Neuroplasticity, Neuroregeneration, and Brain Repair

POSTER SESSION

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1. *PRG3 Attenuates CSPG and LPA Inhibitory Activity by Reducing Myosin Light Chain II Phosphorylation*

Chinyere Agbaegbu Iweka[1,2], Panpan Yu[3], Yasuhiro Katagiri[1], and Herbert M. Geller[1]

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Plasticity-related gene (PRGs) proteins, are integral membrane proteins characterized by six transmembrane domains and are a subclass of the lipid phosphate phosphatase (LPP) superfamily. A quantitative phosphoproteomic screen designed to determine global phosphorylation changes in neurons in response to chondroitin sulfate proteoglycans (CSPGs), revealed PRG3 as a protein whose phosphorylation state was most altered by exogenous CSPG treatment. Here, we report that PRG3 expression in primary neurons overcomes neurite outgrowth inhibition mediated by CSPGs. Furthermore, PRG3 attenuates lysophosphatidic acid (LPA) induced neurite retraction in neuronal cell line by decreased phosphorylation of myosin light chain II. In summary, our data indicates that PRG3 protein modulates neuronal response to CSPGs and LPA, both inhibitory molecules to axonal outgrowth, and therefore may mediate neuronal plasticity. These studies will contribute to a more comprehensive understanding of how neuronal plasticity is modulated and provide an avenue of investigation to improve therapeutic strategies after injury to the CNS.

2. *An* In Vivo *Model of Tau-associated Neurodegeneration Suited for Investigating Neuroplasticity and Neuroregeneration*

Zeshan Ahmed, PhD, Alice Fisher, BSc, Morten Heggenes, MSc, Soraya Meftah, BSc, Tracey K. Murray, PhD, Michael L. Hutton, PhD, and Michael J. O'Neill, PhD

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Neurodegenerative diseases such as Alzheimer's, progressive supranuclear palsy and Pick's disease are classified as tauopathies due to the accumulation and aggregation of the microtubule associated protein tau in neurons, forming neurofibrillary tangles (NFTs). The rTg4510 is a mouse model that overexpresses a mutated form of Tau (P301L) in the forebrain, leading to robust NFT pathology and progressive neurodegeneration similar to that seen in many tauopathies. This model also has an inducible system by which tau expression can be "switched off" using doxycycline (DOX). This feature can be used to halt or slow pathological progression at any given stage to examine spontaneous or drug-induced neuroplasticity and repair. In this study we performed a detailed neuropathological assessment of tau pathology (phospho-tau), inflammation (microglia), neuronal loss (NeuN), synaptic degeneration (synapsin) and neurogenesis (doublecortin) in Tg4510 mice and, compare these to age-matched wild-type mice and DOX-treated Tg4510 mice. The tau-associated neurodegenerative features of Tg4510 mice make them a suitable *in vivo* model for studying and eventually targeting neuroplasticity and/or neuroregeneration for therapeutic benefit.

3. *The Knob Supination Task: An Automated Method for Assessing Distal Forelimb Function*

Samuel D. Butensky[1], Thelma Bethea[1], Joshua Santos[1], Anil Sindhurakar, PhD[1], Eric Meyers, PhD[2,3], Andrew P. Sloan, PhD[2,3], Robert L. Rennaker II, PhD[2,3], and Jason B. Carmel, MD, PhD[1,4,5]

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Current rodent behavioral tasks measure dexterity largely through video analysis of reaching or food manipulation. While these tasks are relatively easy to implement, scoring outcomes is subjective and laborious. In addition, the tests are often insensitive to subtle deficits, including injury to the corticospinal tract. Forelimb supination is sensitive to subtle deficits in rats, and analogous hand supination is critical for dexterity in humans. Therefore, we designed an automated task that measures forelimb supination in rats. Rats are trained to reach and grasp a knob-shaped manipulandum and turn it in supination to receive a reward. Rats can acquire the skill within 20 ± 5 days. While the early part of training is highly supervised, much of the training is done without the need for direct supervision. The task produces both a success score and kinetic measures of how the movement is performed. We provide an intuitive means of analyzing behavioral data using a MATLAB graphical user interface. We also give solutions to common problems encountered during training, and show that minor corrections to behavior early in training produce reliable acquisition of supination. The task captures both supination deficits and endogenous recovery after corticospinal injury. It also demonstrates the effects of rehabilitation on recovery. Together, the task and analysis software enable quantitative evaluation of dexterity in rodents that is well-suited for injury and repair studies.

