UCONN HEALTH

Ray A. Kroc and Robert L. Kroc DEPARTMENT OF NEUROSCIENCE ANNUAL RETREAT

PROGRAM & AGENDA

Tuesday, May 7, 2024
8:00 am – 5:00 pm

Registration begins at 8:00 am

The Mark Twain House & Museum
351 Farmington Avenue
Hartford, CT 06105

UCONN HEALTH

May 7, 2024

Dear Neuroscience Program Faculty, Postdocs, Students and Guests,

Welcome to the 24th annual Neuroscience Program Retreat!

This year's event is again being hosted at the Mark Twain House in Hartford, which used to be a residence of Samuel Langhorne Clemens (Mark Twain), a great American writer. Mark Twain wrote several of his best-known books here. The Mark Twain House is recognized as a National Historic Landmark.

We would like to bring your attention to a few important things:

General

1. The address of the Mark Twain House is 351 Farmington, Hartford, CT 06105. There is space for free parking but please make an effort to carpool to save space for other retreat attendees and museum visitors.
2. **You must bring your university I.D.** to allow the Mark Twain House staff and other retreat participants to identify you.
3. The facility is air-conditioned. You might want to bring a sweater or light jacket in case you find the temperature unpleasant.
4. **Please print or carry an electronic copy of the program brochure with you to the meeting**. Only a printed agenda is available at the check in desk.
5. Free Wi-Fi will be available courtesy of the Mark Twain House. The Wi-Fi password will be provided at the meeting.

Oral presentations - Oral presentations will be made in the auditorium. Speakers **must** upload their files before the session. All presenters will be using a single computer because the system at the Mark Twain house requires rebooting if computers are switched.

Poster presentations - There will be two poster sessions. Session 1 will be before lunch, Session 2 immediately after. All posters should be on boards during both poster sessions. However, each presenter is required to stand beside his/her poster during only one preassigned session. **If you are a poster presenter, please check which session you have been assigned to.**

Presentation awards - Presentations by students and postdocs will be judged for awards. You will be judged on a variety of criteria including but not limited to the quality of your work, the clarity of your presentation, your knowledge of the subject matter, and your responses to questions. Winners will be announced immediately before the closing remarks.

If you have any suggestions for improving the event for the next year, please let us know. We hope you will enjoy the day.

Sincerely,

Byoung-Il Bae, Ph.D.
Assistant Professor

Alice Burghard, Ph.D.
Assistant Professor

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2024 Meeting Program

Time	Event	Location
8:00 – 8:45 am	**Registration & Sign-in** Continental Breakfast	Great Hall
8:45 – 8:50 am	**Welcome Address** Dr. Byoung-Il Bae	
8:50 - 9:50 am	**Symposium A** *Moderator: Dr. Ephraim Trakhtenberg*	Auditorium
9:50 - 10:05 am	*Coffee Break*	Great Hall
10:05 – 10:35 am	**Outstanding Alumni Seminar** **Rodney Ritzel, Ph.D.** **University of Texas, McGovern Medical School** *"Bidirectional neuro-immune dysfunction after chronic experimental traumatic brain injury"*	Auditorium
10:35 – 11:45 am	**Poster Session 1**	Classroom
11:45 – 12:50 pm	*Lunch*	Great Hall
12:50 - 2:00 pm	**Poster Session 2**	Classroom
2:00 - 2:10 pm	**Vendor Recognition Presentation**	Auditorium
2:10 - 3:10 pm	**Symposium B** *Moderator: Dr. Timothy Spellman*	Auditorium
3:10 – 3:25 pm	**Group picture**	Outside front entrance (staircase)
3:25 - 3:40 pm	*Coffee Break*	Great Hall
3:40 – 4:40 pm	**Keynote Address:** **Steven Siegelbaum, Ph.D.** **Columbia University** *"Towards a neural mechanism of social memory and its disorders"*	Auditorium
4:45 – 5:00 pm	**Presentation of Poster/Oral Awards &** **Closing Remarks**	

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Driving Directions to:

The Mark Twain House & Museum
351 Farmington Avenue
Hartford, CT 06105

From Springfield and Points North

Take I-91 South to I-84 West in Hartford. Take Exit 46, Sisson Avenue. At the traffic light, turn right (north) onto Sisson. Continue four blocks to the end of Sisson Avenue. At the traffic light, turn right (east) onto Farmington Avenue. Continue three blocks (approx. 2/10 mile) on Farmington and look for the sign on the right at the entrance to the museum's free parking lot. ***Note:*** The entrance to the parking lot is one block before The Mark Twain House.

From New York City, New Haven and Points South

Take I-91 North to I-84 West in Hartford. Take Exit 46, Sisson Avenue. At the traffic light, turn right (north) onto Sisson. Continue four blocks to the end of Sisson Avenue. At the traffic light, turn right (east) onto Farmington Avenue. Continue three blocks (approx. 2/10 mile) on Farmington and look for the sign on the right at the entrance to the museum's free parking lot. ***Note:*** The entrance to the parking lot is one block before The Mark Twain House.

From Waterbury and Points West

Take I-84 East to Hartford; take Exit 46, Sisson Avenue. At the traffic light, turn right onto Sisson. Continue four blocks to the end of Sisson Avenue. At the traffic light, turn right (east) onto Farmington Avenue. Continue three blocks (approx. 2/10 mile) on Farmington and look for the sign on the right at the entrance to the museum's free parking lot. ***Note:*** The entrance to the parking lot is one block before The Mark Twain House.

From Boston and Points East

Take I-84 West to Hartford; take Exit 46, Sisson Avenue. At the traffic light, turn right onto Sisson. Continue four blocks to the end of Sisson Avenue. At the traffic light, turn right (east) onto Farmington Avenue. Continue three blocks (approx. 2/10 mile) on Farmington and look for the sign on the right at the entrance to the museum's free parking lot. Note: The entrance to the parking lot is one block before The Mark Twain House.

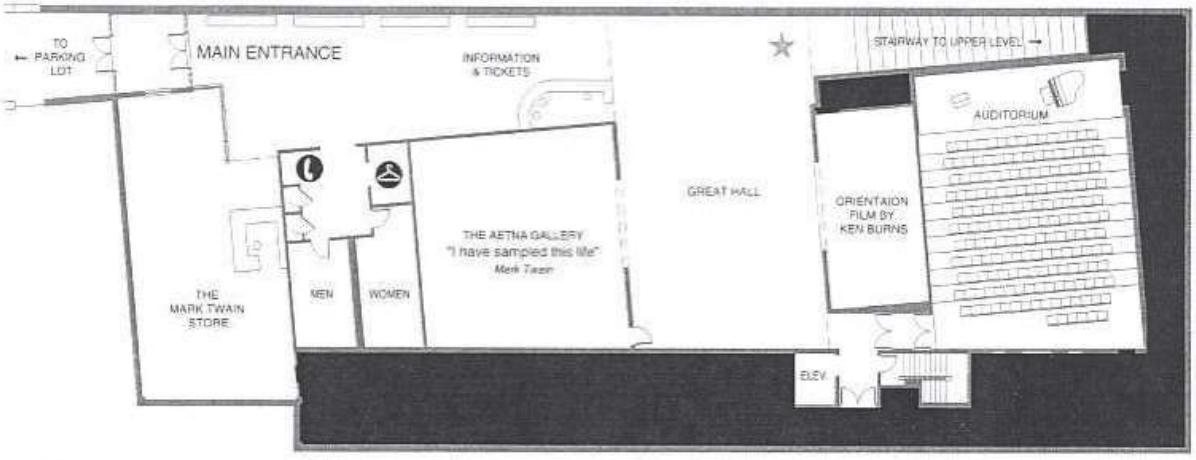
For Passengers with Limited Mobility or LOADING DOCK

(65 Forest Street Entrance)

Follow the above directions, but continue east on Farmington Avenue and go past The Mark Twain House. Take your first right onto Forest Street and look for the sign on the right for the entrance to the Museum Center's rear parking lot.

The Mark Twain House & Museum

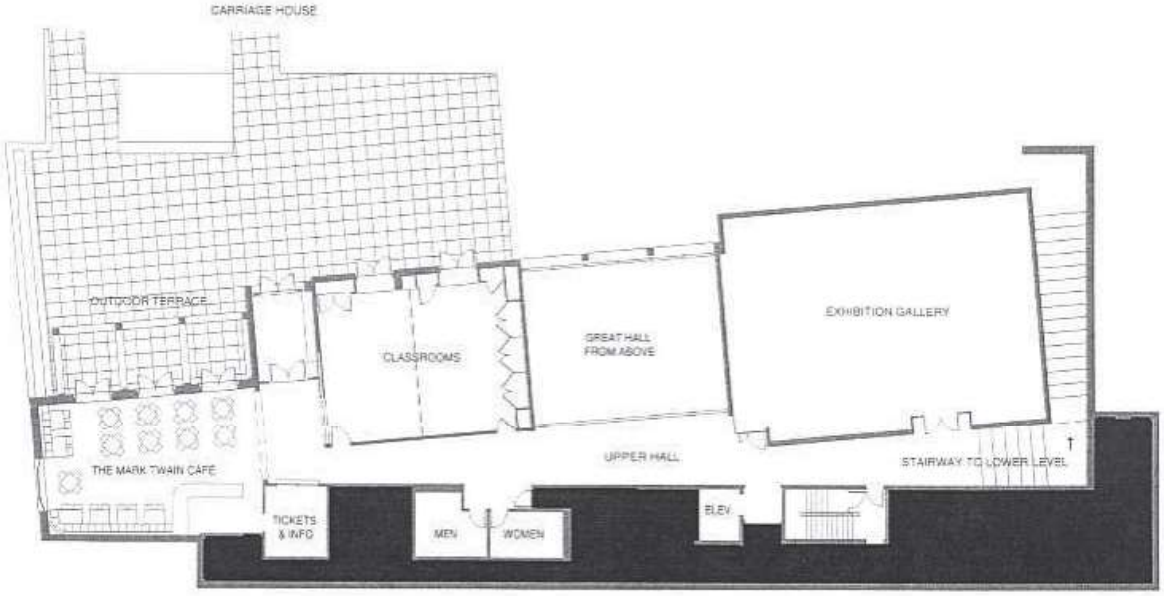
Lower Level / Main Entrance



★ TOURS START HERE

Upper Level

↑ TO THE MARK TWAIN HOUSE



3rd Floor–Research Library (By Appointment Only)

KEYNOTE SPEAKER

Towards a neural mechanism of social memory and its disorders

Steven A. Siegelbaum, Ph.D.

