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ABSTRACTS

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1. The use of EEG Biomarkers in a Chronic Paradigm to Evaluate the Anti-dyskinetic Effect of Drugs in Parkinson's Disease

V. Duveau, A. Evrard, J. Volle, C. Roucard, Y. Roche, H. Gharbi; SynapCell

Abstract State-of-the-art clinical literature shows that motor symptoms of Parkinson's disease (PD) result from a dysfunction of the cortico-basal ganglia circuits. A hyper synchronization of beta rhythms in this circuit, positively correlated to motor symptoms, has been characterized in both parkinsonian patients and animal models. This aberrant excessive beta oscillation is suppressed by dopaminergic treatments, which simultaneously improve motor deficits. However, a chronic L-DOPA treatment induces abnormal involuntary movements (AIMs) and a prominent resonant gamma oscillation.

This project aimed at investigating the effect of the anti-dyskinetic drug amantadine, which is routinely used in the clinic, on L-DOPA-induced gamma oscillations in the 6-OHDA rat model of PD.

In this poster, we will show that chronic administration of L-DOPA low dose (6 mg/kg) induces specific gamma oscillations and AIMs which gradually increase with repeated treatments. We will demonstrate that a pre-treatment with amantadine dose-dependently reduces L-DOPA-induced gamma oscillations and AIMs score.

Our data will illustrate how the preclinical study of cortical beta and gamma oscillations offers relevant and translatable EEG biomarkers that add significant value to drug development as stable, quantitative, and objective endpoints for the development of new antiparkinsonian and antidyskinetic neurotherapeutics.

2. 40 Hz-Auditory Steady-state Response in Rodents, a New Tool for Drug Discovery in Schizophrenia?

J. Volle, C. Habermacher, V. Duveau, A. Evrard, C. Roucard, Y. Roche; SynapCell

Abstract Schizophrenia is a severe psychiatric disorder associated with persistent alterations of diverse neurocognitive functions, leading to lifelong psychosocial disabilities. Although schizophrenia has long been considered as a condition that specifically impairs the higher-order functions, recent research has demonstrated that basic sensory processing is also impaired, especially in the auditory modality.

Neurophysiological approaches have provided evidence that most schizophrenic patients exhibit a wide range of clinically measurable dysfunctions in the processing of auditory stimulations, including the Auditory Steady-State Responses (ASSRs) which is one of the most consistent functional biomarker across schizophrenic patients. ASSRs consist in cortical electrophysiological oscillations entrained by the frequency and phase of a periodic auditory stimulus presented at a rhythm in the gamma range (that is, 30-80 Hz). ASSRs are believed to reflect the interplay between cortical pyramidal neurons and parvalbuminergic interneurons. Consistent with the theory of imbalance between cortical excitation and inhibition in schizophrenia, patients show reduced power and phase locking, to stimuli presented at 40 Hz.

In recent years, we have developed the characterization of ASSRs in mice and rats to propose a translational solution for drug candidates. In this work, we particularly studied the 40 Hz-ASSR modulations in a rat model of schizophrenia, induced by a glutamatergic antagonist MK-801.

We will show in this poster how MK-801 (0.1, 0.15, 0.2 mg/kg) induces a dose-dependent reduction of the 40 Hz-ASSR phase locking in the cortex of rat and how antipsychotics (such as clozapine) modulate this pharmacological effect. We propose the 40 Hz-ASSR phase locking as a specific translatable biomarker useful for the preclinical identification, selection and validation of new innovative therapeutics in psychiatric disorders.

3. Optimising the Discovery and Selection of New Therapeutic Strategies in Epilepsy

C. Roucard, A. Evrard, H. Gharbi, J. Volle, Y. Roche, V. Duveau; SynapCell

Abstract Despite many drugs already on the market, still a significant number of epileptic patients are in needs of more effective and safer drugs for their pathology. These unmet needs call for a different view of how drug discovery (DD) in epilepsy is performed, and to organise the available animal models along DD programs addressing specific questions. Moreover, new strategies are requested by legal authorities to address disease modifying effect or anti-epileptogenic strategies. Over the last years, new technologies and new medical applications have largely been explored such as cell or gene therapies, and drug discovery needs to evolve as well to allow an easy and objective evaluation of them.

SynapCell has developed a translational Drug Discovery program for anti-epileptic drugs (AEDs) that has assessed more than 500 drug candidates and various therapeutic strategies in the last 16 years such as:

- Evaluation of small libraries of anti-seizure compounds to identify the lead compounds
- Classical anti-seizure effect of compounds, with a full range of clinical like designs
- Anti-epileptic and/or disease modifying potential for gene and cell therapies
- Anti-epileptogenic effect of neuroprotective agents
- Identification of therapeutic targets and/or pathways by transposing our validated models to transgenic animals
- Repositioning in related pathologies (Essential Tremor, pain…)

In this poster, we will first present results obtained during our evaluation program of newly developed AEDs. We will describe the pharmacological characterization of a new AED, retigabine on drug-resistant focal epilepsies using our translational model of intrahippocampal kainate, the MTLE mouse. We will show how retigabine at 20, 40 and 80 mg/kg reduces epileptic discharges (HPD) by up to 80%, in a comparative experimental design involving several reference AEDs, such as valproate (150 and 300 mg/kg), carbamazepine (26 and 40 mg/kg), lamotrigine (17 and 34 mg/kg), diazepam (2.5 and 5 mg/kg) and levetiracetam (600 mg/kg). We will also present examples in the context of generalized epilepsy, including our model of absence epilepsy, GAERS. Finally, we will illustrate the use of the MTLE mouse model which provides a convenient window for epileptogenesis, over 3–4 weeks, to explore anti-epileptogenic properties of drugs. Thanks to the stability of the epileptic activities in the MTLE mouse model we can assess the disease-modifying properties, and de-risk the potential tolerance of compounds (i.e. diazepam, 2 × 2 mg/kg over 5 days).

In this work we demonstrate how our epilepsy research programs combined with an experienced team of experts and a powerful technology, EEG with surface and depth recordings, have helped many drug makers over the past 16 years to identify and select the right strategy for the development of their various therapeutic strategies.

4. Accelerating New Therapeutic Approaches for the Treatment of Brain Disorders through NINDS/DTR Translational Research-BPN Funded Program

Mohamed Hachicha, NINDS, Division of Translational Research; Pascal Laeng, NINDS, Division of Translational Research; Rebecca Roof, NINDS, Division of Translational Research; Enrique Michelotti, NIMH, Division of Neuroscience and Basic Behavioral Science; Shamsi Raeissi, NINDS, Division of Translational Research; Carol Taylor-Burds, NINDS, Division of Translational Research; Oreisa O'Neil-Mathurin, NINDS, Division of Translational Research; Ranga Rangarajan, NINDS, Division of Translational Research; and Charles Cywin, NINDS, Division of Translational Research

Abstract Neurological and psychiatric disorders remain an intense field of interest to scientists in academia and industry. The latest biotechnological advances in drug formulation and delivery as well as in stem cells, microarray, small interfering RNA (siRNA) and anti-sense oligonucleotides (ASOs) technologies have helped uncover and validate new potential molecular targets/pathways as new therapeutic approaches in the field of neuroscience. While Neuroscience-focused drug development efforts have been laden by a high-rate failure in clinical trials over the past ten years, a significant number of scientists in academia and industry are renewing their interest in the development of new therapies for the treatment of neurological and psychiatric disorders. To boost drug discovery and development activities in the neuroscience field, the division of translational research (DTR) within NINDS, and in collaboration with other NIH-institutes, launched a series of translational programs to promote neuroscience drug discovery and development efforts to mitigate the current pipeline gaps. In this presentation, we outline to neuroscientists in academia and industry NINDS/DTR-BPN funding mechanism and resources to accelerate the translation of their experimental discoveries into new therapies and support their ongoing preclinical and translational activities in the field of neuroscience.