4. *Pipeline to Screen Gene Knockdown Effect on Neuroregeneration* In Vivo

Devon Chenette, PhD[1], Xingxing Wang, MD[1], Yram Foli, MS[1], Kristin DeLuca[1], Zhaoxin Jiang, MD[2], Yuichi Sekine, PhD[1], and Stephen Strittmatter, MD, PhD[1,3]

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Central nervous system (CNS) injury and age-associated diseases disrupt neuronal network connectivity, and limited regenerative potential causes persistent brain dysfunction. We sought to identify novel intrinsic repressors of axonal regeneration and repair at a genome-wide level. Our previous *in vitro* study identified >400 genes showing enhanced neuronal repair through siRNA screening in cortical neuron cultures. To validate that partial silencing of these genes results in enhanced neural recovery *in vivo*, a pipeline was developed utilizing adeno-associated virus (AAV) delivered shRNA prior to optic nerve crush (ONC). ONC is an ideal model for *in vivo* screening due to the non-invasiveness of the procedure and the limited time to analysis. The optic nerve is composed of retinal ganglion cell (RGC) axons, which show limited regenerative capacity. To generate experimental AAVs, shRNA hairpin sequences were cloned into a GFP-expressing vector that enables visualization of AAV localization. AAVs were produced in HEK293T cells utilizing the helper plasmid Delta F6 and the capsid plasmid serotype 2/2.

Serotype 2/2 showed enhanced selective RGC expression when compared to serotype 2/1. Mice were treated with AAV via intravitreal injection two weeks prior to ONC. 17 days post-ONC, optic nerves were isolated for regeneration analysis utilizing cholera toxin B axon tracing. This pipeline provides a method of

screening large data sets for neuroregenerative effect *in vivo*, providing insightful information to the field of CNS repair.

5. *Astrocytes Response to Reactive Oxygen Species (ROS) Activity in a* Nox3 *Mouse Mutant*

Lina M. Delgado-García, MsC, Gabrielly M. Denadai Chiarantin, MsC, Patrícia Camacho Mazzonetto, MsC, and Marimélia Porcionatto, PhD

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ROS are signaling molecules generated by cell metabolism. High levels of ROS produce oxidative stress and neuroinflammation. Here, we introduce a mouse mutant lineage of *Nox3* (*Nox3*^{N64Y}). Nox3 (NADPH oxidase 3) belongs to a family of transmembrane proteins that reduce molecular oxygen to form ROS. *Nox3*^{N64Y} mouse lacks motor coordination, has increased proliferation of cerebellar neuronal precursors in postnatal development, disorganization of the Purkinje cell layer, and *in vitro* overproduction of hydrogen peroxide. Those findings led us to investigate the engagement of astrocytes in the cerebellar dysfunction, since astrocytes are the key cells in the maintenance of the extracellular environment, been especially sensitive to ROS levels through their interaction with membrane transporter proteins. Additionally, astrocytes Ca^{2+} dynamics serves as a primary sensitive system to mediate the release of cytokines and growth factors to respond to neural activity. *In vitro*, BALB/c astrocytes were homogeneous with cytoplasmic immunolabeling of the glial markers GFAP and S100β. However, *Nox3*^{N64Y} astrocyte cultures showed several reactive astrocytes intensely labeled. Ca^{2+} dynamics assessed by release from the intracellular stores and/or influx from the extracellular space ($[Ca^{2+}]_i$) by Fura-2AM time-lapse fluorescence showed a decreased basal $[Ca^{2+}]_i$ in *Nox3*^{N64Y} when compared with BALB/c. Next, to test the participation of Nox3 in Ca^{2+} dynamics, mice were treated with apocynin, an inhibitor of NADPH oxidases. We observed that Nox inhibition produced a decreased proportion of reactive astrocytes, a homogeneous immunolabeling, and an increase of basal $[Ca^{2+}]_i$. Our data strongly suggest that Nox3 plays a role in astrocyte activation.

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6. *Social Isolation-induced Stress: Influence on Medial Prefrontal Cortex Neurons in African Naked Mole-rats*

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The African naked mole-rat, *Heterocephalus glaber*, provides a unique opportunity to study how different areas of the mammalian brain process complex social behavior. In order to adapt to the harsh environmental conditions below ground in East Africa, naked mole-rats were the first mammals to develop a eusocial organization, where there is only one queen, one to three male breeders, and the other members of the colony — up to 300 animals — are non-reproductive workers (Sansone *et al.*, 2015). One manipulation of the environment we have found to be particularly strong is social stress, which occurs when a naked mole-rat is isolated from its native colony. We found this social stress increases fecal cortisol levels over a three-week period. At baseline, the cortisol levels of the social isolated animals were lower (M = 1.5 ± 0.6 ng/dl) than after being isolated for one week (M = 3.2 ± 2.3 ng/dl) and cortisol levels rose significantly after the second week of being isolated (M = 9.7 ± 1.6 ng/dl). This demonstrates that cortisol levels rise significantly as a result of social isolation over time, $F(2, 5) = 51.11$, $p < 0.001$. In this study, we assess

the effects of social stress on the medial prefrontal cortex, which is a social area of the brain involved in fear and emotional processing (Radley *et al.*, 2004). Using advanced methods in behavioral tracking, physiological measurement, and measuring the morphology of neurons, we can begin to understand the complex "social brain." We found a trend towards significance suggesting that social isolation causes reduction in the density of dendritic spines and difference in spine morphology. Completion of the second cohort will allow us to understand the neuronal response to social stress in this species.