Gerald D. Fischbach, M.D. Professor of Neuroscience and
Professor of Pharmacology
Chair, Department of Neuroscience
Columbia University Irving Medical Center
Investigator, Zuckerman Mind Brain Behavior Institute of Columbia University

Dr. Steven A. Siegelbaum is a pioneer in the study of how electrical signaling and synaptic plasticity in defined neural circuits processes information to encode social memory, an animal's ability to recognize and recall another individual of its own species or conspecific. His lab focuses on the cortico-hippocampal circuit, specifically on the HCN1 hyperpolarization-activated cation channels and the CA2 region of the hippocampus. In fact, it was his lab that discovered that the hippocampal CA2 region is essential for social memory. He has published nearly 150 high-impact papers. His goal is to understand the neural mechanisms that enable an animal to distinguish a novel from familiar conspecific and to determine how alterations in this process may contribute to social dysfunction in neuropsychiatric disorders.

Dr. Siegelbaum received his Ph.D. from Yale University, and completed postdoctoral training at the University College London and Ecole Normale Superieure, Paris. He is the recipient of the Herbert J. Kayden Award of the New York Academy of Sciences in Biomedical Science and other prestigious awards. He has served as an associate editor of *Neuron* and the *Journal of Neuroscience*, and on the editorial boards of the *Journal of General Physiology* and *Channels*. He is also an editor of the textbook *Principles of Neural Science*. He is a Fellow of the American Academy of Arts and Sciences, a Fellow of the American Association for the Advancement of Science, a former Investigator of the Howard Hughes Medical Institute, and a member of the National Academy of Medicine (Institute of Medicine).

https://siegelbaumlab.zuckermaninstitute.columbia.edu/

OUTSTANDING ALUMNI SPEAKER

Bidirectional Neuro-Immune Dysfunction after Chronic Experimental Traumatic Brain Injury

Rodney Ritzel, Ph.D.

Assistant Professor
McGovern Medical School
University of Texas

Dr. Ritzel is interested in the bidirectional relationship between the brain and the immune system. His research is focused on how this interaction changes after insult to the brain such as a stroke or TBI.

His interested in this topic was sparked during his time as a graduate student in Dr. Louise McCollough's laboratory here in the Neuroscience department at UCHC. Under her guidance he studied the role of CD200-CD200R1 signaling in the microglia response to ischemic stroke. After obtaining his PhD in 2016 he went on to train further at the Shock, Trauma and Anesthesiology Research Center at the University of Maryland School of Medicine in Baltimore. Together with Drs. David Loane and Junfang Wu he studied neuroimmune interactions and the role of aging in traumatic brain injury. Based on this work Dr. Ritzel received the inaugural Michael Shipley Postdoctoral Award for excellence in neuroscience research and has been the recipient of NINDS F31, F32, and K99/R00 training awards.

Since 2022 he is running his own laboratory as an Assistant Professor in the Neurology department of University of Texas Health Science Center in Houston, TX. He is using different models of stroke and TBI to investigate the neuroinflammatory aspects of the interaction of the brain and its (changed) environment. His work is funded by two NINDS grants and the UTHS Rising STARs (Science Technology Acquisition and Retention) program. In addition to doing research Dr. Ritzel serves as a reviewer on several grant panels such as the DOD, PRMRP TBI-DIS or TBIPHRP NP panel. He has been a member of the NINDS Strategic Planning Panel of Training and Diversity and serves as a reviewer for several prestigious journals (e.g. Glia, eLife).

Symposium A: Talk No. 1

Bioengineering Approach for Enhanced Large-Gap Nerve Regeneration

Rosalie Bordett[1], Sama Abdulmalik[1], Suranji Wijekoon[1], Michael Arul[3], Ergin Coskun[1], and Sangamesh G. Kumbar[1,2,*]

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Large-gap peripheral nerve injuries (PNI) lead to substantial loss of function, pain, and diminish quality of life. While PNIs have an inherent capacity to heal, the rate is extremely slow, at approximately 1mm per day. Consequently, they often fail to heal large-gap PNI defects exceeding 4cm in humans and impede reinnervation. Such large-gap defects require surgical reconstruction to facilitate guided axon regeneration, using biological nerve graft conduits (NGCs) or engineered NGCs. However, biological NGCs like sural nerve autografts or allografts face limitations due to tissue size availability or compromised physicochemical and biological properties. Current engineered NGCs offer innovative solutions with favorable structural design and physicochemical properties but often lack the necessary bioactivity to enhance the regeneration rate effectively. To address these challenges, we have developed ionically conductive (IC) engineered NGCs with structural, mechanical, and biodegradable features that aids the dual delivery of bioactive molecules and electrical stimulation (ES) to enhance the axon regeneration rate. A single treatment of 4-Aminopyradine (4-AP) or ES immediately following crush nerve injuries has demonstrated complete functional restoration. However, applying them to large-gap PNI defects poses challenges, primarily due to the high water solubility of 4-AP and the requirement of applying ES within the body cavity. Local delivery of 4-AP using scaffolds at the PNI site often leads to dose dumping over a short period. Similarly, delivering ES using electronically conducting polyaniline scaffolds fails due to their lack of redox stability in the biological environment, necessitating the use of metal electrodes protruding through the skin. As a solution, our approach involves using ionically conductive (IC) chitosan conduits with 4-AP encapsulated within halloysite nanotubes to sustain release over an extended period. These IC conduits facilitate sustained electrical stimulation through the counterflow of ions in a biological environment. Our central hypothesis posits that the chemical and electrical cues from bioengineered IC NGCs will facilitate Schwann cell-material interactions, thereby modulating neurotrophin secretion and immune responses. Our findings demonstrate that IC scaffolds support Schwann cell adhesion, proliferation, and neurotrophin secretion in response to 4-AP and ES treatments. Combined treatments resulted in nearly a 6-fold increase in expression in axonal growth and remyelination-related neurotrophins NGF, BDNF, and S100b, in comparison to non-stimulated groups in vitro. The secreted neurotrophins in conditioned media from the ES+4-AP treated Schwann cells created neurite extension in neuronal precursors that had an average neurite length 6 times greater than untreated and 2.5 times greater than the NGF-treated positive control. This translated to IC scaffolds with ES+4-AP treatment in large-gap nerve defects having Improved functional recovery, in terms of significantly greater compound action potential (CMAP), and gastrocnemius muscle weight beyond ES or 4-AP alone. Additionally, the combined treatment quantitatively demonstrated up to a 15-fold increase in expression in neurotrophic and vascularization gene expression. From these studies, we hope to identify the cellular and molecular mechanisms activated in response to the combined ES and 4-AP stimulations to explain their effectiveness as a compelling regenerative treatment for PNI.

Acknowledgement: The funding support by the National Institutes of Biomedical Imaging and Bioengineering of the National Institutes of Health (#R56 NS122753 #R01EB020640 and #R01EB030060); the U.S. Army Medical Research Acquisition Activity (USAMRAA), through the CDMRP Peer Reviewed Medical Research Program under Award No. W81X

Symposium A: Talk No. 2

Trans-synaptic adhesion mediated by C1QL3

Keaven Caro[1], Matthew Sticco[1] , Trevor Religa[1], Hiu Cheung[1], Alex Schouw[1], Maksym Ugrak[1], Shanawaz Alam[1] Susanne Ressl[2] , David Martinelli[1]

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Chemical synapses allow for information transfer between neurons of the brain and their dynamic properties are crucial for proper brain function. Synaptic plasticity and homeostasis (formation and pruning) are implicated in learning and post-natal brain development. Synaptic adhesion molecules (SAMs) make a specialized cell-cell junction across the synaptic cleft, and various complexes have been shown to control synapse formation, dendritic spine morphology, and synaptic plasticity. Dysfunction of SAMs have been implicated in neuropsychiatric disorders such as autism and schizophrenia. Complement component 1, Q subcomponent-like 3 (C1QL3) is a novel potential SAM that has been shown to bind to a post-synaptic receptor adhesion G protein-coupled receptor B3 (ADGRB3). *C1ql3* is expressed in many regions of the brain including the suprachiasmatic nucleus, cerebral cortex, and limbic system. *C1ql3* knock out (KO) in the basolateral amygdala leads to loss of excitatory synapses projecting to the PFC and a subsequent deficit in fear conditioning consistent with a role of C1QL3 in promoting synapse maintenance. We previously demonstrated that C1QL3 promotes cell-cell adhesion in an ADGRB3 and neuronal pentraxin dependent manner in heterologous cells, consistent with the role of a SAM. We show with confocal microscopy and stimulated emission depletion (STED) super-resolution microscopy in mouse primary neuron cultures that C1QL3, NPTX1, and ADGRB3 co-localize at synapses, suggesting the presence of this trans-synaptic adhesion complex. We also show that colocalization of the pre- and post-synaptic binding partners is lost after *C1ql3* KO, suggesting that C1QL3 is required to complete the transsynaptic adhesion complex. This research may elucidate a molecular mechanism underlying C1QL3's role in synaptic maintenance.