5. Preclinical Testing of Drug Mimics of the Ketogenic Diet in Fragile X Mice

Cara Westmark; Alejandra Gutierrez, Molecular Environmental Toxicology Center, University of Wisconsin Madison; Pamela Westmark, Department of Neurology, University of Wisconsin Madison

Abstract The purpose of this study is to determine the efficacy of drug mimics of the ketogenic diet on disease phenotypes in a mouse model of fragile X syndrome (FXS; Fmr1KO mice). FXS is a rare neurodevelopmental disorder and the leading known genetic cause of autism. The ketogenic diet is highly effective at attenuating seizures in refractory epilepsy and accumulating evidence in the literature suggests that it may be beneficial in autism. Our recent work investigated efficacy of the ketogenic diet in Fmr1KO mice. We tested chronic ketogenic diet treatment on seizures, body weight, ketone and glucose levels, diurnal activity levels, learning and memory, and anxiety behaviors in Fmr1KO and littermate control mice as a function of age. We found that the ketogenic diet selectively attenuates seizures in male but not female Fmr1KO mice and differentially affects weight gain and diurnal activity levels dependent on Fmr1 genotype, sex and age. Regarding the attenuation of seizures, we have tested several thousand mice for seizure susceptibility over the past decade in response to over two dozen pharmaceutical, dietary or genetic interventions. The ketogenic diet (3-day chronic treatment) was as effective as the mGluR5 inhibitors MPEP (30 mg/kg) and AFQ-056 (3–10 mg/kg) in attenuating seizures. Seizures were not reduced in female Fmr1KO mice. This is the first time we have observed a strong sex-specific response to an intervention in the seizure assay. We are currently testing the efficacy of drug mimics of the ketogenic diet (beta-hydroxybutyrate, 2-deoxyglucose, tributyrin) on seizure phenotypes in Fmr1KO mice. Methods include chronic drug dosing, testing susceptibility to audiogenic-induced seizures and assessment of hyperactivity by 24/7 actigraphy monitoring. Results indicate partial rescue of seizures in males with the ketone beta-hydroxybutyrate but no rescue with the glucose analog 2-deoxyglucose. Testing of tributyrin and actigraphy are in progress. We conclude that the ketogenic diet is highly effective in reducing seizures and hyperactivity in male Fmr1KO mice. Treatment with a single ketone, beta-hydroxybutyrate, partially recapitulates efficacy. Further studies are required to identify bioactive component(s) of the ketogenic diet and mechanism(s) underlying sex-specific effects.

6. Inhibiting Elevated GCPII Activity in Aging Mouse Muscle Reduces Frailty

Tawnjerae R Joe[1,2], Carolyn Tallon[1,3], Robyn Wiseman[1,4], Ajit G Thomas[1], Barbara S Slusher[1,3,4,5,6,7, 8]

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Abstract Glutamate carboxypeptidase II (GCPII) is a neuropeptidase that catalyzes the conversion of N-acetyl-aspartyl-glutamate (NAAG) into N-acetyl-aspartate (NAA) and Glu. In the PNS, GCPII is expressed in Schwann cells and activated macrophages and is involved in regulating the synaptic pruning of neuromuscular junctions (NMJs) during normal development. Recently, we observed increased GCPII expression in the muscle of the SOD1G93A mouse model of amyotrophic lateral sclerosis (ALS) that was selectively associated with infiltrating activated macrophages. When using 2-(Phosphonomethyl)-pentanedioic acid (2-PMPA), a potent and selective inhibitor of GCPII, we observed a significant delay in muscle function loss and denervation in the ALS mouse. ALS and aging share similarities including the loss of motor neurons and degeneration of the skeletal muscle resulting in reduced synaptic inputs and fine motor skills, muscle weakness or wasting, and neuro-inflammation. Due to these similarities, we determined whether GCPII levels were altered in muscle of aged mice similarly to ALS mice. We collected gastrocnemius and soleus muscle tissue from 4-, 12-, and 20-month-old C57BL/6 mice and examined GCPII protein expression and enzymatic activity levels. We observed low expression of GCPII in 4- and 12-month-old mice gastrocnemius muscle and significantly increased expression in 20-month-old mice. Like in ALS, we observed co-localization of GCPII staining on infiltrating activated macrophages in aged gastrocnemius muscle. We then began treating 15-months-old mice, with daily 2-PMPA, for 5 months. Monthly frailty scoring was performed using an index that tracks a spectrum of aging-related characteristics. After 5 months of treatment, 2-PMPA treated mice had significantly reduced frailty index scores compared with vehicle-treated mice. Additionally, there was a significant delay in body weight loss and body temperature decline. These studies demonstrate that blockade of GCPII activity has potential therapeutic benefits for slowing aging-related frailty.

7. Experimental Substantiation of New Target Links in Complex Therapy of Prenatal CNS Damage. Pharmacological Modulation of HSP70 – Dependent Mechanisms of Endogenous Neuroprotection

Belenichev IF, Aliyeva EG, Popazova OO, Zaporizhzhia State Medical University

Abstract Prenatal hypoxia (PH) causes pathological changes in the brain and can lead to irreversible long-term disorders of its development and the emergence of neuropsychiatric pathologies in children. Pharmacological correction of posthypoxic CNS disorders is a priority problem in modern medicine. The aim of this research was to study the neuroprotective action of drugs with an evidence-based effect on the expression – Angiolin ((S)-2,6–diaminohexanoic acid

3-methyl-1,2,4-triazolyl-5-thioacetate), Thiotriazoline (3-methyl-1,2,4-triazolyl-5-thioacetic acid morpholine), Tamoxifen, Glutoredoxin, Cerebrocurin (contains neuropeptides, S-100 proteins, reelin, nerve growth factor (NGF) (not less than 2 mg/ml) and amino acids), RAIL (selective IL-1b antagonist), Mexidol (2-ethyl-6-methyl-3-hydroxypyridine succinate) and L-arginine in comparison with the reference drug Piracetam in terms of their effect on the expression of endogenous neuroprotection factors to further substantiate their use in the treatment of prenatal CNS damage in a model of chronic hemic PH. Expression levels of mRNA of HSP70, HIF-1, c-fos and the content of HSP70 in the cytoplasmic and mitochondrial fractions of the brain of rat on the 60th day of life after PH were determined by real-time PCR and enzyme immunoassay. It has been established that chronic PH inhibits transcriptional processes in neurons and suppresses the synthesis of HIF1a, HSP70 and c-fos. The studied drugs are able to modulate HSP70-mediated mechanisms of endogenous neuroprotection. The most active among HSP70 modulators in conditions of chronic PH are Cerebrocurin (150 µl/kg) and Angiolin (50 mg/kg), which outperform other studied drugs in terms of increased expression of HSP70 mRNA, HIF-1α mRNA and HSP70 protein concentration in the brain of experimental animals and can be considered as promising neuroprotective agents in complex therapy after PH.