7. In Vivo *Two-photon Imaging of the Effects of Tauopathy and Amyloidopathy on Synapse Dynamics*

Johanna Jackson[1], Francesco Tamagnini[2], James Johnson[1,3], Terri-Leigh Stephen[1], Zeshan Ahmed[1], Alice Oliver-Evans[1], Soraya Meftah[1], Michael L. Hutton[1], John T. Isaac[1], Andrew Randall[2], Michael C. Ashby[3], and Michael J. O'Neill[1]

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A progressive loss of synapses occurs at the early clinical stages of Alzheimer's disease (AD) and has been correlated with cognitive deficits in patients. However, it is relatively unknown how synapse dynamics are affected by the two main pathological hallmarks of AD; the accumulation of tau and beta-amyloid. Here we used *in vivo* two-photon microscopy to assess the temporal dynamics of axonal boutons and dendritic spines in mouse models of human tauopathy (rTg4510) and amyloidopathy (J20). Following a craniotomy, adeno-associated virus expressing green fluorescent protein was injected into the somatosensory cortex to enable the visualisation of neurons and a cranial window was implanted for long-term imaging. GFP-labelled neurons were imaged in both models during a time period which spanned the onset of pathology. The gross morphology of neurites and the dynamics of their synaptic structures were assessed as the pathology progressed. In rTg4510s, gross morphological changes such as the presence of dystrophic neurites were visible as the tauopathy progressed and these were found to have a distinctive morphological phenotype prior to neurite degeneration. Alongside this, synapse instability and loss were also observed and could be prevented by suppressing the P301L transgene. In J20 animals, amyloid plaques increased in size and density over time and, whilst spine density was unaffected, spine turnover was increased in the transgenic animals. Both tauopathy and amyloidopathy had effects on synapse dynamics as the respective pathology progressed. These results will inform subsequent drug discovery studies to identify novel therapies to stabilize synapses in AD.

8. *Progression of Huntington's Disease and Time when Interventions Could Be Most Effective*

Cheryl A. Kennedy, MD[1], Michael McCormack, PhD[1,2], Machteld Hillen, MD[1], Kiran Hirapara, MBBS[1], Eli Kneisser, BS[1], and Barbara Fadem, PhD[1]

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Huntington's disease (HD), a neurodegenerative autosomal dominant disorder, is caused by a CAG repeat expansion in the huntingtin gene on 4p. Postmortem brains show gross striatal pathology, neuronal loss and gliosis. Animal models have shown that mesenchymal stem cells may be helpful in regenerating neurons. To determine when interventions might be most effective, we examined gender differences in patients from the time of onset of symptoms to diagnosis (TSD) & time from diagnosis to placement (TDP) in long term care (LTC). We reviewed 33 records (15 males) for ethnicity, family history, & psychiatric symptoms. Use of psychotropic medication was recorded before and after LTC placement as were CAG repeats size & staging scale values. *Chi-square* analyses of patient variables and *t*-tests of years were

done. There was no significant difference in gender on TSD, but TDP was significantly higher in men than women within one year of diagnosis (p = 0.0034, 17% of women, 66% of men) and within three years of diagnosis (p = 0.047, 39% of women, 73% of men). A two-tailed t-test showed a significant difference for mean TDP (p = 0.035, $mean_f$ = 6.2 years, $mean_m$ = 2.9 years). There was a significant difference in use of anxiolytics in men before entering LTC and after entering LTC (p = 0.006). When data were corrected for CAG repeat size, progression in men appeared to be slower, while women with HD may live longer than men. The variant of PGC-1α (transcriptional coactivator) is associated with earlier age of onset of motor symptoms in men but not in women. Our data suggest that sex differences may exist for disease progression; additional research is required to refine these differences and identify interventions for the neurodegeneration observed in men and women with HD.

9. *Precursor Protein by ADAM10 and BACE1 Regulates Oligodendrocyte Progenitor Cell Development*

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Tissue development, homeostasis, and repair are tightly regulated by signaling mechanisms acting to balance progenitor cell proliferation and differentiation. While Wnt signaling has emerged as a key regulator of oligodendrocyte progenitor cells (OPs) during post-natal central nervous system (CNS) myelination, the mechanisms that modulate Wnt pathway tone are not fully understood. Here, we show that amyloid precursor protein (APP) cleavage by ADAM10 and BACE1 is dynamically regulated during oligodendrogenesis in line with the physiological requirement for Wnt signaling, and in turn, controls the production of mature oligodendrocytes. Supporting this observation, we demonstrate that the α- and β-specific APP cleavage products play opposing roles (pro- and anti-Wnt, respectively). Conditional deletion of ADAM10 in OPs resulted in suppressed Wnt pathway activity, cell cycle exit, and accelerated CNS myelination, while BACE1 inhibition blocked oligodendrocyte lineage progression. Further, we found that this effect is mediated by the interaction between the ADAM10 specific APP cleavage fragment, sAPPα, and the Wnt co-receptor LRP6. Together, these findings reveal how APP cleavage serves as a platform to activate or repress Wnt signaling to direct the fate of OPs.