Supported by
T32 Institutional Training Grant, and Whitehall Foundation
NIH, Common Fund Program, R03DC019290

Symposium A: Talk No. 3

Regulation of β-glucocerebrosidase (GCase) in Parkinson's disease and Dementia

Shifan Chen[1], Jianzhong Yu[2], Yulan Xiong[1]

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Genetic studies in large patient cohorts recently demonstrated that GCase mutations are found in a high percentage of familial and sporadic Parkinson's disease (PD) patients, making GCase the most commonly known genetic risk factor for PD. GCase is synthesized and folded in the endoplasmic reticulum (ER), acquiring 4 N-linked glycans. For further maturation, GCase binds to transmembrane receptors and is transported from the Golgi to the endosomes; meanwhile, additional glycosylation on GCase occurs in the Golgi apparatus. Finally, acidic late endosomes carrying GCase fuse into lysosomes to form a functional autolysosome for hydrolyzing its specific substrate, glucosylceramide (GlcCer). However, how GCase causes PD is still elusive. From one of our initial screen tests, we found that GCase can be regulated by one specific transmembrane receptor, GAP (GCase Associated Protein). GAP is genetically associated with a spectrum of neurodegenerative diseases, but how GAP influences PD and associated dementia disorders is unveiled. In our study, we identified a novel GCase regulator, GAP, that plays an important role in ER stress-induced protein folding by interacting with ER chaperones calnexin (CANX) and GRP78 to synergistically enhance ER proteostasis and intracellular trafficking of GCase. Conversely, loss of GAP leads to ER stress, induces unfolded protein response (UPR), and exacerbates the disease manifestation in the GCase-associated PD mouse model.

Funding: This work was supported, in part, by grants from NIH/NINDS R01NS112506, NIH/NIA K01AG046366 award, Parkinson's Foundation Stanley Fahn Junior Faculty award PF-JFA-1934, UConn Startup fund.

Symposium A: Talk No. 4

Characterization of Sex Differences in the Effects of Dopaminergic Drugs on Effort-based Decision Making in Rats

Alev Ecevitoglu[1], Gayle A. Edelstein[1], Katie Beard[1], Sonya Srinath[1], Niki Meka[1], Alex Goldhamer[1], Matt Mitolo[1], Andrea Verdu[1,2], Régulo Garcia[,2], Merce Correa[1,2], John D. Salamone[1]

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Motivational dysfunctions related to effort exertion are common in psychiatric disorders. Dopamine systems regulate exertion of effort and effort-based choice in humans and rodents. Previous rodent studies mainly employed male rats, and it is imperative to conduct studies in male and female rats. The present studies compared the effort-related effects of IP injections of the dopamine antagonists ecopipam and haloperidol, and the vesicular monoamine transport-2 inhibitor tetrabenazine (TBZ), in male and female rats using the fixed ratio 5/chow feeding choice task. Ecopipam (0.05-0.2 mg/kg) and haloperidol (0.05-0.15 mg/kg) induced a low-effort bias, decreasing lever pressing and increasing chow intake in males and females in the same dose range. With lever pressing, there was a modest but significant dose x sex interaction after ecopipam injection, but there was no significant interaction after administration of haloperidol. In the first study with TBZ (0.25-1.0 mg/kg), there was a robust sex difference. TBZ shifted choice from lever pressing to chow intake in male rats, but was ineffective in females. In a second experiment, 2.0 mg/kg affected choice behavior in both males and females. TBZ increased accumbens c-Fos expression in a sex-dependent manner, with males significantly increasing at 1.0 mg/kg, while females showed augmented expression at 2.0 mg/kg. In conclusion, the neural and behavioral effects of TBZ differed across sexes, emphasizing the importance of conducting studies in male and female rats. This research has implications for understanding the effort-related motivational dysfunctions seen in psychopathology.

Support. This research was supported by funds from the NIH/NIMH and the University of Connecticut Research Foundation to JDS.

Symposium B: Talk No. 1

Melatonin promotes sleep by activating the BK channel through MT1 melatonin receptor

Kiranmayi Vedantham, Adeel Ahmad, Longgang Niu, and Zhao-Wen Wang

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Melatonin, a hormone secreted by the pineal gland, plays a crucial role in promoting sleep by binding to G protein-coupled receptors MT1 and MT2, both of which belong to the G_i family of receptors. While previous research has primarily focused on the $G_i\alpha$-mediated signaling pathway, the downstream molecular targets for melatonin's sleep-promoting effects have remained elusive. Recently, we discovered in *C. elegans* that melatonin promotes sleep by activating the BK channel SLO-1 through a specific melatonin receptor, and in *Xenopus oocytes* that melatonin activates the human BK channel hSlo1 through MT1. In addition, we found that this effect of melatonin on hSlo1 is mimicked by a peptide that releases free Gβγ from G proteins, but inhibited by a Gβγ inhibitor (Niu et al., PNAS 2021). This study aims to investigate whether melatonin can modulate neuronal electrical properties, explore potential physical interactions between MT1 and Slo1, and determine whether melatonin promotes sleep through MT1-mediated Slo1 activation in mammals. To accomplish this, we generated global knockout mice for MT1, MT2, and Slo11 from the CBA/CaJ strain, which, unlike most other laboratory mouse strains, possesses the ability to synthesize melatonin. Electrophysiological analysis of neurons in the suprachiasmatic nucleus revealed prolonged action potentials in $Slo1^{-/-}$ and $MT1^{-/-}$ compared to their littermate controls, along with reduced paxilline-sensitive current in $Slo1^{-/-}$ and $MT1^{-/}$. Western blot analysis with transfected HEK293 indicates a physical interaction between MT1 and Slo1. Electrophysiological experiments with *Xenopus* oocytes suggest crucial roles for the amino terminus of MT1 and the S0-S1 loop of Slo1 in melatonin-induced Slo1 activation and provide further evidence of Slo1 activation by a Gβγ-dependent mechanism. Preliminary electroencephalogram data show impaired REM sleep in both $Slo1^{-/-}$ and $MT1^{-/}$. In conclusion, our results suggest that melatonin regulates neuronal physiological functions and promotes sleep by activating Slo1 through MT1, with Gβγ playing a critical role in this process.

Supported by NIH R01MH085927 and R01NS109388

Symposium B: Talk No. 2

The CB_2 receptor reduces experimentally-induced pruritus in mice

Matt Reck[1], David P. Siderovski[2], & Steven G. Kinsey[1]

[1]School of Nursing and Department of Psychological Sciences, University of Connecticut, Storrs, CT; [2]Department of Pharmacology & Neuroscience, University of North Texas Health Science Center, Fort Worth, TX

Introduction: Pruritus is the experience – akin to pain – that induces one's desire to scratch. Current therapeutic strategies for reducing pruritus are limited by ineffectiveness and adverse side effects, prompting a need for novel treatments. Despite evidence of the antipruritic effects of various cannabinoids, clinical translation is hindered by their CB_1 receptor mediated cannabimimetic effects, particularly in studies that used higher doses of cannabinoids seen to also cause locomotor deficits. The goal of the present study was to test the hypothesis that the cannabinoid receptor full agonist, WIN 55,212-2, reduces compound 48/80-induced scratching via a mechanism requiring the CB_2 receptor.

Methods: Adult male and female C57BL/6J mice were administered WIN 55,212-2 (0.1, 0.3, 1, or 3 mg/kg, i.p.) 50 min prior to compound 48/80 (50 µg in 100 µL, s.c.), and immediately placed in sound-attenuating chambers and video recorded for 30 min. Hind paw scratching time and bouts were quantified by a blinded observer. To probe potential receptor mechanism, a separate cohort of naïve mice were administered the CB_1 receptor-selective antagonist rimonabant (3 mg/kg, i.p.), the CB_2 receptor-selective antagonist SR144528 (3 mg/kg, i.p.), or vehicle 10 min prior to WIN 55,212-2 (0.3 mg/kg, i.p.). The antipruritic effects of the CB_1 receptor positive allosteric modulator ZCZ011 (10 or 40 mg/kg, i.p.) or the CB_2 receptor selective agonist JWH-133 (10 or 20 mg/kg, i.p.) were determined. Finally, the established antipruritic effects of WIN 55,212-2 were tested in male and female CB_2 (-/-) and CB_2 (+/+) littermates.

Results: WIN 55,212-2 (≥0.3 mg/kg, i.p.) reduced compound 48/80-induced scratching without inducing locomotor deficits. The antipruritus achieved by WIN 55,212-2 administration (1 mg/kg) was seen to be attenuated by either rimonabant or SR144528 pretreatment. Because rimonabant is a pruritogen, the CB_1 receptor positive allosteric modulator ZCZ011 was also tested versus compound 48/80-induced scratching. ZCZ011 had no effect, but JWH-133 reduced pruritus without altering locomotor output. Finally, WIN 55,212-2 reduced scratching in CB_2 (+/+) wildtype mice, but this antipruritic effect was absent in CB_2 (-/-) mice.

Conclusions: WIN 55,212-2 reduced experimentally induced scratching, and this antipruritis was blocked by either chemical antagonism or genetic deletion of the CB_2 receptor. Similarly, CB_2 receptor selective agonism reduced scratching, further supporting a CB_2 receptor mediated mechanism of cannabinoid-induced antipruritus.

Acknowledgments: This work was supported financially by the National Institute on Drug Abuse [NIH R01 DA048153] and the UConn Center for Advancement in Managing Pain.

Symposium B: Talk No. 3

REPEATED DELTA-8-TETRAHYDROCANNABINOL IS ANTI-INFLAMMATORY IN TWO NOVEL MEASURES OF PAIN-ALTERED BEHAVIOR

S. Olivia Vanegas[1,2], Arsalan Zaki[3], Caroline Dealy[3,4,5,6], Kinsey, Steven G.[1,2]

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Introduction: Major cannabinoids such as Δ^9-THC produce anti-inflammatory and anti-arthritic effects in preclinical models. However, little research has investigated the effects of minor cannabinoids in arthritis. The goal of the present study was to determine the antiarthritic efficacy of the minor phytocannabinoid delta-8-tetrahydrocannabinol (Δ^8-THC). Female DBA/1J mice are reportedly resistant to developing collagen-induced arthritis (CIA). Thus, an additional goal was to assess whether CIA would develop in female mice using recently refined methods.