8. A Comprehensive Approach to Biomarker Discovery for Chemotherapy-Induced Peripheral Neuropathy (CIPN)

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Abstract Taxanes are a class of chemotherapeutics commonly used to treat solid tumors, including breast and ovarian cancers. Chemotherapy-induced peripheral neuropathy (CIPN) occurs in up to 70% of patients treated with taxanes, impacting quality of life both during and after treatment. CIPN typically manifests as tingling and numbness in the hands and feet and can cause irreversible loss of function of peripheral nerves, and can be dose-limiting, potentially impacting clinical outcomes. The mechanisms underlying CIPN are poorly understood resulting in limited treatment options, and no tools exist to identify which patients will develop CIPN in response to taxane therapy. Although some patients' genetics may predispose them to greater risk, genetic studies for CIPN are inconsistent, complicating the ability to develop definitive biomarkers. Moreover, other molecular markers (e.g., metabolites, mRNA, miRNA, proteins) may also be informative for predicting CIPN onset. To address the clinical gap of identifying patients at risk of CIPN, we initiated the Genetics and Inflammatory Markers for CIPN Study (GENIE) study, a multi-omic assessment of genetic and inflammatory markers of CIPN, as part of the National Institutes of Health (NIH) Helping to End Addiction Long-term (HEAL) initiative (https://heal.nih.gov/). This study aims to use machine learning to build predictive biomarker signatures that identify patients at increased risk of developing CIPN during taxane treatment. Using pre-treatment, on-treatment, and post-treatment blood samples from 400 patients with breast cancer treated with taxanes, we are investigating genetic, transcriptional, epigenetic (DNA-methylation), protein, and metabolic associations with validated self-reported pain questionnaires that measure sensory, motor, and autonomic symptoms, and functional limitations related to CIPN. We hypothesize that there exist (i) molecular biomarker signatures that are indicative of patients with high probability of developing CIPN and (ii) molecular biomarker signatures that will change in the presence of taxanes and serve as a leading indicator for CIPN development. We anticipate that biomarker signatures can be used to identify susceptible patients early in their development of CIPN, enabling personalized dose adjustments to minimize adverse symptoms, optimize therapeutic outcomes, and improve quality of life.

9. The CURE Epilepsy Catalyst Award: Grant Opportunity for Translational Research in Epilepsy

Priya Balasubramanian, PhD; Laura Lubbers, PhD; CURE Epilepsy

Abstract CURE Epilepsy's mission is to find a cure for epilepsy, by promoting and funding patient-focused research. The CURE Epilepsy Catalyst grant program reflects our commitment to this mission by supporting the development

of promising and transformative new therapies for epilepsy. Projects supported by this award mechanism should advance research to clinical trial readiness through the development of biomarkers, optimization of new entities including studies that focus on pharmacokinetics/pharmacodynamics, safety profiles, and/or improved formulations, as well as studies that advance preclinical findings to pilot clinical trials. Small clinical trials are allowed. Established proof-of-concept data for new therapeutic entities are required for this funding mechanism.

This competitive grant program provides funding of up to $250,000 over two years and is available to independent researchers at universities or non-academic institutions including small biotechnology companies developing new interventions to cure epilepsy. All applicants must submit a Letter of Intent (LOI) and selected applicants will be invited to submit full proposals. Priority areas for 2022 include approaches to 1) prevent, modify and/or arrest the development of acquired epilepsy, 2) prevent the onset, or halt the progression of severe pediatric epilepsies, 3) new treatments for pharmaco-resistant epilepsy 4) sleep and epilepsy and 5) new approaches, biomarkers, or therapies to predict and prevent sudden unexpected death in epilepsy or SUDEP. The call for this program will be released in May 2022.

10. Digital Assessment of Patients with Glioblastoma in a Multicenter Trial

Yasaman Damestani[1], Minesh Mehta[2], Howard Colman[3], Kevin Camphausen[4], Michael Weller[5], Eva Galanis[6], Martin Van den Bent[7], John de Groot[8], Andreas F Hottinger[9], L Burt Nabors[10], Ruiyang Shi[1], Kai Li[1], Patrice Melikian[1], Shijie Tang[1], Sharon Tamir[1], Eran Shacham[1], Jatin Shah[1], Sharon Shacham[1], Patrick Wen[11]

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Abstract Background: Among the primary aims of new therapies for glioblastoma (GBM) are the reduction of morbidity and restoration or preservation of quality of life (QoL). Selinexor (SEL) is a first-in class, oral, selective inhibitor of nuclear export which blocks exportin 1 (XPO1), forcing the nuclear retention and reactivation of tumor suppressor proteins, ultimately causing cell death in cancer cells. SEL is approved for the treatment of triple refractory multiple myeloma and relapsed/refractory DLBCL. XPORT-GBM-029 (NCT04421378) is a phase 1 dose finding study followed by an open-label randomized phase 2, 3-arm trial to evaluate SEL in combination with standard therapies for newly diagnosed and recurrent GBM (n = 350): Arm A– radiation ± SEL; Arm B– radiation and temozolomide ± SEL; Arm C – lomustine ± SEL at first relapse. We have implemented the use of technology to provide sensitive, reliable, and clinically meaningful digital assessments of the performance status of patients. After discussions with the study team and patient advocacy partners at Endbrain-Cancer, we surveyed GBM patients and their caregivers to better understand the symptoms that most affect their QoL and developed this patient-centric tool. The survey revealed four main objectively measurable domains, cognitive function, lateralization, fatigue, and sleep, which impact patient QoL, and can also be affected by GBM therapies.

Method: XPORT-GBM-029 incorporates standard clinical and imaging evaluations of GBM progression. In addition, we have incorporated with novel wearable digital tools that objectively measure motor and cognitive function. The study is conducted at 50 sites globally. Patients wear inertial sensors to measure their activity and sleep and complete a cognitive battery at baseline and before each MRI.

Results: Associations between objective digital measures of activity, gait, fatigue, sleep, and cognition will be examined with respect to clinical assessments including physical examinations, mRANO, NANO, KPS and PRO QoL questionnaires. Descriptive summary statistics and plots are employed in exploratory data analysis, and other advanced data mining methods may also be considered.

Conclusion: To the best of our knowledge, the XPORT-GBM-029 trial is the first large, prospective, longitudinal study in GBM patients employing digital technology and may provide useful information regarding the utility of wearable and mobile devices for measuring functional outcomes in clinical trials.