10. *The Developmental Relationship Between Microglia and Dopamine D1 Receptors in the Nucleus Accumbens Is Altered by Adolescent Morphine Exposure*

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Drug taking is often initiated in adolescence when the dopaminergic “reward circuitry,” including the nucleus accumbens (NAc), is developing, and thus vulnerable to external influences. Indeed, male rats given a five-day morphine treatment during adolescence, but not young adulthood, have persistently impaired molecular signaling in the NAc and increased risk of reinstatement (i.e. relapse) much later in life. However, how the reward circuitry develops naturally, and how addictive substances modify this development, is unknown. The immune cells of the brain, microglia, are important for normal neural development, notably via engulfment and elimination of synapses ‘tagged’ by the complement system of proteins, including complement protein C3 (i.e. synaptic pruning). Moreover, microglia have been implicated in playing a critical role in the adverse effects of drugs of abuse. Our data suggest that NAc dopamine D1r receptors are ‘tagged’ by C3 for microglial-dependent synaptic elimination during adolescent development in male rats.

Five days of morphine during the adolescent period increases microglial engulfment of D1rs and reduces D1r levels after drug cessation, raising the possibility that the developmental pruning process may be over-activated by drug use. If so, increased (i) C3 levels, (ii) C3-tagged D1rs, and (iii), microglial engulfment of C3-tagged D1rs, may occur prior to D1r elimination. C3 levels are, indeed, increased after drug cessation, but there is no change in C3-tagged D1rs and decreased engulfment of C3-tagged D1rs. These data collectively suggest that adolescent morphine exposure dysregulates the C3 tagging process, thus resulting in uncoordinated and exaggerated microglial elimination of D1rs in the NAc.

11. *Advantages and Costs of Adaptation to Corticospinal Injury in Neonatal Rats*

Sophia Lall, BA[1], Tong-Chun Wen, MD, PhD[1], Corey Pagnotta, BA[1], James Markward, BS[1], Disha Gupta, PhD[1], Jeremy N. Hill, DPhil[1], Shivakeshavan Ratnadurai-Giridharan, PhD[1], and Jason B. Carmel, MD, PhD[1,2]

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Injury to the developing corticospinal tract (CST) triggers persistence and remodeling of spared descending motor circuits. After neonatal CST lesion, spared pathways from either cerebral hemisphere can provide motor control to the impaired forelimb. We tested whether connections and control arose from the injured hemisphere, via a bypass circuit through the brainstem, or via ipsilateral connections from the uninjured hemisphere. Using inactivation of each motor cortex, we found that in uninjured rats the forelimb is controlled by the contralateral motor cortex, whereas rats with neonatal CST injury exhibited control from both motor cortices. In contrast, tract tracing and microstimulation mapping indicate anatomical and physiological adaptations only in the uninjured hemisphere. Stimulation of the motor cortex in the uninjured hemisphere produced responses from both forepaws but stimulation of the injured hemisphere produced responses in neither. Additionally, injured rats had strong CST connections stemming from the spared tract to both halves of the spinal cord. Interestingly, both forelimbs had a different representation within the uninjured hemisphere, suggesting one hemisphere can encode separate control of the forelimbs. However, there is a cost to adaptation after injury, as the representation of the unimpaired forelimb becomes weaker.

12. *The Examination of the Role of Prostacyclin In Neuroregeneration* In Vitro *Using a Novel Hybrid Enzyme*

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Neuroinflammation is the hallmark of Alzheimer's disease. However, so far, non-steroidal anti-inflammatory drugs (NSAIDs) showed limited success. It is known that neuroinflammation can result in resolution, leading to neuroregeneration (with anti-inflammatory mediators), or neurodegeneration (with pro-inflammatory mediators). Using NSAIDs will inhibit both pathways. Our previous data and current study supported that prostacyclin, a metabolite of arachidonic acid, promoted neuroregeneration. To further explore, we created three novel hybrid enzymes, COX-2-10aa-mPGES-1, COX-1-10aa-PGIS, and COX-1-10aa-TXAS to redirect the metabolism of arachidonic acid specific to prostaglandin E_2, prostacyclin, and thromboxane, respectively. The cDNA of these three hybrid enzymes were transfected to HT-22 cell, a well-established mouse hippocampal neuronal cell line. The transfected HT-22 cells were challenged with amyloid β (Aβ) peptide (25-35), and it was observed that COX-1-10aa-PGIS transfected cells were resistant to Aβ-induced neurotoxicity. Furthermore, we cultured primary hippocampal neurons from postnatal day 0-1 transgenic mice (over expressing COX-1-10aa-PGIS), and challenged with Aβ peptide (amino acid sequence 25-35).

We found that the cultured primary prostacyclin producing-neurons were resistant to the Aβ 25-35-induced cellular damages, and these effects were blocked by aspirin, which inhibits COX-1-10aa-PGIS activity. Additionally, WT primary hippocampal neurons treated with Iloprost, a synthetic analogue of prostacyclin, promoted neuroregeneration against Aβ peptide (amino acid 1-42)-induced neurotoxicity. However, this effect was abolished by Ro1138452, a prostacyclin receptor (IP receptor) antagonist, which suggested that the protective effects exerted by prostacyclin is possibly through activating IP receptor. Therefore, these data suggested that prostacyclin could redirect neuroinflammation to neuroregeneration.