Methods: Adult male DBA/1J mice were inoculated with an emulsion of collagen and complete Freund's adjuvant injected (s.c.) into the tail. Twice daily injections of Δ^8-THC (3 or 30 mg/kg), the steroid dexamethasone (2 mg/kg), or vehicle were administered for two weeks following a second collagen treatment, 21 days after the first. Paw measurements and clinical arthritis scores were recorded daily and latency to fall from an inverted grid was measured on alternating days to determine arthritis severity and functional impairment. On the final day of testing, spontaneous wire-climbing behavior and temperature preference in a thermal gradient ring were measured to assess CIA-depressed and -conditioned behavior, respectively. To assess the sex-specific effects of our CIA preparation, a second group of female DBA/1J mice were subjected to the same methods as above only without Δ^8-THC or dexamethasone treatment.

Results: The Δ^8-THC treatment (30 mg/kg) reduced paw swelling and clinical signs of arthritis. Δ^8-THC also blocked CIA-depressed climbing and CIA-induced preference for a heated floor without producing locomotor effects but did not affect latency to fall from a wire grid. In histological assessments, Δ^8-THC reduced synovial inflammation and bone erosion in the ankle joint. Finally, Δ^8-THC attenuated CIA-induced levels of IL-1β, IL-6, and VEGF-A proinflammatory cytokines in paw tissue. There were also no sex differences between mice subjected to CIA, indicating that females had developed arthritis to the same extent as males.

Conclusions: Δ^8-THC not only blocked morphological changes but also prevented functional loss caused by collagen-induced arthritis. Also, female DBA/1J mice were susceptible to CIA using these methods, so future experimentation should explore sex-specific effects of antiarthritic treatments.

Acknowledgments: Research was supported financially by the National Institutes of Health (R01 AT010773) and the UConn CAMP Trainee Pain Research Grant.

Symposium B / Talk No. 4

The role of hippocampal mossy cells on detection of changes in an environment

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The hippocampal dentate gyrus (DG) is central to memory encoding due to its ability to detect changes in the environmental context based on spatial and non-spatial input arriving from the external world. However, the mechanisms underlying this process, in particular the contribution of mossy cells (MC), a key component of the DG circuit remains largely unknown. We recorded DG neural responses to the alteration of object layouts, with or without chemogenetic silencing of the mossy cells. In the vehicle condition, we observed that manipulating the landmark's position lead to an equivalent shift of DG neuron place fields closely associated with the landmark. In contrast, replacing the landmark induced place field changes throughout the entire belt. Interestingly, the chemogenetic silencing of MCs reduced the rate and extent of remapping triggered by changes in the belt layout compared to vehicle condition. Based on these results, we developed a neural network model, where mossy cells detect a change between the current and previous representation, then spread this information throughout the DG. The model reproduced a distinct response of DG neurons to spatial and non-spatial alteration by normalizing change in MCs activity. Overall, these results indicate that MCs play a crucial role in detecting, amplifying, and spreading information about changes in the environment. As such we predict that pathologies that affect MC activity and the microcircuits they regulate, may lead to deficits in memory encoding that occur with mild cognitive impairment and dementia.

Poster Session 1 / No. 1.1

Voltage Imaging of Synaptically-Evoked Cortical Depolarizations in a Mouse Model of Alzheimer's Disease

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Sensory stimulations at 40-Hz gamma (but not any other frequency), have shown promise in reversing Alzheimer's disease (AD)-related pathologies. What distinguishes 40-Hz? We investigated propagation of voltage transients in brain slices from AD mouse model animals (5xFAD). Extracellular (synaptic) stimuli were delivered in cortical layer 4 (L4). Leveraging a voltage indicator (VSFP) expressed in cortical pyramidal neurons, we simultaneously monitored evoked cortical depolarizations at multiple sites, at 1 kHz sampling frequency. Experimental animals, categorized into four groups (AD-Female, CTRL-Female, AD-Male, and CTRL-Male), were tested at three stimulation frequencies (20, 40, and 83-Hz). Despite our initial hypothesis, two parameters, namely [i] temporal summation of voltage waveforms and [ii] strength of propagation through cortical neuropil, did not reveal any distinct advantage of 40-Hz stimulation. Intriguing findings emerged when examining regions of interest (ROIs) furthest from the stimulation site, where synaptic potentials dominate optical signals. The AD-to-CTRL differences were particularly pronounced with 83-Hz stimulation, which is known to enhance cognition and working memory in humans. Our physiological measurements detected significant differences between AD and Control mice in terms of both [i] temporal summation and [ii] spatial propagation at 83-Hz, while the 40-Hz stimulation frequency was not remarkable.

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Poster Session 1 / No. 1.2

The Protective Effects of Tetrahydrobiopterin (BH4) on Myelin Pathology in Multiple Sclerosis

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Background and Significance: Multiple Sclerosis (MS) is a demyelinating disease with more prevalence in women. Motor and Bladder dysfunction are one of its most reported and debilitating symptoms. Recently, a study published by our group showed cortical demyelination is linked to bladder irregularities in a non-immune- mice model of MS. Tetrahydrobiopterin (BH4) is an endogenous cofactor involved in multiple antioxidant pathways. Previous work has reported that hypoxia reduces brain BH4 levels and BH4 supplementation can rescue myelination. We evaluated BH4 in Multiple sclerosis (MS) patients and examined whether a clinical formulation of BH4 (Kuvan™) impacts oligodendrocyte differentiation and CNS myelination.
Methods: Mass spectrometry of plasma was done to measure BH4, administration of BH4 via oral gavage to C57BL/6 mice undergoing cuprizone (0.2% w/w). Transmission electron microscopy analysis was done to measure axonal myelination (Gratio). Immunocytochemistry with (Olig2+/MBP+) was done on Primary oligodendrocyte progenitor cells (OPCs) to measure maturation. Accelerated rotarod assay and void spot assays (VSA) were performed to measure motor coordination and bladder function, respectively. Seurat package in R was used to explore published single cell RNA sequencing data from human postmortem brain.
Results: Plasma BH4 among MS patients and healthy controls (HC), (n=40) confirmed lower levels in MS patients [(6 ± 2) was (7.7 ± 2) ng/mL versus age and sex matched HC, $p<0.01$]. Application of BH4 (10uM) increased oligodendrocyte maturation (Olig2+/MBP+). Administration of BH4 via oral gavage to C57BL/6 mice undergoing cuprizone (0.2% w/w) for 4 weeks enhanced axonal myelination and dramatically improved motor coordination as assessed by accelerated rotarod assays. Interestingly, BH4 treatment improved motor coordination even 4 weeks after discontinuation of treatment. Importantly, supplementing BH4 for 2 weeks showed improvement in bladder function via reducing the number of voiding spots (less urinary frequency), increasing average surface area of individual spots (less urinary retention) and decreased the ratio of center/corner voiding spots (an indicator of unhealthy voiding pattern and urinary incontinence). Single cell RNA sequencing data from human MS postmortem brains revealed that de novo synthesis gene pyruvoyltetrahydropterin synthase (PTPS) required for BH4 production was downregulated, while the salvage pathway gene dihydrofolate reductase (DHFR) was concomitantly upregulated, suggesting impaired metabolism of BH4 within demyelinated MS lesions.
Conclusion: These data provide insights to the potential endogenous role of BH4 and its regulation in MS as it relates to CNS demyelination. Defining how BH4 supplementation can enhance OPC differentiation and offset CNS demyelination may identify novel links to the consequences of altered BH4 metabolism in MS patients as they contribute to chronic demyelination related symptoms.

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Poster Session 1 / No. 1.3

Elucidating the role of non-imprinted genes in Dup15q syndrome neuronal phenotypes

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Dup15q syndrome is caused by maternal duplication or triplication of the chromosome 15q11-q13 region and is characterized by developmental delay, motor deficits, seizures, and autism. Of the duplicated genes in this region, *UBE3A,* which encodes a ubiquitin ligase, is exclusively expressed from the maternal allele in neurons and is believed to be the major driver for Dup15q syndrome phenotypes. However, overexpression of *UBE3A* alone in mouse models fails to fully recapitulate behavioral phenotypes, suggesting a contributing role of other genes in the region. To gain a better understanding of the pathophysiology underlying this syndrome, we use patient-specific neurons derived from induced pluripotent stem cell lines as well as isogenic CRISPR-corrected lines. Using patch clamp electrophysiology, we have shown that human Dup15q neurons exhibit increased intrinsic excitability, altered action potential properties, and elevated levels of excitatory synaptic activity. We have also found that overexpression of *UBE3A* alone is insufficient to mimic all cellular phenotypes, which suggests a role for other non-imprinted genes in the duplicated region. Non-imprinted genes in this region include a cluster of $GABA_A$ receptor subunit genes (*GABRB3, GARBA5,* and *GABRG3),* and *HERC2*, another ubiquitin ligase, all of which are associated with neurodevelopmental disorders. To evaluate the roles of these genes, we have normalized the expression of *GABRB3* and *HERC2* in Dup15q neurons using antisense oligonucleotides and performed electrophysiological recordings at various developmental time points. Preliminary results suggest that *GABRB3* overexpression is not required for intrinsic hyperexcitability and altered action potential properties. However, normalizing *GABRB3* expression prevented some of the synaptic phenotypes in Dup15q neurons early in neural development, indicating a potential role for this gene in Dup15q. Ongoing experiments will determine if *HERC2* overexpression also contributes to hyperexcitable phenotypes in this syndrome. Identifying the roles played by non-imprinted genes in this region is important for developing more effective therapies and for generating improved mouse models of Dup15q syndrome.

