different organs. We monitored blood BHB, glucose and lactate during an alternating KD to assess their systemic dynamics. The neurometabolic impact of the KD is commonly investigated at the whole-brain level using techniques such as PET and MRI. However, these methods do not provide information on the different cell types responsible for the observed effects. To evaluate metabolite levels and fluxes in the mouse cortex at the single-cell level, we combine genetically encoded sensors with two-photon fluorescence lifetime imaging (FLIM). This quantitative technique allowed us to assess how a KD impacts glucose levels and the redox ratio of both neurons and astrocytes in the awake mouse. Using acute brain slices, we were also able to employ pharmacological protocols to measure the glycolytic rate in both cell types from mice on a KD and directly contrast the glucose and redox states to the in vivo condition. Overall, our work shows a cell-specific and quantitative effect of a KD on brain metabolism, complementing information from whole-brain studies.

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Year joined IPT
2022

Felipe Velasquez*
PhD in the Weber Lab

Quantitative microscopy techniques for in vivo brain imaging

My research focuses on advancing in vivo brain imaging by addressing challenges in accurately quantifying molecular concentrations. While techniques like two-photon excitation fluorescence microscopy (TPEF) have been successful, limitations such as fluorophore expression, scattering, absorption, and sample motion hinder precise quantification in vivo. My project integrates two advanced non-linear optical techniques, two-photon fluorescence lifetime imaging (FLIM) and stimulated Raman scattering (SRS), to overcome these challenges. The project has three primary objectives: First, extending FLIM capabilities for high-speed, multi-channel imaging of fast biological processes. Second, integrating SRS imaging into a two-photon microscope for multimodal in vivo imaging with small molecular tags. Finally, developing a self-supervised quantitative denoising pipeline to enhance signal-to-noise ratio (SNR) in FLIM and SRS images. My work combines hardware development with classical and deep-learning-based signal processing, focusing on enabling the application of these technologies for in vivo brain imaging. Achieving these objectives will improve quantitative imaging of brain energy metabolism and enable the study of rapid physiological processes.

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Year joined IPT
2020

Jeanne Droux*
PhD in the Weber Lab

Neutrophils as key players in microvascular injury and failure in stroke

Despite clot removal in ischemic stroke, over 50% of patients have a severe outcome. The main reasons behind a lack of treatment efficacy are microvascular failure and injury. In a mouse model of stroke, we have shown that neutrophils obstruct brain capillaries leading to the no-reflow phenomenon. However, the precise mechanism by which stroke affects blood circulating neutrophils and how/why neutrophils obstruct brain capillaries remains incompletely understood. We therefore investigated neutrophils in blood circulation of stroke mice, and herein describe an in-depth analysis of neutrophil phenotypes in the brain microvasculature after stroke. Intravital microscopy, orthogonal profiling and cell mechanics measurement strategies revealed atypical sticky neutrophils in the blood circulation endowed with morphological and transcriptional changes after stroke. Indeed, a subpopulation from blood circulating neutrophils becomes sticky occluding the capillary vascular bed and hinder brain reperfusion. These morphological and mechanical changes were driven by several actin cytoskeleton rearrangement factors. Pharmacological and transgenic targeting of these pathways reverted the flowing behaviour of neutrophils in the blood circulation and improved stroke outcome. Our study unveils how stroke dysregulated blood circulating neutrophils and supports the concept of a critical neutrophils role in the blood flow recovery after cerebral ischemia.

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Year joined IPT
2024

Hanna Preuss*
PhD in the Weber Lab

The Growing Network: Constructing an Atlas of Brain Vascular Development

The brain's vascular system is essential for meeting neural metabolic demands, but the developmental mechanisms guiding its formation, particularly the role of microglia, are not fully understood. Microglia are now recognized as key regulators of vascular patterning and maturation. This project investigates microglia–endothelial interactions during brain vascular development in mice from embryonic day 12 (E12) to E19. We developed a novel in vivo para-uterine two-photon imaging platform that enables real-time visualization of individual macrophages and blood vessels of living mouse embryos while they remain connected to the pregnant mother. Vasculature was labeled using intravenous dextran and an endothelial cell-specific transgenic reporter line. Post-mortem analysis included fixation and immunohistochemistry with vessel-specific markers. Preliminary findings reveal early vascular plexus formation, amoeboid microglia, and immature arterial/venous structures. Deeper vessels appeared tortuous and less developed than adult vasculature. Immunohistochemical analysis using DAPI and collagen IV revealed a distinct vascularization pattern surrounding the neural tube, forming a characteristic ring-like structure. As a result, we successfully implemented an in vivo para-uterine imaging approach to investigate embryonic vascular development. Our preliminary findings demonstrate a clear developmental fingerprint of both the vascular system and associated cell types, such as macrophages.