13. ***A Comparison of the Cerebellar Lobules Across Primate Species Reveals the Evolutionary Seeds of Human Intelligence***

Vincy Mathew

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There is a general consensus that the capacity to learn links between thoughts and actions and the context in which they are executed is fundamental to our notion of “intelligence”. However, little is known about the evolution of the neural substrate, the cerebellum, leaving open some very fundamental questions about how intelligent arose in humans and other primates. This study investigates differences between 20 primate species (including humans) in their relative volumes of cerebellar lobules (HVI, Crus I, Crus II and HVIII-X). These comparative differences are then used to estimate patterns of evolutionary change along individual lineages of the primate tree of life. Results elucidate how the neural substrate to learn links between thoughts and actions changes over time and when in evolutionary time an expansion of this capacity arose. Findings point towards an exceptional expansion of lateral cerebellar lobules HVIII-X in great apes and humans, suggesting that working memory was a crucial factor in the evolution of intelligence. These results provide a working hypothesis that can be further investigated in future research on the evolution of human and animal intelligence.

14. ***Multiple Presentations with Plausible CADASIL Diagnosis***

Fiorella Melendez, MS, Kelissa Shillingford, Carlo Villania, William Zeleznak, Edmond Mala, and Damian Casadesus, MD

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CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is caused by a genetic mutation in the *NOTCH3* gene and has variable presentations that mirror multiple neurological disorders. Provided are three cases with plausible CADASIL diagnosis.

Case 1: 50-year-old African American woman with PMH of multiple sclerosis, who complained of diplopia. Genetic testing confirmed a mutation in the *NOTCH3* gene and she was treated symptomatically.

Case 2: 48-year-old Caucasian male with PMH of ETOH dependence, depressive disorder and neurosyphilis was admitted for inappropriate behavior, AMS, ataxia, seizures and an unexplained fall. Further investigation confirmed a positive family history of CADASIL.

Case 3: 43-year-old Hispanic male with PMH of HTN, obesity, multiple suicide attempts and polysubstance abuse was admitted for AMS and right-sided weakness. Genetic testing was offered, but patient refused; though two weeks later he was admitted for yet another CVA.

These cases prove the variability of symptomatology presented with CADASIL. Thus, it is crucial to obtain a detailed history and clinical evaluation to approach an accurate diagnosis. Nonetheless, genetic testing and a positive family history of CADASIL alone are confirmatory.

15. *Nicotinic Activation of Somatostatin Inhibitory Neurons Restores Cortical Plasticity in Adulthood*

Masato Sadahiro[1], Michael P. Demars, PhD[1], Poromendro Burman[1], Priscilla Yevoo[1], Milo R. Smith [1], Andreas Zimmer, PhD[2], and **Hirofumi Morishita**, MD, PhD[1]

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Experience-dependent cortical plasticity is heightened during developmental critical period but declines into adulthood, posing a challenge for recovery of function following injury or brain disorders later in life. A network of inhibition is critical for plasticity, yet contributions of interneurons other than Parvalbumin (PV) interneurons have largely been unexplored. Here we show Lypd6, an endogenous positive modulator of nicotinic acetylcholine receptors (nAChRs), as a specific molecular target in Somatostatin (SST) interneurons to reactivate cortical plasticity in adulthood. Lypd6 decreases its expression in adult primary visual cortex in concert with declining ocular dominance plasticity. Overexpression of Lypd6 specifically in adult SST-cells reactivates plasticity through α2 subtype of nAChR by activating SST-cells which in turn inhibit PV-cells, a key early trigger of plasticity in juvenile cortex. Chemogenetic activation of SST-cells alone confirmed the causal role of SST-cell activity in reactivating plasticity. Lypd6-overexpression-based plasticity was normalized by chemogenetic activation of PV-cells. Together this highlights a key role of nAChR2α2 signaling through SST->PV disynaptic inhibitory circuits in plasticity regulation. Identification of the first SST-cell specific plasticity regulators provides an important basis for future therapeutic development for disorders with limited recovery due to diminished plasticity, and neurodegenerative disorders with deficits in SST-cells.

16. *Lasting Augmentation of Spinal Sensorimotor Circuits in Awake, Intact Rats Using Paired Electrical Stimulation of Motor Cortex and Cervical Spinal Cord With Chronic Electrodes*

Ajay Pal, PhD[1], Asht Mishra, PhD[1], Aldo Garcia-Sandoval, MS[3], Shivakeshavan Ratnadurai-Giridharan, PhD[1], Walter Voit, PhD[3,4], and Jason B Carmel, MD, PhD[1,2]

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The spinal cord is key site of sensorimotor integration. Yet, unlike cortex, the interaction between descending motor pathways and afferent pathways in the spinal cord has not been targeted for paired electrical stimulation. We hypothesized that paired stimulation of corticospinal and large diameter afferents would create synergistic effects through convergent input on spinal cord interneurons. We paired suprathreshold motor cortex stimulation with subthreshold cervical spinal cord stimulation. When spinal cord stimulation was stimulated 10ms after motor cortex stimulation, motor evoked potentials were more than doubled. Paired stimulation produced even larger augmentation when stimulating electrodes were

placed over the dorsal root entry zone. When these two sites were paired repeatedly over 5 minutes, motor cortex and spinal cord excitability was potentiated for more than 60 minutes. We adapted this paradigm in awake rats using chronic spinal epidural electrode, which are thin, flexible, and long lasting. These electrodes are stiff at room temperature and become supple after implantation into the spinal epidural space. Chronic electrodes take the shape of the underlying spinal cord and produce robust neuromodulation for more than five months. In addition, no behavioral or histological evidence for injury to the spinal cord was observed. Thus, we conclude that chronic electrodes are safe for spinal cord stimulation and effective for lasting neuromodulation.