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Poster Session 1 / No. 1.4

Unraveling granule neuron progenitor cell state transitions in the mouse cerebellum

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Granule cells (GCs) are the most abundant neuronal population in the mammalian brain, comprising more than 80% of total neurons in humans. In the postnatal cerebellum, granule cell precursors (GCPs) are highly proliferative, and dysregulation can lead to medulloblastoma, the most common type of childhood brain tumor. Despite extensive studies, the events preceding GCP differentiation remain unclear, largely because previous studies commonly treat GCPs as a homogeneous cell population. Using single-cell RNA sequencing and spatial transcriptomics, we have identified five distinct GCP populations, including Shh-responding transit-amplifying cells and quiescent mitogen-activated protein kinase (MAPK)-responding cells, in the postnatal mouse cerebellum. Genetic fate-mapping experiments showed the quiescent subpopulation of GCPs contributed to the central lobe and the lateral-most regions of the cerebellum, which display late-onset growth, suggesting that this population acts as a reserve for the postnatal expansion of the cerebellar hemispheres. We demonstrated that quiescent GCPs were resistant to antimitotic treatment and later contributed to the replenishment of granule neurons. To address the molecular regulators underlying the transition between quiescence and transit amplification, we altered MAPK activities in a GCP-specific manner. Strikingly, constitutive expression of MAPK MEK1 in GCPs enriched quiescent stem cells and resulted in larger hemispheres, whereas blockage of MAPK activity through expression of a dominant negative downstream effector, *Etv4*-DN, led to a decrease in this population and smaller hemispheres. Together, our new findings suggest that the balance between rapid division and quiescence is crucial for the normal development of the mammalian brain.

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Poster Session 1 / No. 1.5

Observational Learning: A Social, Behavioral and Procedural Approach

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Observational learning is a change in behavior following the observation of another animal performing a task rather than personally performing the task. Our lab studies observational learning in a food location task. In our task, student rats must learn to watch a teacher rat in an adjacent chamber respond at one nose poke and choose the corresponding nose poke in their own chamber. The behaviors of both the teacher, student and their interactions are tracked and related to the student's success or failure on a trial.

The automated nature of this task allows for multiple trials per session and results in rapid social learning. The current task also encompasses up to 80 observation trials per session, allowing for an in-depth analysis of the multitude of behaviors that can occur throughout the session. With this type of data collection, performance of the teacher was measured, as well as distance and heading orientation of the student to the teacher throughout the task. While successful observation is of course based on the behavior of the student rat, the behavior of the teacher rat is also important. Precise behavioral assessment of both the learner and teacher rats is possible through a machine learning assisted program, Social LEAP Estimates Animal Poses (SLEAP), that can track their movements (Pereira et al., Nature Methods, 2022).

Importantly, there are crucial intervals of time when the observation must take place in order to succeed on a given trial. The teacher rat has up to 6 seconds from when it is cued regarding the correct response to hold its nose in the cued nose-poke hole. Thus the student must be attending to the teacher during that specific interval. We are currently comparing the behavior of the teacher during these 6 second trial in which the student successfully learns and those it chooses the incorrect location. This will allow us to determine what behavioral characteristics of the teacher rat facilitated successful observational learning.

Social factors, such as dominance, may also influence the behaviors of both teacher and student rats in this task. To quantify social hierarchies and dominance we are using a battery of tasks requiring competition between pairs of rats. These include a water maze competition task, a tube test, and a food competition task. These will provide data on the degree an animal is high or low within the social hierarchy and the relationship between specific pairs of teacher-student rats.

Taken together the results should provide for a better understanding behavior variables related to successful and unsuccessful learning in the dynamical processes of social learning in rats.

Poster Session 1 / No. 1.6

Evaluation of Different Classes of Monoamine Transport Inhibitors: Effects on Effort-based choice

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Current antidepressant development efforts include the evaluation of triple reuptake inhibitors (TRIs). TRIs exert their effects by blocking uptake of the monoamines (dopamine (DA), serotonin (5-HT), norepinephrine (NE)) and increasing extracellular concentration. It is hypothesized that TRIs could have superior effects due to enhancing neurotransmission of all three monoamines, which could result in improved efficacy and quicker onset of antidepressant response in comparison to commonly prescribed antidepressants. Previous testing of the TRI NOE-115, failed to increase selection of the high effort option on our effort-based choice task. It is hypothesized that this was due to the compound not having a high enough potency at the DA transporter (DAT). Previous evidence suggests that compounds that facilitate DA transmission, but not 5-HT or NE, increase the selection of the high effort behavior or reverse the behavioral effects of the VMAT-2 inhibitor tetrabenazine (TBZ) on effort-based choice tasks. It is hypothesized that for a TRI to be able to reverse the effects of TBZ on the fixed ratio (FR) 5 chow feeding choice task, the compound must have its greatest potency at DAT. To deconstruct the role of different monoamines and test this systematically, three different monoamine transport inhibitors (NET inhibitor atomoxetine; serotonin-norepinephrine uptake inhibitor (SNRI) duloxetine; norepinephrine-dopamine uptake inhibitor (NDRI) nomifensine) have been tested for their ability to attenuate TBZ-induced shifts in behavior on the FR5 chow feeding choice task. Finally, the TRI diclofensine was also tested for its ability to attenuate TBZ-induced shifts in behavior on the FR5 chow feeding choice task. Behavioral results showed that only the compounds that block DAT and increase extracellular DA (JJC8-088, nomifensine, diclofensine) are able to reverse the effects of the VMAT-2 inhibitor TBZ. Additionally, microdialysis with high-performance liquid chromatography methods and techniques have been developed to measure extracellular concentrations of all three monoamines within the same sample. These techniques are being utilized to measure extracellular concentration of DA, NE, and 5-HT in awake and behaving animals after administration of the compounds listed above.

Poster Session 1 / No. 1.7

An extra-axonal derived recombinant protein promotes retinal ganglion cell survival and axon regeneration after optic nerve injury i*n vivo*

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Retinal ganglion cells (RGCs) are central nervous system (CNS) projection neurons of the retina and responsible for the relay of visual information from the eye to the brain. Like all mature CNS projection neurons in mammals, RGCs fail to regenerate their long-distance axons after injury or disease resulting in irreversible loss of vision. Currently there are no clinically available therapeutics that can promote axon regeneration, leaving millions who suffer from traumatic optic neuropathies and diseases such as glaucoma without resolution. To overcome this unmet clinical problem, we identified a component of the extra-axonal environment that promotes long-distance axon regeneration after optic nerve crush injury in mice. Using bioinformatic analyses, we analyzed single cell RNA-seq of RGCs to predict molecules of the extra-axonal environment that could interact with RGC axons and regulate their ability to grow. We tested whether these molecules could promote axon regeneration of RGCs following optic neve crush injury. Without treatment, RGCs survive poorly and do not spontaneously regenerate their axons. Here we determined that one of these molecules (masked due to proprietary information) increased axotomized RGC survival following injury and promoted long-distance axon regeneration. Next, we synthesized a recombinant variant of this molecule, and found that its targeted delivery promoted axon regeneration after optic nerve cush injury *in vivo*. Thus, this recombinant molecule presents a novel potential therapeutic for neuroprotection and axon regeneration treatments. Finally, we wanted to determine whether the immune stimulating treatment zymosan, which promotes axon regeneration, increased the amount of this extra-axonal molecule. We determined that zymosan substantially increased the amount of this extra-axonal molecule compared to our control conditions.

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Poster Session 1 / No. 1.8

Does Encephalomyosynangiosis promote mature angiogenesis?

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Current treatments for ischemic stroke patients are largely ineffective, underscoring the need for innovative therapeutics. The brain's inherent ability to heal itself post-ischemic stroke is hampered by inadequate blood supply to the affected region. Encephalomyosynangiosis (EMS), a neurosurgical intervention, has proven successful in promoting angiogenesis in patients with Moyamoya disease. We have previously shown that EMS can increase blood vessel density (i.e., angiogenesis) after stroke in the implanted region. However, it is not known if those blood vessels are stable or mature. Given that EMS provides balanced proangiogenic growth factors, we hypothesized that EMS enhances stable or mature cerebral angiogenesis in the cortical region surrounding the muscle graft. Following a 60-minute period of transient middle cerebral artery occlusion (MCAo), mice were randomly assigned to either MCAo alone or MCAo followed by EMS. EMS was conducted 3-4 hours after MCAo induction. Mice were sacrificed at 7, 21, or 70 days post-MCAo. A mouse angiogenesis and proteomic profile array was employed to quantify the expression of angiogenic and neuromodulating proteins. Immunohistochemistry was utilized to visualize the bonding of the graft with the brain cortex, changes in vessel density, and pericyte coverage to assess the degree of normal or mature angiogenesis. Preliminary data indicate successful graft implantation and a significantly increased vessel density ($P<0.05$ compared to the MCAo alone) in proximity to the muscle graft, signifying increased angiogenesis after stroke. EMS-treated mice exhibited an early improvement in sensorimotor deficits post-stroke. Analysis of the angiogenesis and proteomic profile array data unveiled a downregulation of anti-angiogenic factors (such as interleukin-10 and Fetuin A) and an upregulation of pro-angiogenic cytokines or growth factors (including Fibroblast Growth Factor and C-X-C Motif Chemokine 12) in the EMS group. Co-immunostaining of the endothelial cell marker (Lectin) with the pericyte marker Platelet-Derived Growth Factor Receptor Beta (PDGFRβ) after 84 days of EMS suggested the stability and maturity of new blood vessels. In summary, the EMS procedure appears effective, holding promise for enhanced stable angiogenesis which may help to expedite recovery following ischemic stroke.