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Year joined IPT
2021

Tina Notter*
Principal Investigator in the Weber Lab

Astrocytes in Development and Behavior

One distinctive feature of the PFC is its protracted adolescent maturation, which is necessary for acquiring mature cognitive abilities in adulthood. One of our primary aims is to determine the role of astrocytes in the structural and functional maturation of the PFC. Long thought to act merely as a structural support of neurons, astrocytes are now known to actively integrate, process and contribute to neuronal signaling. They are essential for early brain development regulating synaptogenesis and assuring correct wiring of the brain. More recently, astrocytes have been shown to actively participate in the rewiring of neuronal connections during brain maturation, a process involving the elimination of superfluous synapses, whereby neuronal circuits are optimized. Using a multi-disciplinary approach including chemogenetics, in-vivo two-photon imaging, immunohistochemistry, and behavioral analyses in mouse models, we investigate whether astrocyte-dependent synaptic elimination is indispensable for the normal development of neuronal networks subserving adult cognitive functions. In addition, we thrive to unravel the functional and behavioral consequences of aberrant astrocyte activity in the matured PFC. We hereby focus on understanding how astrocytes actively integrate, process and contribute to PFC synaptic signaling and thereby modulate behavioral and cognitive functions with relevance to psychiatric disorders.

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Year joined IPT
2023

Viktor Beilmann*
PhD in the Weber Lab

Overactivation of prefrontal astrocytes alters local neuronal activity and impairs cognition via acting on the kynurenine pathway

Astrocyte dysfunctions have long been implicated in psychiatric and cognitive disorders, yet the precise mechanisms underlying this association remain elusive. In my project I demonstrate that chemogenetic activation of prefrontal astrocytes in mice impairs short-term memory and sensorimotor gating, while attenuating the activation of parvalbumin interneurons and increasing the activity of principal cells in the prefrontal cortex. These alterations are accompanied by increases in prefrontal levels of kynurenic acid (KYNA), a key metabolite of the kynurenine (KYN) pathway and endogenous antagonist of NMDA receptors. Pharmacological inhibition or astrocyte-specific knockdown of kynurenine aminotransferase II, the key enzyme mediating the transamination of KYN to KYNA, reinstates the astrocyte-mediated impairments in short-term memory and sensorimotor gating, and normalizes the deficits in prefrontal neuronal activity. Taken together, my work aims to identify a mechanistic link between overactivation of prefrontal astrocytes, increased production of KYNA, and cognitive as well as cellular dysfunctions involved in major psychiatric disorders and beyond.

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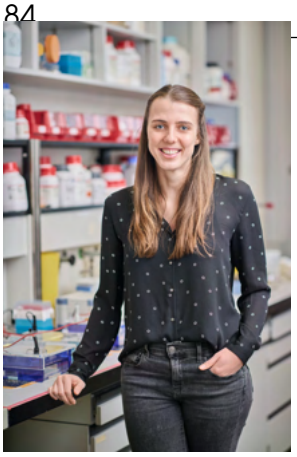

Year joined IPT
2022

Johanna Furrer*
PhD in the Weber Lab

The Role of Astrocytes in the Functional Maturation of the Medial Prefrontal Cortex

Functional and structural abnormalities of the prefrontal cortex (PFC), a brain region governing executive and cognitive functions, are implicated in psychiatric disorders like schizophrenia (SZ). During adolescence, the PFC undergoes substantial maturation, which involves synaptic pruning, input rearrangement, and interneuron maturation. Astrocytes contribute to postnatal synaptic refinement in sensory cortices, but their contribution to PFC maturation is still unclear. In this study, we first characterized medial PFC (mPFC) synaptic refinement via immunohistochemistry and in vivo 2-photon spine imaging. We found that synapse density increased from PND 21 – 28 and subsequently declined throughout adolescence. To probe astrocyte involvement in the mPFC maturation, we enhanced the Gq-protein coupled signaling pathway using hM3DGq-DREADDs in prefrontal astrocytes from PND 30 – 50. This activation led to transient synapse loss during adolescence and reduced parvalbumin expression in adulthood. Additionally, temporally restricted astrocyte activation during adolescence, but not adulthood, caused persistent adult cognitive and behavioral deficits. Our findings are the first to suggest that astrocytes actively contribute to the functional maturation of the mPFC and thus could play a role in the etiopathological mechanisms underlying major psychiatric disorders.