17. ***The Antibody Rhigm22 Facilitates Hippocampal Remyelination and Ameliorates Memory Deficits in the Cuprizone Mouse Model of Demyelination***

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Multiple sclerosis (MS) is a chronic, inflammatory demyelinating disease of the CNS. In addition to the various neurological symptoms, such as motor, sensory and visual deficits, MS is also characterized by hippocampal demyelination and memory impairment, with prevalence rates ranging between 40% and 75% of patients. Recent studies have shown that a recombinant human-derived monoclonal IgM antibody, designated rHIgM22, which is in clinical development for people with MS, accelerates remyelination of the corpus callosum in the brain of the cuprizone mouse model of demyelination and spontaneous remyelination. The present study investigated the effects of rHIgM22 in the hippocampus of the cuprizone mouse model. Cuprizone-fed mice treated with rHIgM22 were examined at the end of a six-week cuprizone diet (0.3% cuprizone), as well as at various time points during the recovery period with regular food (spontaneous remyelination), and were compared with cuprizone-fed animals treated with either vehicle or human IgM isotype control antibody. Mice fed only regular food were used as normal controls. The CA3 and the dentate gyrus regions of the hippocampus were analyzed. Both regions were severely demyelinated in all groups of cuprizone-fed animals at the end of the cuprizone diet. Treatment with rHIgM22 significantly accelerated their remyelination. The enhancing effects of rHIgM22 on hippocampal remyelination were accompanied by significantly improved performance in the Morris water maze and amelioration of the memory deficits induced by cuprizone-mediated demyelination. These data further confirm the remyelination-promoting capabilities of rHIgM22 and support additional investigation of its therapeutic potential in MS.

18. ***Reduced Glucose Uptake Impairs Brain Angiogenesis by Reducing Lactate Production and Impairing Astrocyte-endothelial Cell Communication as Shown in GLUT1-deficiency Syndrome Model Mice***

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GLUT1-deficiency syndrome (GLUT1-DS) is a severe neurodevelopmental disorder caused by haploinsufficiency of the SLC2A1 gene and reduced levels of the Glucose Transporter Type 1 (GLUT1) protein. The immediate metabolic consequence is a decreased level of brain glucose, the primary metabolic fuel, leading to tissue starvation. However, precisely how neuroglycopenia produces the complex GLUT1-

DS phenotype is unclear. One interesting biomarker of GLUT1-DS patients is a decrease in cerebrospinal fluid (CSF) lactate levels. According to the astrocytic-neuronal lactate shuttle (ANLS) theory (Pellerin *et al*., 1998), lactate is the main neuronal substrate. Lactate is the end product of glycolysis in the astrocyte before being shuttled to the neuron by the monocarboxylate transporters (MCT). In essence, decreased CSF glucose transport across the endothelial and astrocytic membranes leads directly to decreased brain lactate. The tissue consequences of blunted lactate production have not been studied in detail. Lactate has been described not only as the main oxidizable substrate for neuronal metabolism, but also as an important pro-angiogenic signaling molecule facilitating astrocytic to endothelial cell communication (Hunt *et al.*, 2008, Salmina *et al.*, 2015). Indeed, other mice model that have impaired glycolytic lactate production, such as the phosphofructo-2-kinase-fructose-2,6-biphosphatase 3 (PFKFB3) deficient mice, show impaired angiogenesis (De Bock *et al.*, 2013, Xu *et al.*, 2014). The precise molecular mechanism connecting decreased brain glucose delivery to impaired cerebral angiogenesis in Glut1 (+/-) mice remains unknown (Tang *et al*. submitted). Furthermore, the relation between deficient cerebral microvasculature in the Glut1 mice, acquired microcephaly (Wang *et al.*, 2006, Ullner *et al.*, 2009) and impaired task performance in behavioral tests is a fundamental question that we are addressing in this project. This study also helps to explain why the ketogenic diet effectively controls seizures in GLUT1-DS patients but does not ameliorate the complex cerebral dysfunction. Ketone bodies enter the metabolic pathway at the level of the mitochondrial acetyl-coA pool. As a result, ketone bodies do not replenish glycolytic intermediates and hence, decreased tissue lactate persists. In summary, lactate deficiency is a likely explanation for cerebral hypovascularity and limited perfusion of the developing brain in the Glut1 (+/-) mice model. Our preliminary results with Glut1 (+/-) astrocytic cultures confirm decreased lactate production in the presence of physiological glucose concentrations. We hypothesize that Glut1 deficiency causes a cataplerotic effect on glycolytic intermediates ultimately leading to brain lactate deficiency and diminished cerebral microvasculature.