11. Evolution of EEG Spiking after Brain Injury

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Utah, Salt Lake City, UT, USA; [5]Tulane University School of Medicine, New Orleans, LA, USA

Abstract Studies of human acquired epilepsy have failed to find a consistent relationship between spikes in electroencephalography (EEG) and subsequent epileptogenesis, partly because spikes may occur in brain-injured patients without evidence for spontaneous recurrent seizures (SRSs). Here, we test the hypothesis that EEG spike frequency changes after brain injury, even in subjects that do not develop epilepsy.

Rats were implanted with epidural wire electrodes over both hemispheres using two-channel wireless EEG. At postnatal day 30, 43 rats were subjected to hypoxia–ischemia (HI) for 2 h (i.e., Rice-Vanucci model) or sham-control treatment. Animals were monitored continuously for an average of 109 days. Although HI-induced lesions were only observed in a few rats, and no SRS were detected, several other brain injuries or abnormalities were observed. After perfusion fixation, gross anatomic observation, and MRI imaging, rats were grouped according to severity/type of brain damage, such as electrode injury.

We identified 25 rats based on the duration of longitudinal EEG recordings (minimum recording length for inclusion was 75 days). From this group, 24 randomly selected 7.5-min time segments per day on three representative days (i.e., days 5, 40 and 75) after treatment were extracted and anonymized per animal. Waveforms that were considered "inter-ictal simple spikes" were initially identified by a computer program using a custom heuristic and then verified by a human interpreter. We found in most rats that electrographic spikes occurred without any detected seizures. Furthermore, spike frequency typically increased with time after brain injury ($p=0.006$ via linear regression, day 5 through 75).

These data suggest that EEG spike rate increases over time, and that this increase may occur after a variety of different types of brain injury. Future studies will aim to relate the time-dependent increases in EEG spike frequency to the structural characteristics of the brain injury, based on anatomic and MRI data.

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12. Niemann-Pick Disease Type C1 Inhibition Leads to Loss of Barrier Integrity and Altered Metabolic Phenotype in Brain Microvascular Endothelial Cells

Bilal Moiz, Andrew Li, Alisa Morss Clyne; University of Maryland College Park

Abstract Vascular dysfunction is implicated in common neurodegenerative diseases but little is known about how vascular changes contribute to the pathology of rare inherited neurogenetic disorders. Niemann-Pick Disease Type C (NPC) is a rare autosomal recessive disorder caused by a mutation in the intracellular cholesterol trafficking protein NPC1. This mutation leads to endolysosomal cholesterol accumulation and membrane cholesterol depletion. Recent clinical evidence demonstrates cerebral glucose hypometabolism in NPC1 patients, which suggests reduced cerebral glucose transport by brain microvascular endothelial cells. We therefore hypothesized that altered cholesterol trafficking in NPC1 leads to altered glucose metabolism and barrier integrity by depleting membrane cholesterol. In this study, we differentiated human induced pluripotent stem cells into BMECs (hiBMEC) and treated them with U18666A, a potent NPC1 inhibitor. We first used filipin staining to validate that NPC1 inhibition with U18666A leads to membrane cholesterol depletion and intracellular accumulation in hiBMECs. We then experimentally assessed barrier function, glucose transport and metabolism, cholesterol uptake, and expression of cholesterol synthetic enzymes. We also curated a genome-scale metabolic model to understand the systems-level metabolic impact of NPC1 inhibition in hiBMEC. Treatment with U18666A significantly increased barrier permeability and decreased tight junction protein integrity. Despite increased permeability, we observed decreased glucose transport across the endothelial barrier. Extracellular flux measurements revealed that U18666A-treated hiBMECs consumed more glucose and secreted more lactate, suggesting an increasingly glycolytic phenotype following U18666A treatment, which was confirmed with Seahorse flux assays. Furthermore, U18666A-treated hiBMEC dramatically increased in exogenous cholesterol internalization and increased cholesterol biosynthetic gene expression. Finally, our genome-scale metabolic model predicted that several metabolic subsystems, including fatty acid oxidation, mitochondrial transport, and extracellular transport, were significantly altered in U18666A-treated hiBMEC. Together, these results suggest that NPC1 inhibition increases blood–brain barrier permeability while increasing hiBMEC glycolysis and upregulating compensatory cholesterol pathways. This study improves our understanding of how membrane cholesterol depletion alters hiBMEC function, which can inform targeted NPC drug delivery strategies that exploit altered BMEC transport and metabolic pathways.

13. Deep Brain Stimulation: Neutral Tissue Response and Analysis of Adverse Events

Young Scholar Mabel Chen, Mounds View High School; Sujata Bhatia, MD, PhD, PE, Harvard University Biotechnology

Abstract Deep brain stimulation (DBS) is a common treatment for numerous neurological disorders, especially movement disorders, including, but not limited to, Parkinson's

disease, essential tremor, and dystonia. Despite growing recognition, drastic shortcomings of DBS include infection, inflammation, hardware breaks, and extreme withdrawal syndrome. Brain-machine interfaces can be implemented only if the neural tissue response to electrodes and implants is understood and optimized. In this study, we analyzed adverse events resulting from DBS implantation. Through the past decade of DBS implant malfunctions, injuries, and deaths, it is apparent that high impedance and lead problems are major blockages. High impedance blocks the transmission of signals to the brain stimulator, deeming it useless. Leads are known to cause infection, especially along the incision site of implantable pulse generators (IPG). While the surgical technique depends on the skill of the surgeon, infections occur in a significant number of patients. Infection often means complete removal of the IPG, which could cause severe withdrawal syndrome; Parkinson's patients may experience severe motor symptoms such as akinesia or rigidity, dystonia patients can develop status dystonicus, epilepsy patients may experience an increase in seizures, and obsessive–compulsive disorder (OCD) patients may have worsening neuropsychiatric symptoms and suicidal ideation. In addition, studies have shown that quality-of-life scores after DBS are usually lower than preoperative scores, indicating that the long-term efficacy of DBS for treating these disorders may not be beneficial. However, recent studies on antimicrobial catheters may present an effective and inexpensive strategy against infection. As DBS is a relatively new technique, large, randomized clinical trials are still needed to provide necessary data to draw conclusions on long-term efficacy and safety, and device modifications may be needed to optimize the tissue response.