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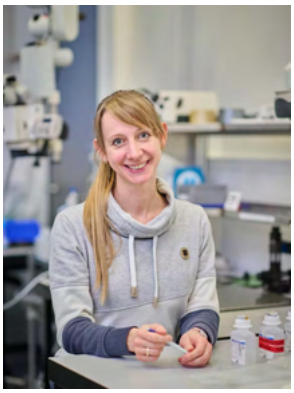

Year joined IPT
2021

Marina Herwerth*
Principal Investigator in the Weber Lab

Herwerth group is dedicated to understanding the astrocyte regenerative mechanisms and astrocyte-neuron communication in neuroinflammatory conditions, such as Neuromyelitis Optica, MOG-associated disease and Multiple Sclerosis. We utilize various imaging techniques and different animal models to advance the development of new biomarkers and neuroprotective strategies in neuroinflammation. Herwerth group is also affiliated with the Department of Neurology at USZ, with the endeavour to translate preclinical neuroscience into clinical application in the field of Neuroimmunology. Please find additional information on the webpage.

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Year joined IPT
2021

Nicola Schmid*
PhD in the Weber Lab

Studying Astrocyte-Neuron Interaction In Vivo via Specific Astrocyte Depletion

In the healthy brain, astrocytes support neurons in numerous aspects: For instance, astrocytes provide energy substrates, take up and recycle neurotransmitters, neutralize reactive oxygen species, and are involved in neurovascular coupling. Deprived of astrocytic support, neurons could be limited in their metabolic capacities, suffer deficits in signalling capacity, and display changes in morphology. However, in vivo models of focal selective astrocytopathy to study glial-neuronal interactions are rare. Autoantibodies against the water channel protein aquaporin-4 (AQP4) which is expressed almost exclusively by astrocytes within the CNS are known to be the causative agent of the severe neuroinflammatory disease Neuromyelitis Optica Spectrum Disorder (NMOSD). Their binding leads to complement-dependent selective lysis of astrocytes. Experimentally, injection of AQP4-antibody into the mouse cortex leads to a local ablation of astrocytes. Here, using in vivo two-photon microscopy via chronic cranial window and genetically encoded sensors we are able to follow individual neurons without their partnering astrocytes over time. With this, we can address questions about changes in neuronal energy homeostasis and neuronal signalling activity in the absence of astrocytes. Furthermore, longitudinal imaging studies allow detailed observation of changes in neuron morphology and cell survival in astrocyte depleted areas.

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Year joined IPT
2024

Anna Lasne*
PhD in the Weber Lab

Microglial contribution to the regeneration of aquaporin-4-antibody mediated astrocytopathy-driven neuroinflammation

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a chronic autoimmune condition of the central nervous system (CNS), driven by AQP4-IgG autoantibodies targeting astrocytic water channels. This triggers inflammatory cascades, causing myelin damage, neuronal loss, and severe relapses with poor recovery. Although astrocyte loss is a hallmark of NMOSD, their regenerative capacity remains poorly understood. To explore this, we used longitudinal in vivo two-photon microscopy in a mouse model of focal AQP4-IgG–mediated pathology. We observed that perilesional astrocytes exhibit notable plasticity, temporarily adopting a reactive, progenitor-like state. These astrocytes repopulated lesion sites and restored the network without forming glial scars. Spatial transcriptomics confirmed accompanying changes in gene expression. We also investigated microglia using imaging and pharmacological depletion (PLX3397 diet). Reactive microglia were closely associated with regenerating astrocytes, and their absence worsened lesion severity, indicating a context-dependent protective role. Collectively, these findings highlight an intrinsic regenerative program in astrocytes in close interplay with neighbouring microglia, that may be harnessed for therapeutic benefit.

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Abstracts - Zeilhofer group

The Zeilhofer Lab*

The Zeilhofer lab investigates sensory processing in the spinal dorsal horn - the primary termination area of sensory nerve fibers arriving in the central nervous system from the body trunk and the extremities. At this site, the incoming sensory signals are integrated with signals from a local network of excitatory and inhibitory interneurons and fibers descending from supraspinal CNS areas. A large body of evidence indicates that maladaptive plasticity at this site underlies chronic pain states. Understanding of the principles of normal and pathological neural processing in the dorsal horn should hence lead one day to new and better therapies for chronic pain conditions that affect almost 20% of our general population. More recently a critical role of such networks has become apparent for acute and chronic itch. Our research focuses around two major themes.