19. *HIV-1 gp120 Leads to Pre-mature Brain Aging*

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Even with the advancement in HIV treatment with cART (combinatory anti-retroviral therapy), HIV-associated neurocognitive disorders (HAND) such as learning disability exist as a major problem among HIV-1 infected patients. Anatomically, several of these functions are assured by the neurons of the hippocampus — an area in the brain known to be affected by HIV-1. Clinically, it has been observed that HIV infection causes disability in learning and memory, but the mechanisms involved in it remain to be elucidated. Several reports have described that released viral proteins (e.g. gp120, tat, vpr) or other toxins (e.g. TNFα) might be responsible for neuronal dysfunction.

Regarding neurocognitive disorders, HIV/AIDS patients complained of **Spatial and Declarative Memory Impairments (SDMI)** even with low HIV viral titers. The mechanisms leading to these cognitive impairments remain unknown.

Studies from other neurodegenerative diseases described the CREB (cAMP responsive-element binding**)** protein as a **Key Regulator of the Memory**. These studies have also showed that loss of CREB protein expression and phosphorylation leads to the development of neurocognitive impairments such as Learning Deficit and Declarative Memory Alteration.

Unfortunately, studies linking CREB protein to the development of HAND are lacking. In here, we showed that exposure of neuronal cells to HIV-1 gp120 protein decreases expression level of CREB protein, prevents its phosphorylation, and inhibits its function. We **reversed** gp120 effect *in vitro* (cell line) and *in vivo* (animal model) and restored CREB function in cells and animals treated with Rolipram (a selective phosphodiesterase-4 inhibitor), and induced CREB protein expression and phosphorylation.

20. *A Novel Model of Lacunar Stroke Targeting the Forelimb Representation of the Internal Capsule in Rats*

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Lacunar strokes of the internal capsule are common, and they can cause substantial and lasting impairment, particularly in hand function. Current rat models of internal capsule stroke can produce focal lesions, but the portion of the internal capsule that is lesioned can vary due to anatomical differences between animals. We describe the organization of the internal capsule in the rat and a technique to specifically target the forelimb representation. To our knowledge, the somatotopy of the internal capsule in the rat has only been described with anatomical techniques. To better characterize the somatotopy, we performed electrophysiological motor mapping of the rat internal capsule in addition to tracing fibers emanating from the forelimb and hindlimb motor cortex. For mapping, we used a microelectrode to stimulate the internal capsule and characterized the responses as forelimb, hindlimb, or both. From both anatomy and physiology, we found largely separate representations of the forelimb and hindlimb. To ablate the forelimb fibers, we adopted the Rose Bengal photothrombotic technique. The key innovation is the use of an optrode, which is a sharp electrode and an optical fiber glued together, with a total width of 200 microns. The electrode is used to stimulate the internal capsule and determine the “hot spot” of the forelimb representation, and the adjacent optic fiber used to deliver green wavelength light to activate the Rose Bengal. The duration of the light exposure was adjusted to produce a highly localized lesion. Rats had strong impairments in forelimb function, as measured by a pasta manipulation task. Our novel approach allows us to investigate changes in adjacent neural circuits after selective ablation of the forelimb representation. In sum, with this new approach we can achieve reproducible anatomical, physiological and behavioral changes that enable us to test hypotheses about how the corticospinal system adapts to lacunar stroke.

21. *Integrative Bioinformatics Approach to Understand the Role of Plasticity in Neurodegenerative Disease*

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Neuroplasticity is essential to normal brain function throughout life. Identifying brain diseases wherein neuroplasticity is disrupted will uncover novel disease pathophysiology and identify therapeutic targets. Using the well-characterized ocular dominance model of experience-dependent cortical plasticity, we generated transcriptional signatures of plasticity, which we matched to 436 disease signatures using a molecular matching algorithm. We identified diverse diseases associated to plasticity, and implementing a novel Disease Leverage Analysis, found inflammatory pathways as a putative common pathology to suppress experience-dependent plasticity, which we validated *in vivo* using the lipopolysaccharide model of inflammation (Smith, *eNeuro* 2016). Inflammation is a hallmark biological pathway common to all neurodegenerative diseases. Consistent with a relationship between plasticity and inflammation, we identified a range of neurodegenerative diseases as strongly associated with plasticity signatures, including Alzheimer's disease, Huntington's disease (HD), Parkinson's disease, and Amyotrophic Lateral Sclerosis, suggesting that experience-dependent plasticity may be disrupted in neurodegeneration. Interestingly, the expression patterns of genes in neurodegenerative disease signatures were heterogeneously correlated with plasticity signatures; independent signatures of the same disease (e.g. HD) indicated both anti-

correlated and correlated expression patterns. Given that pre-symptomatic HD individuals have heightened plasticity-dependent perceptual learning (Beste, *Current Biology* 2012), the finding that HD has both correlated and anti-correlated expression relative to plasticity suggests a dynamic transcriptional landscape across the natural history of the disease. These findings call for additional work to fully elucidate the transcriptional trajectory of HD and other neurodegenerative diseases to facilitate discovery of the right treatment at the right time to restore plasticity and cognition.