14. Analysis of Adverse Events Associated with Neurovascular Embolization Devices

Young Scholar Aaron Tang, The Bronx High School of Science; Sujata Bhatia, MD, PhD, PE, Harvard University Biotechnology

Abstract Neurovascular embolization is a frequently used procedure for treating non-ruptured cerebral aneurysms. However, due to device malfunctions and manufacturing errors, the procedure can often result in adverse effects such as intraprocedural ruptures, ischemia, and rebleeding. This study aimed to analyze the adverse events associated with neurovascular embolization devices, using data from the Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database. The entire database was searched for the decade 2011 to 2021, using the search terms "neurovascular" and "embolization," and the number of reported deaths, injuries, and malfunctions were recorded for each year. The data reveal that the number of reported malfunctions increased dramatically over the decade, from 464 reported malfunctions in the year 2011, to 2004 reported malfunctions in the year 2021. This increase represents a greater than four-fold rise in the number of reported malfunctions for neurovascular embolization devices. This study further characterized the number of reported malfunctions attributed to each device manufacturer. According to analysts, Penumbra, Inc. has held a ~ 90% market share since 2020 and has had consistent yearly revenue, most recently at 25% growth in 2021. Over the decade from 2011 to 2021, the percentage of all neurovascular embolization malfunctions attributed to Penumbra neurovascular embolization devices rose significantly. In 2011, Penumbra devices accounted for 14% of total reported malfunctions of neurovascular embolization devices. In 2021, Penumbra devices accounted for 86% of total reported malfunctions for neurovascular embolization devices. On average, yearly deaths attributable to Penumbra devices were 0.7% of yearly malfunctions, and yearly injuries were nearly 18.7% of yearly malfunctions, which may suggest incomplete or underreported data. These results suggest the need for continuous improvement in neurovascular embolization devices in a concentrated market in order to improve device performance and patient outcomes.

15. Patient Profiles in Drug Resistant Epilepsy (DRE): VagusNerve Stimulation (VNS) vs. Responsive Neurostimulation (RNS)/Deep Brain Stimulation (DBS)

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Abstract Drug resistant epilepsy (DRE) is defined as failure of at least two anti-seizure medications (ASMs) to achieve sustained seizure freedom. Neurostimulation (vagus nerve stimulation [VNS], responsive neurostimulation [RNS], deep brain simulation [DBS]) is an important therapeutic option for patients with DRE. These devices all have demonstrated efficacy in DRE; however, little is known about their comparative effectiveness. Real-world data (RWD) represents an ideal medium to conduct comparative effectiveness studies, as it reflects the actual patient experience in clinical practice; however, the lack of random treatment allocation may introduce biases that confound these comparisons. The data source for our research was the IBM MarketScan® Commercial and Medicare Supplemental

Database, which includes medical (inpatient and outpatient) and prescription claims and administrative data for > 250 million US individuals. All patients with epilepsy who received VNS, DBS, or RNS during the study period were selected; earliest date of neurostimulation was set as index date. Demographic characteristics (e.g., age, sex, geographic region) were assessed as of index date; prevalence of selected comorbidities assessed were based on relevant diagnosis codes (ICD-9-CM, ICD-10-CM) during 24-month pre-index period. The study yielded several results. Patients who undergo neurostimulation for DRE have high levels of comorbidity, in addition to epilepsy. Patients who undergo VNS for epilepsy are younger than those who receive RNS/DBS and have fewer chronic comorbidities. VNS is predominantly implanted in outpatient settings; RNS/DBS, in inpatient settings. Between one-in-four and one-in-three patients had evidence of depression and anxiety, respectively; about one-in-five had evidence of vitamin deficiencies known to be associated with long-term ASM use. Collectively, our findings may indicate a substantial toll associated with long-term DRE. Further research is warranted on the role and timing of use of neurostimulation. Our findings indicate real-world patients who undergo VNS for epilepsy differ in important ways from those who undergo RNS/DBS. This apparent channeling bias should be ascertained and controlled using appropriate statistical adjustment methodologies before undertaking assessments of comparative effectiveness.

16. Life After the Coronavirus Disease of 2019 Pandemic: Lessons Learned and Recommendations for Reducing Non-Compliance in Clinical Research

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Abstract Since the first case of coronavirus disease 2019 (COVID-19) was identified, 265.1 million cases and 5.2 million deaths have occurred globally. Despite the benefit of mitigating measures, such as travel restrictions, the adverse effects these disruptions had on participant safety are rare in the literature. Therefore, the purpose of this study was to investigate the impact of these measures on the rates of non-compliance at the National Institute of Neurological Disorders and Stroke. This study analyzed non-compliance occurring from July 2019 to August 2021 that were stratified by the date of non-compliance (before and after restrictions). Events were described by size, site of protocol procedures, non-compliance type, primary category, subcategory, and cause. Additionally, non-compliance due to COVID-19 and measures to reduce the spread of COVID-19 were analyzed. The median and interquartile range of data were reported. In total, 395 non-compliance events occurred across 14,453 enrolled participants at risk. The overall rate of non-compliance increased from 0.016 events per participant to 0.034 events per participant after the COVID-19 restrictions ($p < 0.001$). For onsite protocols, the rate of non-compliance increased from 0.006 (0.000–0.067) events per participant to 0.067 (0.001–0.460) events per participant after the restrictions ($p = 0.01$). For small sized protocols, the rate of non-compliance increased from 0.048 (0.000–0.167) events per participant to 0.192 (0.014–0.700) events per participant ($p = 0.03$). The rate of major non-compliance events, failure to follow policy, and participant caused events decreased significantly after the restrictions. For events related to COVID-19 restrictions, 188/190 (99%) were minor deviations, 189/190 (99%) were procedural non-compliance, 122/189 (65%) were an incomplete study visit, and 53/189 (28%) involved an out of timeframe study visit. These results have implications for the conduct of clinical research. Protocols should be written with flexibility to facilitate the capture of all safety data, such as enabling broad study visit windows, blood draws in the community, and remote monitoring visits, without compromising scientific quality or participant safety. This recommendation should be considered when changes occur to protocols that are outside of the principal investigator's control.

17. Pharmacokinetics of Single Domain Antibodies and Conjugated Nanoparticles Using a Hybrid Near Infrared Method

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Abstract This study was conducted to develop imaging methods and pharmacokinetic models to aid the future development of a novel family of brain MRI molecular contrast agents. A near-infrared (NIR) imaging method was established to monitor single domain antibodies from camelids (VHH) and VHH conjugated iron oxide nanoparticle kinetics in mice using a hybrid approach. Pharmacokinetics in blood were assessed by direct sampling, and pharmacokinetics in kidney, liver, and brain were assessed by serial in vivo NIR imaging. Using this approach, we constructed a five-compartment PK model that fits the data well for single VHHs, engineered VHH trimers, and iron oxide nanoparticles conjugated to VHH trimers. The establishment of the feasibility of these methods lays a foundation for future PK studies of candidate brain MRI molecular contrast agents.

18. A Prescription Digital Therapeutic for Substance Use Disorder: Real World Engagement and Abstinence Patterns

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Abstract Methods: An observational evaluation of patients with SUD treated for 12-weeks with a PDT comprising 61 therapy lessons (31 "core" and 30 "keep learning" lessons), 4 lessons per week recommended. Patients were eligible for contingency management rewards (positive reinforcement message or monetary gift card) based on lesson completion (up to 4 per week) and negative urine drug screens (UDSs). The primary endpoint was PDT engagement (completion of ≥ 1 module/week) throughout the prescription. The secondary endpoint was abstinence (UDS or self-report) in weeks 9–12 of the prescription.

Results: Evaluated were 602 patients who completed at least one lesson (median age 37 years, 32% female, 41% male, 27% un-reported sex). Mean lessons completed in 12 weeks was 31 ± 19; 52% completed all core lessons. At prescription end 41% of patients remained engaged with the PDT, as shown by completion of ≥ 1 module in week 13 (73.6% showed any activity in the PDT during weeks 9–12). During weeks 9–12, 62% were abstinent (patients with no data were considered positive).