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Year joined IPT
2021

Camilla Beccarini*
PhD in the Zeilhofer Lab

Characterization of translatomic changes of spinal cells after peripheral nerve injury

Peripheral Nerve Injury (PNI) can lead to neuropathic pain, a chronic pain condition characterized by spontaneous pain and increased responses to noxious and innocuous stimuli. Previous research showed that neuropathic pain development and maintenance occurs via maladaptive plasticity in peripheral and central pain circuits. The persistence of these changes depends on processes of transcription and translation. To systematically investigate the effect of PNI, we focused on its effects by observing molecular changes first on a global level in the whole mouse spinal cord and then on 4 major spinal cell types: astrocytes, inhibitory neurons, and 2 types of excitatory neurons. Using Bulk RNA-seq combined with TRAP-seq techniques, we explored the different PNI response profiles across different conditions and time points. We found very extensive baseline differences between the total spinal cord transcriptome and translatome of naïve mice. In contrast, we showed a robust correlation between PNI transcriptome and PNI translatome, suggesting that when looking at translating mRNAs of all spinal cord cell populations, there is no dampening or boosting of the PNI response. However, when translation is observed on a cell type specific resolution, heterogeneous responses were captured instead. Collectively, these data contribute to further understanding the molecular mechanisms underlying central sensitization after PNI and highlight the importance of translational control in chronic pain.

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Year joined IPT
2024

Eshita Kamal*
PhD in the Zeilhofer Lab

Imaging pain in the brain: a physiological readout of nociception

Bidirectional communication between the ascending and descending pain pathways enables modulation of pain signals and regulation of pain perception. However, the mechanisms underlying the emergence of pain sensation and the circuits that convey this information are still unclear. It is also not yet understood how noxious sensory experiences are converted to complex, emotional and cognitive experiences. The development of a novel mouse line called Phox2a-Cre now enables access to a majority of neurons from the anterolateral system (AS), a major ascending pain pathway conveying information about nociception, skin temperature, and itch from the periphery to the brain. Recent studies have shown that Phox2a AS neurons do not solely convey noxious information but are also active during locomotion and salient stimuli and appear to play a role in the generation and maintenance of chronic neuropathic pain as well. To further examine the functional properties of these neurons and their projections to the brain in the context of nociception, we are currently using in-vivo calcium imaging to investigate the output of Phox2a AS neurons in the brain and how various states (anesthetized vs awake, pain expectation, chronic pain) affect the activity of these neurons. This approach aims to better understand how the brain receives and processes information from the spinal cord and the level at which this information is altered or influenced by the animal's state.

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Year joined IPT
2023

Misa Oyama*
Post-Doc in the Zeilhofer Lab

Electrophysiological and behavioral analysis of glycine and GABA receptor PAMs

About 20% of the world's population suffers from chronic pain, and the development of new non-opioid analgesics is a high priority in terms of the side effects of currently existing therapeutic drugs. It is reported that Glycine and GABA, representative inhibitory neurotransmitters, their inputs are attenuated in chronic pain conditions, therefore, enhancement of their action can produce analgesic effects. In order to enhance the effects of glycine and GABA in the spinal cord, which is a crucial area to regulate pain sensation, I have been focused on their receptors' positive allosteric modulators (PAMs). Our recent behavioral study has shown that both glycine and GABA receptor PAMs have analgesic effects in chronic pain model mice. Furthermore, electrophysiological whole-cell patch-clamp technique in the spinal dorsal horn neurons of the adult vGAT::ChR2 transgenic mice was used to clarify their synaptic mechanisms contributing to pain relief. As results, glycine and GABA receptor PAMs prolonged the weighted tau of the light-evoked glycinergic or GABAergic postsynaptic currents (le-IPSCs), respectively, provoked by the 4 ms blue light at a frequency of 0.1 Hz recorded with the CsCl-based internal solution and a holding potential at -70 mV. Hence, potentiation of glycine and GABA inputs in the spinal cord through their receptors' PAMs has the potential to be non-opioid analgesics.