22. *Minocycline Plus N-acetylcysteine Restores Synaptic Plasticity, Limits Gray Matter Injury and Improves Navigation in a Closed Head Injury Mouse Model*

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Traumatic brain injury (TBI) leads to long lasting cognitive and behavioral deficits. Patients often wait days after a TBI to seek treatment only when their symptoms do not abate. Therefore, to be effective, a drug to treat TBI must retain potency when dosed hours to days after an injury. We tested the potency of minocycline (MINO) plus N-acetylcysteine (NAC) when first dosed 72 hours after a closed head injury (CHI) to mice. CHI produces both behavioral deficits as well as gray and white matter damage. The hippocampus is particularly susceptible to TBI. We show that CHI damages the hippocampus both ipsilateral and contralateral to the impact site. This results in hippocampal neuronal loss, decreased dendritic density and altered spine morphology. Fourteen days after injury, hippocampal slices isolated from injured mice have impaired LTP. Injured mice with impaired LTP also have behavioral deficits on Barnes maze, a spatial memory task that requires one intact hippocampus. MINO plus NAC treatment beginning at 72 hours after CHI restored hippocampal LTP in the contralateral hippocampus. The treated contralateral hippocampus maintained dendritic structure, spine density and spine morphology. MINO plus NAC also improved performance on Barnes maze. These data suggest that: (1) CHI induces long-term changes to synaptic connections that result in electrophysiological and behavioral impairments and (2) MINO plus NAC can be dosed within a clinically useful time window to reverse these impairments. Thus, our results identify dendritic morphology and synaptic plasticity as injury mechanisms that can be targeted pharmacologically. Both MINO and NAC are FDA-approved drugs suggesting that this combination could be used to limit cognitive and behavioral deficits after clinical TBI.

23. *Identifying Mechanisms Underlying Intellectual Disability Linked to β-catenin Disruptive Mutations*

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Intellectual disability (ID, IQ<70) affects 2-3% of the United States population. Despite its prevalence, the underlying pathophysiology is poorly defined, so effective pharmacological treatments are lacking. Several ID-linked human gene mutations have been identified, including disruptive mutations in the *CTNNB1* gene, encoding the β-catenin protein. β-catenin, through its roles in synaptic adhesion complexes and as a mediator of Wnt-target gene expression, is required for proper brain development, synaptic function, and plasticity. Human and mouse genetic studies suggest that the period of peak synaptogenesis in the brain may be a critical window for pathophysiological changes that can lead to ID. However, the pathophysiological changes caused by β-catenin loss in the brain during this window are unknown; their identification is essential to advance the design of effective therapeutic interventions to ameliorate ID. To gain insights into the pathological consequences of β-catenin loss-of-function in the developing brain, we

have generated a novel mouse model with β-catenin conditionally knocked-out (β-cat cKO) during peak synaptogenesis in glutamatergic neurons. Our preliminary studies show that β-cat cKO mice display memory impairments, compared with wild-type littermates. We have also found several novel molecular changes in the hippocampus, including reduced levels of two β-catenin binding partners critical for synaptic adhesion and stability, N-cadherin and α-catenin. Consistent with these changes, preliminary findings suggest decreases in synaptic spine density and maturity on hippocampal CA1 pyramidal neurons in the β-cat cKO. Moreover, preliminary data indicates hippocampal TBS-LTP is also reduced at CA3/CA1 synapses, suggesting reduced synaptic plasticity required for learning and memory. As an unanticipated change, the β-cat cKOs exhibit increases in γ-catenin, a homologue of β-catenin with partial overlapping function. γ-catenin's neural specific role is unknown, and normally γ-catenin levels are very low in neurons. Our studies will elucidate γ-catenin's neural functions, with particular emphasis on the composition of the cadherin based synaptic adhesion complex and Wnt-target gene expression. Together, these studies are providing new insights into molecular changes that can lead to intellectual disabilities.

24. *Integrin-mediated Dendrite-substrate Interactions Counter Age-related Somatosensory Neuron Decline in Drosophila*

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Aging correlates with deficits in sensory, motor, cognitive abilities, and increased incidence of nervous system disorders. We developed a *Drosophila* model to study the molecular basis of age-related dendritic decline. We find that dendrites of adult *Drosophila* sensory neurons show age-related atrophy associated with thinning of the extracellular matrix, loss of stable microtubules, decreased number and altered distribution of dendritic mitochondria, and altered mechanosensitivity. Age-related dendritic decline was robustly rescued by over-expression of integrin receptors for the extracellular matrix in neurons. Conversely, loss of integrins led to premature simplification of arbors. Integrin rescued dendrites retained several features of youthful dendrites, including a space-filling arborization, stable microtubules throughout the dendrite branch, organelle distribution, and mechanosensitivity. Thus, integrin-mediated interactions between neurons and the extracellular environment are essential for long-term stability of complex dendritic architecture during aging and enhancement of integrin activity can extend the vitality of aged arbors.