Conclusions: These data demonstrate that patients with SUD exhibit robust engagement with the reSET PDT in a real-world setting. Most patients who did any lessons completed at least half of the core program. Use of reSET was associated with high levels of abstinence, as measured by composite self-report and UDS endpoints.

19. Real-World Use and Clinical Outcomes After 24 weeks of Treatment With a Prescription Digital Therapeutic for Opioid Use Disorder

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Abstract Background: Behavioral therapy is a key element in any treatment plan for patients with opioid use disorder (OUD). Prescription digital therapeutics (PDTs) are FDA-authorized software-based treatments delivering evidence-based behavioral therapies on mobile devices.

Methods: An observational evaluation of patients treated for 12- and 24-weeks with the reSET-O^{O} PDT for OUD. Engagement and retention data in weeks 9–12, or 21–24 were collected via the PDT and analyzed with descriptive statistics. Substance use was evaluated as a composite of patient self-reports and urine drug screens (UDS). Missing UDS data were assumed to be positive. A regression analyses of hospital encounters for 12- vs. 24-week prescriptions controlling for covariates was conducted.

Results: In a cohort of 3,853 individuals with OUD who completed a 12-week reSET-O prescription, a second cohort of 643 was prescribed a second 12-week "refill" prescription. Mean age of the 24-week cohort was 39 years, 56.7% female. At 24 weeks, abstinence in the last 4 weeks of treatment was 86%. Over 91% of patients were retained in treatment. Patients treated for 24 weeks had a 27% decrease in unique hospital encounters compared to those who got the first 12-week prescription only.

Conclusions: These data present real-world evidence that treatment for 24 weeks with the reSET-O PDT for OUD is associated with high levels of engagement, improved outcomes, and fewer hospital encounters compared to a single prescription for the PDT.

20. The NIH HEAL Initiative/National Institute of Neurological Disorders and Stroke Early Phase Pain Investigation Clinical Network (EPPIC-Net): Year 2 Update

Barbara Karp, Rebecca Hommer, MD, Marlene Peters Lawrence, RN, Jennifer Beierlein, PhD, Clinton Wright, MD

Abstract The NIH Helping to End Addiction Long-term (HEAL) InitiativeSM is an aggressive, trans-NIH effort to speed scientific solutions to stem the national opioid public health crisis. Within the HEAL initiative, NINDS developed the Early Phase Pain Investigation Clinical Network (EPPIC-Net) to focus on understanding pain mechanisms and developing effective, non-addictive treatments for pain by designing and conducting phase 2 clinical trials of novel, non-addictive pain therapies. EPPIC-Net provides phase 2 clinical trials for novel, non-addictive pain therapeutics accepted through its application process.

Opened in 2019, EPPIC-Net resources include a collaborative network of multi-disciplinary pain experts who provide novel clinical trial designs, study conduct, and data analysis for phase 2 trials incorporating proof-of-concept testing and biomarker validation. After a rigorous 3-stage application and review process, trials built around accepted assets are run at no cost to asset providers. The asset owner retains intellectual property rights to their therapeutic asset. EPPIC-Net accepts and reviews applications from academic and industry sponsors worldwide on a rolling basis.

EPPIC-Net established a robust clinical trial infrastructure that includes a Clinical Coordinating Center, Data Coordinating Center, and 12 Specialized Clinical Centers (Hubs and their affiliated Spokes) across the US with broad outreach to diverse pain populations. EPPIC-Net utilizes unique application and review processes. The preliminary application form and information on EPPIC-Net review can be found on the EPPIC-Net website: https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/NINDS-Role-HEAL-Initiative/NINDS-Role-HEAL-Initiative-EPPIC. EPPIC-Net trials are funded under NIH's "Other Transactions" Authority.

In the first 2 years of operation, 3 asset clinical trials have been funded. The first trial is currently open to enrollment. EPPIC-Net is also developing an innovative master platform protocol for therapeutics targeted to painful diabetic peripheral neuropathy. The master protocol will run in parallel with clinical trials for additional accepted therapeutics addressing other pain conditions of high unmet need.

Standing up a clinical trial network of EPPIC-Net's size and scope has presented challenges. This poster describes the accomplishments to date and lessons learned along the way.

21. The NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP) Efforts to Accelerate Development of Non-opioid, Non-addictive Pain Therapeutics: Validation of the Monoiodoacetate (MIA) Model of Osteoarthritis Pain and Chemotherapy-induced Neuropathy in the Rat

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Abstract The Preclinical Screening Platform for Pain (PSPP) program aims to accelerate the discovery and development of new non-opioid, non-addictive pain therapeutics. PSPP is collaborating with PsychoGenics, Inc. to validate preclinical models and endpoints to enable screening and profiling of assets. Here, we describe the validation of monoiodoacetate (MIA) model of osteoarthritis pain and the paclitaxel and oxaliplatin models of chemotherapy-induced peripheral neuropathy in the rat.

Methods: Adult male and female Sprague Dawley rats (N = 10, each sex) were used in these studies. MIA was injected intraarticularly into the left hindlimb knee joint. Tactile sensitivity, weight bearing, changes in gait, and paw pressure were systematically evaluated in both sexes for 4–6 weeks. Pharmacological validation of the model was established using morphine, duloxetine, and ketoprofen after acute and repeated dosing. For the paclitaxel studies, paclitaxel was injected at several doses on alternate days to determine the optimal dose and route of administration. For the oxaliplatin studies, oxaliplatin was injected 2 days per week for 4 weeks. Hind paw tactile sensitivity and cold sensitivity were evaluated.

Intraarticular injection of MIA into the hindlimb knee joint produced unilateral hind paw tactile hypersensitivity and changes in weight bearing. Acute subcutaneous injection of morphine reduced hind paw tactile hypersensitivity and weight bearing deficits in male and female rats, whereas acute oral administration of ketoprofen and duloxetine were less effective. Repeated treatment with ketoprofen or duloxetine significantly reduced these endpoints.

Both the paclitaxel and the oxaliplatin models showed reproducible bilateral hind paw tactile and cold hypersensitivity in male and female rats which were significantly inhibited by morphine. The results from these carefully validated studies using evoked and non-evoked endpoints in the rat MIA model and using both mechanical sensitivity and cold allodynia in the two chemotherapy induced pain models suggest that these models may be used to identify and differentiate novel therapeutics for treatment of osteoarthritis and chemotherapy induced neuropathic pain within the NIH HEAL Initiative's PSPP program.