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Year joined IPT
2021

Francesca Pietrafesa*
PhD in the Zeilhofer Lab

Prime Editing of a pathogenic Scn1a allele alleviates seizures in a GEFS+ mouse model

Generalized Epilepsy with Febrile Seizures Plus (GEFS+) is an inherited epileptic disorder predominantly linked to autosomal dominant mutations in the SCN1A gene. It is characterized by a spectrum of seizure types, often beginning with febrile seizures in early childhood and progressing to generalized tonic-clonic seizures later in life. Here, we use prime editing to correct a human pathogenic SCN1A mutation in a mouse model for GEFS+. Adeno-associated viral (AAV) vectors were employed to deliver an intein-split prime editor into the cerebral ventricles of neonatal Scn1aK1259T/+ mice, resulting in 34.7 ± 14.5% correction of the mutant allele in the cortex. Correction rescued postnatal mortality, restored cortical inhibitory transmission, and led to the reduction of induced febrile seizures close to the levels of wild-type littermates. These findings propose therapeutic potential of prime editing for treating SCN1A-associated GEFS+.

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Serotonin and GABA co-transmission from descending inhibitory terminals from the Rostral Ventromedial Medulla to the dorsal horns of the spinal cord

The descending control of nociception is operated by a wide variety of brain structures. Among them, the Rostral Ventromedial Medulla (RVM) in the hindbrain is a key regulatory center. The RVM is composed of an ensemble of nuclei that differ in their neurochemical nature and connectivity. In this study, we focus on two populations of descending inhibitory and serotonergic neurons located in the Lateral Paragigantocellularis Nucleus (LPGi). Preliminary data collected in our lab suggest that the activation of the vGat-positive population is strongly antinociceptive in vivo, likely due to the inhibitory effect of GABA and glycine released in the spinal dorsal horn. Interestingly, through immunohistochemistry, we found that these synapses also contain serotonin (5-HT). Moreover, activation of TPH2-positive neurons elicits antinociceptive effects similar to those observed with the inhibitory population. Additionally, through in situ hybridization, we found neurons in the LPGi of the RVM co-expressing vGat and TPH2 mRNA. Using slice electrophysiology combined with optogenetics, we measured a slow inhibitory post-synaptic current upon 20Hz stimulation of descending inhibitory terminals, which was entirely blocked by htr1a antagonist, suggesting a frequency-dependent 5-HT release. Taken together, these findings suggest that 5-HT and GABA are co-released from some of the descending terminals from the LPGi and possibly contribute to the post-synaptic inhibition.

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Descending Inhibitory Neurons of the RVM Cause Widespread Bilateral Antinociception and Contribute to the Pain-Inhibits-Pain Phenomenon

Acute painful stimuli applied to one body site reduce pain at other sites. The circuit basis of this "pain-inhibits-pain" phenomenon, also known as diffuse noxious inhibitory control (DNIC) in animals or conditioned pain modulation (CPM) in humans, is largely unknown. Using anatomical and optogenetic circuit tracing, we identified a population of descending inhibitory neurons of the rostral ventromedial medulla (RVM) that densely and bilaterally innervate the spinal cord along its rostrocaudal axis. Activating these neurons reduced heat and cold sensitivity widely in healthy mice and caused similarly widespread antihyperalgesia in chronic pain models, while their silencing evoked mechanical allodynia and spontaneous pain-like behaviors. Noxious stimuli activated subsets of these neurons in the lateral paragigantocellularis nucleus (LPGi), which inhibited nociception upon chemogenetic reactivation. Spinally-projecting inhibitory RVM neurons are hence ideally positioned to function as circuit elements of DNIC and CPM, while their dysfunction may contribute to widespread chronic pain syndromes.

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Tmem117, an oligodendrocyte-enriched regulator of NCX activity, links myelin homeostasis to counterregulation and metabolic health

The counterregulatory response (CRR) to hypoglycemia is a fundamental, evolutionarily conserved homeostatic mechanism orchestrated by the central nervous system to ensure survival during glucose scarcity. In individuals with diabetes, this response is frequently impaired, contributing to life-threatening episodes of hypoglycemia. Tmem117 was previously identified in a genetic screen as a promising hypothalamic regulator of CRR. Our previous work highlighted its contribution to CRR through regulation of vasopressin secretion. Here, we reveal that Tmem117 is also enriched in cells of the oligodendrocytic lineage and we characterize the contribution of oligodendrocytic Tmem117 in CRR. We show that depletion of Tmem117 from either all oligodendrocyte lineage cells or only mature oligodendrocytes leads to myelin deficits and male-specific defects in CRR. Furthermore, we reveal that transient, adult-onset depletion of Tmem117 in mature oligodendrocytes is sufficient to induce long-lasting metabolic imbalances in male mice, suggesting that defects in oligodendrocytes and myelin can affect peripheral glucose homeostasis. Mechanistically, we provide for the first-time insights on the function of Tmem117 showing that it regulates intracellular calcium dynamics through its interaction with the sodium-calcium exchanger NCX1.