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Poster Session 1 / No. 1.9

Ethanol differentially affects excitatory and inhibitory synaptic transmission in visual cortex of wild-type and adenosine A_1R knock-out mice

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Ethanol is one of the most commonly used and abused substances in the world. While the behavioral effects of ethanol are well characterized, mechanisms of its action on neurons and synapses remain elusive. Prior research suggested that ethanol could affect neurons by interfering with metabolism of biologically active molecules, such as adenosine. Here, we explored the involvement of adenosine A_1 receptors (A_1R) in mediating ethanol's effects on synaptic transmission to layer 2/3 pyramidal neurons of visual cortex using wild type (WT) and A_1R knock-out (KO) mice. Ethanol differentially affected excitatory and inhibitory transmission in WT and KO mice. In slices from WT mice ethanol had heterogeneous effects on excitatory transmission (facilitation, suppression or no change), with no net change. Ethanol's effects remained heterogeneous during acute blockade of A1Rs with a selective antagonist DPCPX. However, in A_1RKO mice ethanol consistently suppressed excitatory transmission, with no cases of enhancement observed. Inhibitory transmission was suppressed by ethanol in both WT and A_1RKO mice. At both excitatory and inhibitory synapses, changes of response amplitude correlated with changes of paired-pulse ratio, suggesting involvement of presynaptic mechanisms. We conclude that A_1Rs are not involved in mediating effects of ethanol on synaptic transmission in mouse visual cortex. However, A_1Rs are necessary for development of mechanisms mediating facilitation at some excitatory synapses. Our results add evidence for the diversity of ethanol's effects and mechanisms of action on synaptic transmission in different brain structures, and even in the same brain area (visual cortex) in different species, rats vs mice.

Poster Session 1 / No. 1.10

Presenilin functions in concert with ryanodine receptor to regulate neurotransmitter release and protect neurons from degeneration in *C.elegans*

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Mutations in presenilin (PS) are the primary cause of early-onset familial Alzheimer's disease (FAD), yet the underlying molecular mechanisms remain contentious. Previous studies indicate that conditional double knockout (cDKO) of *PS1* and *PS2* in CA3 (presynaptic) but not CA1 (postsynaptic) neurons in mouse hippocampus inhibits neurotransmitter release by reducing ryanodine receptor (RyR)-mediated Ca^{2+} release from the endoplasmic reticulum, and that this effect of the cDKO on RyR function results from decreased RyR protein levels. However, it remains unclear how PS may regulate RyR expression and whether RyR dysfunction is linked to neurodegeneration. We investigate how mutations of presenilins may cause RyR dysfunction and neurodegeneration using *C. elegans* as a model system. In this organism, *sel-12* serves as a presenilin homolog, while *ryr-1* (*unc-68*) is the sole RyR gene. Our findings reveal that mutations in either *ryr-1* or *sel-12* lead to decreased neurotransmitter release at the neuromuscular junction, as indicated by reduced amplitude of evoked postsynaptic currents (PSCs) and lower frequency and mean amplitude of miniature PSCs. Remarkably, these synaptic defect of *sel-12* mutant is rescued by expressing the wild-type *sel-12* in neurons (presynaptic) but not in body-wall muscle cells (postsynaptic). Furthermore, double mutants do not exacerbate the synaptic abnormalities, suggesting a shared molecular pathway involving SEL-12 and RYR-1 in regulating neurotransmitter release. Intriguingly, mutation of a highly conserved aspartate residue essential for the γ-secretase activity of presenilins does not affect SEL-12's synaptic function. In contrast to findings in the mouse hippocampus, *sel-12* mutation does not alter the expression level of GFP-tagged endogenous RYR-1, indicating a potential regulatory role of SEL-12 in RYR-1 function. Notably, mutations in *sel-12* or *ryr-1* result in axon degeneration in the PLM mechanosensory neuron, commonly utilized for assessing neurodegeneration phenotypes due to its suitability for morphological analysis. Our results suggest that presenilin mutations may trigger neurodegeneration by interfering with RyR function. Given the absence of an obvious mechanistic link between presenilins and RyRs, we propose that presenilin mutations impair RyR function via intermediary molecules. We are actively exploring these potential intermediaries to gain insights into the mechanisms underlying the development of FAD.

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Poster Session 1 / No. 1.11

Enhancing expression of CX3CL1-C-terimnus for reducing neurodegeneration in an HD mouse model

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Huntington's disease (HD) is a fatal genetic neurodegenerative disorder, which is caused by an increased number of CAG repeats in the Huntingtin gene (Htt). Mouse models carrying mutant Htt genes share many pathological features, including behavioral disturbances, cognitive decline, and motor disorders, similar to that seen in HD patients. There are currently no disease modifying treatments for HD, and it is essential to explore treatment options that will decrease HD pathologies and improve HD patients' quality life. We recently discovered that the intracellular domain of CX3CL1 (CX3CL1-ICD), released from membrane bound CX3CL1 by γ-secretase, is able to enhance neurogenesis in the adult as well as promote neuronal survival, due largely to altered gene transcription pathways initiated from the TGFβ2/3, Smad2/3 and the insulin receptor. Considering the fact that HD exhibit age-dependent neurodegeneration and defects in neurogenesis and neurodevelopment, we attempt to explore whether increased expression of CX3CL1-C-terminal fragment will mitigate neuronal loss in HD mouse models and whether behavioral phenotypes will be ameliorated. In order to test our hypothesis, we generated two CX3CL1-C-terminal overexpression HD models. We crossed an inducible transgenic mouse overexpressing the CX3CL1-C-terminus under the CAMKIIA promotor with both the YAC128 and Q175 mouse models. Starting at 3-months, mice of both sexes underwent behavioral tests including the open-field, Y-maze and Rota-rod every three months. Although no significant differences were observed in the open-field or Y-maze at 3-months, we noted a significant improvement in Rota-rod performance in mice overexpressing the CX3CL1-C-terminus compared to controls at 6-months of age ($p=0.0031$ and 0.0022, 2-way ANOVA) as well as improved working memory on the Y-maze at 9-months. We further saw that Q175 HD mice overexpressing CX3CL1-C-terminus had ameliorated long-term potentiation between cortical-striatal synapses. This study provides first evidence that overexpression of the CX3CL1-C-terminus in YAC128 and Q175 HD mice ameliorates motor and memory deficits. Future studies are planned to evaluate the potential role in histopathological outcomes. Together, enhancing expression of CX3CL1-ICD is likely a novel approach for HD treatment.

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Poster Session 2 / No. 2.1

Mouse Model of Alzheimer's Disease for Studying Electrical Activity of Fast-Spiking Parvalbumin (PV) Containing GABAergic Interneurons

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We postulate that pyramidal neuron hyperexcitability observed in Alzheimer's disease (AD) is, in large part, due to aberrant activity in cortical inhibitory interneurons. Current physiological measurements, used in AD model animals, produce an indirect view of the interneuron's synaptic physiology. In the AD model animals, the cellular and synaptic physiology of PV+ interneurons is typically inferred from oscillatory rhythms (electroencephalography - EEG and local field potential – LFP recordings). Oscillatory rhythms are made jointly by different neural circuits comprising a multitude of cellular mechanisms. Studies based entirely on this "high-level behavior" (e.g., spontaneous oscillations, sleep) are not optimal for deciphering the fundamental neuronal properties and basic molecular mechanisms affected by AD. We hypothesize that AD pathology disrupts electrical or chemical synapses between PV+ interneurons. It is currently unknown how synapses between PV+ GABAergic interneurons respond to AD. Physiological recordings of membrane potential changes in interneurons, and a mechanistic approach based on a low-level behavior (e.g., evoked synaptic depolarizations), are needed to fill this gap. The current project utilizes recent improvements in genetically encoded voltage indicators (GEVIs) and population voltage imaging. We expressed a GEVI variant (ASAP2s) in PV+ interneurons selectively, to generate experimental preparation (transgenic mice), in which all optical signals belong to PV+ interneurons. Using extracellular stimulation and voltage imaging, we started comparing synaptically-evoked voltage waveforms, between AD model (NLGF) and Control mice (healthy littermates). In the AD group, we seek to determine if propagation of the fast voltage transients through the PV+ interneuron network may be different from the healthy Control group (AD vs Control), and if any physiological impairments occur before the accumulation of plaques (Before vs After plaques). A new understanding of neuronal physiological dysfunction in early stages of AD may identify potential therapeutic strategies.

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Poster Session 2 / No. 2.2

Psychosine alters the neuroinflammatory astrocyte secretome

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Globoid cell leukodystrophy (GLD) also known as Krabbe's disease, is a rare fatal lysosomal storage disease. In GLD, loss of function mutations in the galactosylceramidase (GALC) gene results in pathological accumulation of a sphingolipid named psychosine in the central nervous system (CNS), which plays a causal role in driving neuropathology. Early activation of glial cells (astrocytes, microglia) and aberrant upregulation of inflammatory cytokines and chemokines in CNS are pathological hallmarks of GLD. However, specific contribution of astrocytes in driving neuroinflammation and subsequent neuropathology in GLD has rarely been studied. Here, we examined the profile of inflammatory genes regulated by psychosine in astrocytes using an unbiased cytokine and chemokine array over. We found that when compared with untreated controls, psychosine treatment alone did not alter astrocytic expression of most of the cytokines and chemokines examined. However, psycosine treatment induced expression of cytokines interferon (IFN)-γ, interleukin (IL)-6, granulocyte macrophage- colony stimulating factor (GM-CSF) and chemokine C-X-C Motif chemokine Ligand (CXCL)-1. Furthermore, astrocytes treated with other proinflammatory stimuli IL-1β or lipopolysaccharide (LPS) alone, resulted in increased production of these same factors (IFN-γ, IL-6, GM- CSF, CXCL1). IL-1β treatment alone additionally induced C-C motif chemokine ligand (CCL)-5 production, whereas LPS treatment found to elevate production of CCL3 and IL-12p40/p70. Thereafter, we investigated whether psychosine modulates astrocytic neuroinflammatory gene expression profile induced by IL-1β or LPS. We found that psychosine did not significantly alter IL-1β induced gene expression. In contrast, psychosine in combination with LPS was found to enhance astrocytic secretion of GM-CSF. Taken together, these preliminary data indicate that psychosine alone does not appear to significantly modify inflammatory gene expression in astrocytes whereas it may amplify the inflammatory activity of astrocytes in response to coincident inflammatory stimuli. Our data also indicate that the elevated presence of psychosine in GLD can modify the dynamic response of astrocytes to other inflammatory stimuli which might play an important role in modulating monocytes and or T cell responses which have been implicated in GLD pathology.