22. Brain Penetrant scFv Antibody Block of P2X4 Receptor for Treatment of Chronic Pain

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Abstract There is a critical need for non-addictive, non-opioid analgesics. The goal of these studies was to generate non-opioid single-chain variable fragment (scFv) antibodies for blocking P2X4 receptor (P2X4R) to be utilized as preferred targeting therapy for reversal of chronic neuropathic pain. Engineered scFv antibodies feature binding affinity and activity similar to or better than monoclonal antibodies because they are much smaller in size. More importantly, they are brain/nervous tissue penetrant due to their small size and have promising biotherapeutic applications for both the nervous and immune systems, now recognized as interactive in chronic pain with increased brain/tissue penetrability, stronger binding affinity, reduced self-immunogenicity, and large-scale production is relatively inexpensive. scFvs can be easily modified to adjust their vivo half-life for short-term diagnostic or long-term therapeutic purposes. Ribosome display is a powerful cell-free technology and this technology

is widely used to select single-chain antibody fragments against the target of choice. This method is inexpensive, rapid, and was used to quickly develop repertoires of high-affinity antibodies targeting P2X4R. In our hands the scFvs developed have high affinity in the picomolar range, superior stability and solubility. The innovation of this project includes the developing and testing of the P2X4R scFv antibody therapy for the first time in a mouse model of chronic neuropathic pain and in sensory neurons. Characterization of effects on neuronal activation responses was examined post-mortem in vitro in trigeminal ganglia neurons. Data finds a single dose of our newly engineered P2X4R scFv antibody provides restored sensory behaviors, i.e. pain- and anxiety-related behaviors at baseline where they remain over many weeks. In contrast, mechanical hypersensitivity and anxiety-related responses persist many months in our chronic models. The scFv antibody reduces hyperexcitability of sensory neurons in patch clamp electrophysiological studies. This project opens new avenues for research to develop non-opioid therapeutic interventions for chronic pain. Characterizing and validating the efficacy of two lead P2X4R scFv antibodies with in vivo and in vitro studies is advancing toward new drug application status and the patent published (US 2021/0340265 A1).

23. Inhibition of EV Biogenesis Reduces Tau Propagation in a Seeded Tau Model of Alzheimer's Disease

Carolyn Tallon, Benjamin J Bell, Medhinee M. Malvankar, Kaleem Coleman, Tawnjerae R. Joe, Anjali Sharma, Erden Eren, Kannan Rangaramanujam, Dimitrios Kapogiannis, Barbara S. Slusher; Johns Hopkins University

Abstract Alzheimer's Disease (AD) is the most common form of dementia worldwide, yet no effective therapeutics are available despite three decades of research. AD is characterized by progressive neurodegeneration and cognitive decline, with the accumulation of two putative pathological proteins; Amyloid- and hyperphosphorylated Tau. Numerous clinical trials focusing on reducing Amyloid- plaque levels in patient brains have been unsuccessful in alleviating symptoms. This has prompted a renewed focus on tau, which spreads throughout the brain along characteristic pathways and correlates strongly with the severity of disease progression. Recent evidence has highlighted the importance of extracellular vesicles (EVs) in enabling the transcellular transmission of pathological tau in the brain in a 'prion-like' manner and identified the inhibition of EV biogenesis via small-molecule inhibitors of nSMase2 as a potential avenue for clinical intervention. However, presently available tool compounds are unsuitable for clinical development. To assess the therapeutic potential of nSMase2 inhibitors, our lab performed a high-throughput screen and identified two classes of compounds with nSMase2 inhibitory activity. The first, PDDC, has excellent potency (IC50 = 300 nM), oral bioavailability (F% = 87), and brain penetration (AUCbrain/AUCplasma = 0.6), as well as in vitro and in vivo EV inhibition. The second, DPTIP, had even higher potency, but poor pharmacokinetics. We affixed this molecule to a brain-penetrable dendrimer and demonstrated CNS target engagement following oral dosing. To characterize their potential as AD therapeutics in vivo, we optimized a rapid seeded tau mouse model in which we unilaterally stereotaxically inject an AAV vector containing mutant human tau into the CA1 hippocampal region in WT mice, and quantify the degree of phosphorylated tau in the contralateral dentate gyrus region after 6 weeks. During this period, mice were dosed with PDDC-containing chow or oral dendrimer-DPTIP, or matched vehicle controls. In both treatment paradigms, nSMase2 inhibition reduced propagation of pThr181 phosphorylated tau to the contralateral hippocampus. Similarly, drug treatments reduced both the number and tau contents of neuronal-derived EVs circulating in mouse plasma compared to vehicle-treated controls. These results confirm the potency of nSMase2 inhibition at retarding tau propagation through EVs, and highlight these promising small-molecule therapeutics as potential treatments for AD.

24. Non-Addictive Analgesic Small Antibody Therapeutic Development Targeting CCK-BR

Adinarayana Kunamneni, SRA Alles, KN Westlund; Mayo Clinic, Jacksonville, Florida and University of New Mexico Health Science Center

Abstract Cholecystokinin B receptor (CCKBR) and neuropeptide ligand, CCK, are widely expressed and upregulated in brain circuitry involved in stress, anxiety, reward/addiction, cognition, and pain. Patient studies and social stress rodent models used CCK to induce experimental anxiety and panic attacks. Conversely, blocking CCKBR centrally inhibits anxiety-like and fear-like behaviors. We generated a single chain Fragment variable (scFv) targeting a unique 14-amino-acid peptide sequence in CCKBR. Its small size is ~ 1/6 the size of a monoclonal antibody and can access the central nervous system. Cultured trigeminal nerve sensory neurons from mice with neuropathic pain at peak pain-like behaviors validated efficacy in vitro. The lead scFv produced a statistically significant reduction ($p < 0.05$, ANOVA, 20–30 neurons per condition) in neuronal firing frequency of trigeminal neurons from neuropathic mice. This reduction was potentiated when cultures were pre-treated with CCK-8. Immunofluorescent staining intensity of neurons was scFv-dose-dependently significantly reduced. The in vivo efficacy

was a 70% reduction of mechanical and cold hypersensitivity in mice with established models of chronic trigeminal (male and female) and sciatic neuropathic pain. The single dose post-treatment allowed persistent reduction of the pain-related measures through at least an additional 7 weeks with no development of the anxiety- and depression-like behaviors seen in untreated mice. While the hypersensitivity significantly reduced cognitive function tested with the novel object test, no deficit developed in the CCKBR scFv treated mice. Further work is planned to humanize the CCKBR scFv by replacing framework amino acids in the murine CCKBR scFvs with well-characterized human framework sequences. The humanness for the parental and humanized antibodies will be assessed by T20 humanness score. Randomization of the humanized scFv CDRs, as well as a pool of kappa light chain shuffled VL sequences, will be employed to generate diverse libraries for affinity maturation. The variants will be expressed in the bacterial cytoplasm and tested as cytoplasmic extracts to assess affinity for both the human and mouse CCK-BR peptides. Ideally, the candidates will be screened utilizing the Octet platform. Purified recombinant antibody will be retested in studies which verified that the lead humanized antibody had similar characteristics as the original murine scFv.