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Clearly Sweet and Painful: Investigating the effect of Western diet on Myelin Homeostasis

Chronic pain affects ~20% of adults and is increasingly linked to lifestyle factors such as diet. The Western diet (WD) has been implicated in chronic pain and demyelinating diseases like multiple sclerosis, likely via systemic inflammation and oxidative stress caused by metabolic imbalances. However, the mechanisms remain unclear, limiting nutritional guidelines for disease management. Oligodendrocytes (OLs) are metabolically sensitive, vulnerable to oxidative stress, and their loss alone induces pain-like behavior in mice. To investigate the complex interplay of WD, CNS myelination, and pain, we use transgenic mouse models of both sexes with genetically induced demyelination and nociceptive testing (thermal hyperalgesia, cold, and mechanical allodynia). Additionally, we employ a triple transgenic mouse model enabling fluorescent labelling of OLs/myelin and OPCs to assess WD effects on myelin morphology and OL dynamics. After 12 weeks on WD, brain and spinal cord tissue is dissected, cleared with the SHIELD clearing method, and imaged with the light-sheet mesoSPIM microscope. Our results so far indicate that the SHIELD transformation strategy for whole-CNS tissue clearing is suitable for our purposes. This protocol allows for the protection of the physiochemical properties and ensures proper fluorescent preservation of both brain and spinal cord tissue. Therefore, enabling us to image myelin dynamics throughout the CNS.

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The role of oligodendrocytes in Western diet-induced pain

Over $\frac{1}{3}$ of diabetic and obese individuals experience pain, while impaired glucose tolerance correlates with an increased neuropathic pain prevalence. Western Diet (WD) triggers pain-like responses in preclinical rodent models. So does the sole depletion of oligodendrocytes (OLs). OLs respond to metabolic imbalances and inflammation, particularly oxidative stress, and as such, are a promising contributor to diet-induced myelin defects. In this project WD is used to induce metabolic imbalances in a transgenic mouse model, contributing to the development of pain-like responses. WD effects on the spinal cord transcriptome are investigated by single nucleus RNA sequencing (snRNAseq). Mice on WD divide into two groups based on mechanical sensitivity: (I) sensitivity as regular diet mice and (II) prolonged hypersensitivity. snRNAseq shows that WD highly affects OLs, with diet-related downregulation of oxidative phosphorylation transcripts. Moreover, we detect pain-related downregulation of myelin and mRNA processing genes. Thus, our data suggest that defects in OLs and CNS myelin could be the link connecting metabolic imbalances with pain development.

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The role of oligodendrocytes in Western diet-induced pain

Chronic pain is a debilitating condition affecting 20% of the adult population. The increased prevalence of chronic pain in metabolic syndrome and diabetes suggests that dietary habits influence pain outcomes. Western Diet (WD) induces pain-like responses in preclinical rodent models. Similarly, depletion of oligodendrocytes (OLs) triggers pain-like behaviors. OLs are sensitive to metabolic imbalances and inflammation, particularly to oxidative stress. In this project, the impact of WD on OL dynamics and myelin integrity was investigated. Single-nucleus RNA sequencing was performed on spinal cord OLs. Differentially expressed genes were analyzed to identify transcriptomic adaptations. Based on mechanical sensitivity tests, mice classified as either exhibiting pain-like behaviors or not, allowing the identification of associations between transcriptomic OL changes and pain-like responses. We identified dysregulation in processes essential for OL homeostasis and myelin sheath formation. Most affected pathways included mitochondrial function, lipid metabolism, protein folding and splicing, cell adhesion and axon–glia communication. The low expression of core myelin genes (Cnp, Plp1, Mag, Mog and Mbp) in the sensitive cohort indicated destabilized myelin sheaths, while increased expression in the non-sensitive reactive OLs suggested a protective adaptation in response to WD-induced stress. These results provide insight into the transcriptomic landscape of spinal cord OLs and highlight the role of a WD in the generation pain-like responses and impaired myelination.

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