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Poster Session 2 / No. 2.3

Optical and electrical access to long-term memory ensembles in mice navigating virtual environments.

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Forming cognitive maps useful for navigating environments is a critical function of the hippocampal memory system, and deficits in spatial memory are a common comorbidity in neurological diseases such as dementia. Successfully using cognitive maps for navigation requires several functions, including initial encoding of environmental topology, the ability to discriminate between similar but distinct environments, and the ability to locate salient stimuli within each map. Cognitive maps are known to form spontaneously upon exploration while continuing to evolve through further experience and the process of memory consolidation. However, the neural circuit mechanisms and computational principles guiding this memory formation process, or how they go awry in disease, remain largely unknown. Here, we present a novel approach to study the encoding, consolidation, and retrieval of cognitive maps in which we simultaneously combine: 1) two-photon calcium imaging, 2) large-scale electrophysiological recordings, 3) 3D virtual reality exploration, and 4) real-time pupillometry. Complementing the calcium imaging of thousands of neurons tracked across weeks, simultaneous electrophysiological recording across the entire hippocampus provides temporally precise information about ongoing network states and inputs within neural circuits. Virtual reality environments offer unprecedented control over sensory inputs and behavioral paradigms, enabling precise manipulation of cognitive processes. Simultaneously tracking pupillary responses provides an independent measure of task engagement, arousal, and attention providing access to processes known to influence memory formation on sub-second timescales. Currently, we are combining this approach with a closed-loop network-state triggered optogenetics for targeted manipulations of the circuits of spatial memory consolidation. By leveraging the strengths of each technique, this novel combinatorial approach offers a comprehensive approach to the study of the neural mechanisms underlying memory processes, paving the way for targeted interventions in memory-related disorders and cognitive enhancement strategies.

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Poster Session 2 / No. 2.4

Differential roles of 2-AG and anandamide in hippocampal long-term depression

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It is widely accepted that exogenous cannabinoids can impair short-term memory and cognition in humans and other animals. This is likely related to the disruption of synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD), by the global and sustained activation of CB1 cannabinoid receptors by exogenous agonists. Conversely, the temporally and spatially restricted release of endogenous cannabinoid ligands may mediate or enhance synaptic plasticity in a synapse-specific manner. The functional roles of endocannabinoids (eCBs) are complex because they can modulate synaptic transmission via suppression of GABA and glutamate release, with opposing effects on postsynaptic excitability. We examined the role of eCB signaling in LTD by recording fEPSPs in the CA1 stratum radiatum in hippocampal slices from juvenile mice. LTD was induced by 1 Hz paired-pulse stimulation of the Schaffer collaterals or by brief exposure to the metabotropic glutamate receptor agonist DHPG. Significant LTD (~50% decrease from baseline) could be induced by either 15 min of 1 Hz electrical stmulation or 10 min of exposure to DHPG. The magnitude of both forms of LTD was significantly reduced by blocking cannabinoid receptor activation with the CB1 receptor antagonist NESS-0327. The roles of the endogenous ligands 2-AG and anandamide were examined by using selective inhibtors of DAG-lipase and NAPE-PLD, respectively. Electrical stimulation-induced LTD was significantly reduced by the NAPE-PLD inhibitor LEI-401, but was not affected by the DAG-lipase inhibitor DO34. DO34, however, significantly reduced DHPG-induced LTD. These results indicate that both stimulation-induced LTD and DHPG-induced LTD require activation of CB1 receptors. Interestingly, the endogenous cannabinoid anandamide is required for sitmulation-induced LTD. 2-AG does not appear to contribute to stimulation-induced LTD, but is required for DHPG-induced LTD.

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Poster Session 2 / No. 2.5

The Role of Dopamine in Effort-Based Decisions: Insights from Bupropion, Nomifensine, and Atomoxetine

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Motivational dysfunction is a prevalent and debilitating aspect of many psychiatric illnesses. The most commonly prescribed antidepressants, selective serotonin reuptake inhibitors (SSRIs), often fail to effectively address motivational dysfunction and may even induce or exacerbate these symptoms. To effectively model these effort-related motivational symptoms, animal models of effort-based choice tasks are employed. These tasks provide an animal with a choice between a more preferred reinforcement that requires high effort to obtain, and a less preferred reinforcement that requires minimal effort. A well validated animal model of effort-based decision making is the fixed ratio 5 (FR5) chow feeding choice task where rats are presented with the choice between lever pressing for a high-carbohydrate pellet (high effort, more preferred reinforcement option) or approaching and consuming concurrently and freely available laboratory chow (low-effort, less preferred reinforcement option). Previous studies demonstrate that the DA-depleting agent tetrabenazine (TBZ) induces a shift from a baseline high-effort bias to a low-effort bias, thereby decreasing lever pressing and increasing chow intake. Prior research has shown that compounds that inhibit the dopamine transporter (DAT) such as GBR12909, PRX14040, modafinil, and modafinil analogs, are effective in reversing the TBZ-induced low-effort bias. In contrast, the norepinephrine transport (NET) inhibitor desipramine and the serotonin transport (SERT) inhibitors fluoxetine and s-citalopram fail to reverse the TBZ-induced low-effort bias and can further decrease selection of the high effort option. The present study investigated the efficacy of NET/DAT inhibitors bupropion (BUP) and nomifensine (NOM), and NET inhibitor atomoxetine (ATO) for reversing the behavioral effects induced by TBZ. Male rats (n=34) received TBZ or vehicle co-administered with either BUP (5.0, 10, or 20 mg/kg), NOM (1.25, 2.5, and 5.0 mg/kg), ATO (0.125, 0.25, 0.5, and 1.0 mg/kg), or vehicle. It was found that BUP effectively reversed the effects of TBZ on lever pressing at the intermediate and highest doses, and reversed the effects of TBZ on chow intake at the highest dose. NOM partially reversed the effects of TBZ on lever pressing at the lowest and intermediate doses, and dose-dependently reversed the effects of TBZ on chow intake across all doses. Conversely, ATO failed to reverse the effects of TBZ on lever pressing and chow intake at all doses. These findings indicate that targeting NET/DAT, rather than selectively targeting inhibition of NET, is the most efficacious strategy for reversing the motivational deficits in rats tested on the FR5 chow feeding choice task. This has implications for drug development that targets the neurochemical substrates implicated in motivational impairments.

Poster Session 2 / No. 2.6

Inducible depletion of mature oligodendrocytes modifies glial scar architecture following optic nerve crush injury

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Upon damage to the central nervous system (CNS), glial cell populations including microglia, astrocytes, and oligodendrocytes infiltrate the damaged site and form a protective barrier known as the glial scar. In the absence of injury and under homeostatic conditions, oligodendrocytes are responsible for the myelination of CNS axons. However, in response to injury, they make up the core of the glial scar and contribute to the inability of CNS axons to regenerate through the expression of inhibitory molecules. In our prior report, we determined that newly born oligodendrocytes infiltrate the glial scar and prematurely myelinate CNS projection neuron axons, resulting in their failure to regenerate. Furthermore, we demonstrated that inducing demyelination using cuprizone, we can combat this inhibitory effect and promote axon regeneration of retinal ganglion cells (RGCs), the major projection neurons of the eye. In doing so, we focused on determining the effect of oligodendrocytes on glial scar architecture. We utilized the tamoxifen inducible PLP-CreER mouse line to specifically excise out myelin regulatory factor (Myrf) preventing myelination and inducing oligodendrocyte cell loss. To accomplish this, we performed tamoxifen injections on 6-week-old mice, performed optic nerve crush injury to sever all RGC axons, and evaluated glial scar formation at 17-weeks of age. Our preliminary data qualitatively demonstrates a reduction in the number of mature oligodendrocytes in the injury site as marked by Cc1+ staining. However, we did not determine changes distally to the injury site. Furthermore, we demonstrate differences in microglia and astrocyte localization to the glial scar injury site. Finally, myelin basic protein (MBP) was qualitatively reduced in both the injury site and distal to the injury site in tamoxifen administered animals compared to control. Together these data demonstrate a model in which we can decrease myelin expression by oligodendrocytes, while simultaneously altering glial scar architecture.

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Poster Session 2 / No. 2.7

Phagocytic potentials of purinergic receptor P2x4 blockade after ischemic stroke

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Ischemic stroke (IS) stands as a significant contributor to disability and ranks as the fifth leading cause of mortality within the United States, underscoring the imperative for novel and efficacious therapeutic modalities extending beyond the acute phase. Previous investigations have delineated that the genetic ablation and short-term pharmacological inhibition of the P2X4 receptor (P2X4R), a purinergic receptor mediating adenosine triphosphate (ATP) signaling, confer neuroprotection by mitigating acute inflammatory cascades, thus presenting promising avenues for therapeutic intervention in ischemic stroke. Nevertheless, the mechanisms underlying the long-term beneficial effects of P2X4R blockade remain elusive. In this study, we posit that P2X4R blockade augments the phagocytic clearance of necrotic or apoptotic tissue, thereby fostering expedited recovery processes. To investigate this hypothesis, we utilized 1µm fluorescent phagocytic beads (Polyscience Inc) and pHrodo Red zymosan A Bioparticles conjugate (Thermofisher) to assess *in vitro* and *ex vivo* phagocytic uptake by lipopolysaccharide (*LPS*) (200 µg/ml for 2 hours) primed Bone Marrow Derived Macrophages (BMDMs) sourced from P2X4R knockout (KO) and littermate wildtype (WT) murine models. Additionally, flow-sorted Ly6Chi and Ly6Clo monocytes were utilized to examine phagocytic uptake in perilesional ipsilateral brain tissue obtained from P2X4R KO and WT mice at 3 or 7 days post-stroke induction via 60 minutes of transient middle cerebral artery occlusion (MCAo). Our findings reveal a marked increase in phagocytic uptake, as evidenced by both phagocytic beads and pHrodo bioparticle studies, in BMDMs derived from P2X4R KO mice compared to their WT counterparts (1.5- and 2-fold increase, respectively; $P < 0.05$, Student's t-test; $n = 4$ mice/group × 2 technical replications). Moreover, FACS-sorted infiltrated Ly6Chi inflammatory monocytes from global P2X4R KO mice exhibit significantly elevated phagocytic bead uptake relative to WT controls (*$P > 0.05$). Furthermore, these monocytes demonstrate heightened expression of CD36, a scavenger receptor marker, at 7 days post-stroke, indicative of an enhanced phagocytic phenotype. Collectively, our study elucidates that P2X4R blockade confers swift and sustained neuroprotection by bolstering the phagocytic clearance of damaged tissue after ischemic stroke.

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Poster Session 2 / No. 2.8

Pharmacological Validation of Advanced Gamma Peptide Nucleic Acid (PNA) Based miR Inhibitors for Ischemic Stroke Treatment

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Our prior work demonstrated the potential of targeting miR-141-3p to mitigate ischemic stroke damage. In this study, we aimed to synthesize and validate more advanced and efficacious gamma peptide nucleic acid (PNA) based anti-miR 141-3p inhibitors, comparing them with regular PNA and phosphothiorate (PS) based counterparts. These inhibitors were subsequently encapsulated in poly(lactide-co-glycolide) (PLGA)-based nanoparticles (NPs) for treatment in a mouse model of ischemic stroke. In-house synthesis yielded PS, PNA, and gamma-PNA anti-miR 141-3p, encapsulated in PLGA NPs via double emulsion solvent evaporation. After physiochemical characterization, in vitro safety and efficacy were evaluated in HEK293 cells via MTT, LDH cytotoxicity assays, and qPCR for gene expression. In vivo efficacy studies employed the most potent gamma-PNA based anti-miR 141-3p, administered intraperitoneally 4 hours after 60-minute of transient middle cerebral artery occlusion (MCAO). Mice were sacrificed at 3 (acute) or 30 (chronic) days post-stroke. Acute cohort brain tissues were analysed for miRNA and target mRNA levels, along with infarct volume. Chronic cohort mice were subjected to weekly behavioral task to major sensorimotor deficit or recovery. twenty-four-hour exposed HEK-293 cells were no sign of mortality and toxicity at concentration range of 0.015-1.5ug/mL of various anti-miR 141-3p. Gamma-PNA based anti-miR exhibited notably higher efficacy in inhibiting miR-141-3p (IC50=0.05ug/mL) compared to PS (IC50>1.5ug/mL) or regular PNA (IC50>1.5ug/mL). A single dose of gamma-PNA-based anti-miR significantly reduced ($P<0.05$ vs. Scramble control) infarct injury and brain tissue miR-141-3p levels (>2-fold vs. scramble control). Gamma-PNA treatment also led to swift improvement in sensorimotor deficits in the rotarod task. We also identified TGFβ-SMAD2/3 signalling pathway as potential regulator of gamma-PNA based neuroprotection and neuro-rehabilitation. NPs of gamma-PNA-based anti-miR 141-3p were both safe and potent in vitro and in vivo. They effectively mitigated infarct injury, improved neurobehavioral deficits, demonstrating promising translational potential for ischemic stroke treatment. In future we aim to explore more mechanistic studies to explore it mode of action.

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Poster Session 2 / No. 2.9

Enhanced Motor Learning in Adenosine A1 Receptor Knockout-Mice

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To address the role that adenosine A1 receptors (A1Rs) might play in motor learning, we employed genetically modified mice with knock-out of adenosine A1 receptors (A1RKO), and compared to wild-type (WT) animals. Motor function and learning was assessed using an accelerating rotarod procedure. Both WT and A1RKO mice show an increase in latency to fall during 5 days of training and retain learned motor skills one week after training. Despite indications that WT animals perform better on the first training day, A1RKOs perform significantly better than WTs on the 5th day of training. Furthermore, improvements in performance (increase in the latency to fall) on all subsequent training days relative to Day 1 were significantly greater in A1RKOs than in WTs. Elevated plus maze and open field control tests suggest that observed disparities in motor learning are unlikely to stem from differences in anxiety level or locomotor activity between groups. These results indicate that genetic deletion of A1Rs (A1RKO) enhances motor learning. While our research did not explore the mechanistic basis of this effect, we speculate that it could be mediated by the interactions between A1Rs and other receptor types. Of particular interest here is the antagonistic relationship between dopamine D1 receptors and A1Rs in the striatum, as well as A1R modulation of metabotropic glutamate receptor-gated plasticity at the synapse between parallel fibers and Purkinje cells of the cerebellum.
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Poster Session 2 / No. 2.10

Chloride-Conducting Postsynaptic Receptors Mediate Cholinergic Synaptic Transmission from Locomotion Interneurons to Motor Neurons in the *C. elegans* Backward Circuit

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A bilateral pair of locomotor interneurons, AVA, plays a central role in *C. elegans* backward locomotion by activating A-type cholinergic motoneurons (A-MNs) through acetylcholine (ACh). However, the molecular identities and biophysical properties of the postsynaptic receptors involved remain poorly understood. Previous studies have identified two ACh receptors in A-MNs: a postsynaptic LGC-46 receptor and an extrasynaptic ACR-2 receptor, the latter being a heteromeric complex of ACR-2, ACR-3, ACR-12, UNC-38, and UNC-63. However, questions remain as to how LGC-46 mediates excitatory synaptic transmission from AVA to A-MNs, since its amino acid sequence resembles that of chloride channels, and whether the ACR-2 receptor functions as a postsynaptic receptor. In our electrophysiological analyses of VA5, representative of A-MNs, we observed that AVA-induced spontaneous postsynaptic currents (sPSCs) are significantly inhibited in loss-of-function (*lf*) mutants of either *lgc-46* or the genes encoding ACR-2 receptor subunits, and that sPSCs are essentially absent in an *lgc-46;acr-12* double mutant. In addition, VA5 sPSCs are strongly enhanced in an *acr-2* gain-of-function mutant, and this phenotype is suppressed by *lf* mutations of *acr-12*, *unc-38*, or *unc-63* but not *lgc-46*. These results suggest that both LGC-46 and ACR-2 receptors function independently as postsynaptic receptors. Consistent with their putative function as postsynaptic receptors, independent expression of GFP-tagged ACR-2, ACR-12, UNC-38, and UNC-63 in A-MNs under the control of the *unc-4* promoter resulted in punctate localization in the ventral and dorsal nerve cords. Surprisingly, sPSCs were absent under experimental conditions that prevented net chloride flux across the VA5 cell membrane and were unaffected by substituting extracellular Na^+ with $choline^+$, suggesting that both LGC-46 and ACR-2 receptors function as chloride channels. This challenges the conventional notion that activation of chloride channels can produce excitatory effects only in immature neurons. The discovery of an unexpected role for chloride channels in mature neurons and the unexpected synaptic mechanism by which locomotor interneurons control motor neurons in *C. elegans* prompts speculation that chloride channels may also play an excitatory role in some mature neurons of other species, including mammals.

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Poster Session 2 / No. 2.11

Investigating the Role of Astrocyte CXCL14 in Alzheimer's disease

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Alzheimer's disease (AD) is the most common cause of dementia worldwide and currently lacks disease-modifying therapies. Abnormal accumulation of extracellular amyloid beta (Aβ) leads to a cascade of neuropathological changes resulting in gliosis, impaired synaptic function, neuroinflammation, and neuronal death. Previous work has shown that astrocyte-specific knockout (KO) of β-site amyloid precursor protein cleaving enzyme 1 (BACE1), the enzyme responsible for generation of Aβ, significantly reduces Aβ pathology in a mouse model of AD. Analysis of differentially expressed genes from single-cell transcriptomic studies on BACE1 KO astrocytes reveals a significant upregulation of chemokine (C-X-C) ligand 14 (CXCL14). CXCL14 is a secreted chemoattractant protein for peripheral immune cells such as macrophages and neutrophils. Interestingly, genome-wide association studies have identified several single nucleotide polymorphisms near the *CXCL14* gene locus associated with increased risk of AD pathology. Furthermore, *CXCL14* is one of three genes upregulated specifically around Aβ in the middle temporal gyrus of AD patients. However, the role of CXCL14 in AD and its effect on glial cell function is poorly understood. Here, we show that CXCL14 co-localizes with astrocytes surrounding Aβ plaques in AD mice. Additionally, *in vitro* bulk RNA sequencing of CXCL14-treated BV2 mouse microglia cells showed upregulation of pathways associated with metabolism, immune cell functioning, and phagocytosis. This corresponded to altered lysosomal degradation of Aβ by BV2 cells treated with CXCL14 *in vitro*. These studies could identify astrocyte CXCL14 as a novel regulator of microglial function around Aβ plaques in the AD brain.

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THANK YOU for attending this year's retreat.

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We hope you enjoyed yourselves!

WE LOOK FORWARD TO SEEING YOU NEXT YEAR!

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