25. Alzheimer's Disease Preclinical Efficacy Database: Improving the Scientific Rigor, Reproducibility, and Predictive Value of Preclinical Research for Alzheimer's Disease

Shreaya Chakraborty; Ali Sharma, Zane Martin, Jean Yuan, Suzana Petanceska, Lorenzo Refolo; National Institute on Aging/National Institutes of Health

Abstract The Alzheimer's Disease Preclinical Efficacy Database (AlzPED) is a publicly available data repository created by the National Institute on Aging (NIA) to address the poor scientific rigor, predictive value, and translatability of preclinical efficacy studies in Alzheimer's disease (AD) animal models. The database is designed to house published and unpublished preclinical therapeutic studies incorporating experimental details of both positive and negative data. AlzPED specifically incentivizes the submission of unpublished negative data by providing a platform to create citable reports of these data. Studies are submitted to AlzPED through a curator and obtained from multiple sources. Prior to publication in the database, each study is carefully curated by two experts for data on authors, AD animal models, therapeutic targets and agents, outcomes and most importantly evaluated for rigor in study design and methodology with a Rigor Report Card consisting of a standardized set of expert-recommended study design elements.

AlzPED currently hosts curated summaries for nearly 1200 published therapeutic studies in AD animal models. The database provides easy access to information on study design, 195 animal models, 1019 therapeutic agents, 225 therapeutic targets, more than 2000 AD-related outcomes, principal findings, funding sources, patents, and related clinical trials. Evaluation of Rigor Report Cards from each study demonstrates significant under-reporting of critical elements of methodology such as power/sample size calculation, blinding for treatment, blinding for outcomes, randomization, balancing for sex, animal genetic background, and inclusion/exclusion criteria, these being reported by fewer than 30% of the nearly 1200 curated studies.

Our analysis of curated studies demonstrates serious deficiencies in reporting critical elements of methodology. These deficiencies diminish the scientific rigor, reproducibility, and translational value of the preclinical studies. Adopting a standardized set of best practices like those proposed by AlzPED can improve the predictive power of preclinical studies in AD animal models and promote the effective translation of preclinical drug testing data to the clinic.

26. Novel, Non-opioid, Non-addictive Intrathecal Therapy for the Treatment of Chronic Pain

James Campbell, Jonathan Walker, Lynne Sole, Randall Stevens, B. Duncan X. Lascelles; Centrexion Therapeutics

Abstract A major issue with drug development for CNS disease is getting the drug to the target without off-target effects. One way to overcome these issues is to directly administer drug to the cerebrospinal fluid (CSF), thereby bypassing the blood brain barrier. This is a particular opportunity in the case of pain disorders because the processing of nociceptive signals occurs at the superficial level of the spinal cord in apposition to the CSF. Fully programmable pumps may be implanted and thus afford the opportunity to micro-dose the lower spinal cord. Despite the availability of these pumps, only two drugs have been FDA approved for intrathecal delivery to manage chronic pain. Ziconotide, an N-type calcium channel blocker, was the last approved drug (2004), and has overall been disappointing because of a very narrow therapeutic window. CNTX-3001 is a highly potent small molecule agonist of the receptor for the endogenous peptide, nociceptin (NOPr). As an example of the analgesic effects of spinally delivered NOPr agonists, delivery of nociceptin to the lumbar CSF is strongly analgesic in non-human primates. Contrariwise, systemic delivery or direct brain delivery of NOPr agonists may have hyperalgesic effects. Centrexion conducted studies in Sprague Dawley rats whereby bolus doses of CNTX-3001 were delivered through an indwelling intrathecal catheter at the region of the lumbar spinal cord. Blinded placebo-controlled studies

were conducted using the monoiodoacetate (MIA) model of osteoarthritis. Statistically significant improvements in lameness and gait relative to placebo were observed. CNTX-3001 effects were seen at doses (1 and 10 μg in 10 μL) lower than what was observed with intrathecal morphine (15 μg). Picomolar EC50 and Ki, receptor selectivity, water solubility, efficacy in analgesic studies, and other physiochemical properties support the further development of this molecule as an innovative treatment option for patients with otherwise intractable pain using the intrathecal drug pump.

27. Fenfluramine (Fintepla®) Treatment Improves Everyday Executive Functioning in Preschool Children with Dravet Syndrome: Analysis From 2 Pooled Phase 3 Clinical Trials

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Abstract Fenfluramine's dual activity at serotonergic and Sigma-1 receptors has positive effects on memory, learning, and cognition. In prior studies, fenfluramine significantly improved executive function (EF) in 6–18 year-olds with Dravet syndrome (DS). Here, we evaluate whether fenfluramine improves everyday EF in preschool-aged children with DS during early formative years for neurodevelopment. Patients received placebo or fenfluramine (0.2, 0.4, or 0.7 mg/kg/day) in 1 of 2 14–15-week randomized clinical trials (RCTs). EF was evaluated at baseline and Week 14–15 for children aged 2–4 years with parent ratings on the Behavior Rating Inventory of Executive Function®—Preschool Version (BRIEF®-P); raw scores were transformed to T-scores based on the normative sample and were summarized in the Inhibitory Self-Control Index (ISCI), Flexibility Index (FI), Emergent Metacognition Index (EMI), and overall Global Executive Composite (GEC). Clinically meaningful improvement in BRIEF®-P index/composite T-scores from baseline to Week 14–15 was defined using Reliable Change Index (RCI) ≥ 90% and ≥ 95% certainty; worsening, RCI ≥ 80%. The association between fenfluramine and placebo treatment groups and the likelihood of clinically meaningful worsening or improvement were evaluated via cross-tabulations and Somers' D statistic. Data were analyzed for 61 children (placebo, n = 22; fenfluramine, n = 39; median age, 3 years). At baseline, 55%-86% of children had elevated T-score (T ≥ 65) for ISCI, EMI, and GEC, and ~ 33% for FI. Treatment with fenfluramine was associated with significant and clinically meaningful improvement (RCI ≥ 90%) vs placebo in ISCI (31% vs 5%; p = 0.003), FI (21% vs 0%; p = 0.002), and GEC (21% vs 0%; p = 0.002). A similar pattern emerged at RCI ≥ 95%, with significant and clinically meaningful improvements after fenfluramine vs placebo in FI (18% vs 0%; p = 0.004) and GEC (21% after fenfluramine vs 0% in placebo; p = 0.002). Fenfluramine treatment was associated with no significant worsening (RCI ≥ 80%) in any of the BRIEF®-P index/composite T-scores compared to placebo (p > 0.13). In this analysis of preschool-aged children with DS who had substantial baseline EF impairment, ~ 1 in 5 children treated with fenfluramine for 14–15 weeks experienced clinically meaningful improvement in EF. Longer-term studies are warranted.

Sponsor: Zogenix.

28. Interim Safety, Pharmacokinetics (PK), and Cerebral Spinal Fluid (CSF) Exposure Data from the Phase 1/2a MONARCH Study of STK-001, an Antisense Oligonucleotide (ASO), in Children and Adolescents with Dravet Syndrome (DS)

Linda Laux, Colin Roberts, Kelly Knupp, John M. Schreiber, Matt Lallas, Elaine Wirrell, Orrin Devinsky, James Stutely, Charlene Brathwaite, Javier Avendaño, Kimberly A. Parkerson, Meena, Nancy Wyant, Barry Ticho, Joseph Sullivan; Ann & Robert H Lurie Children's Hospital of Chicago; OHSU; University of Colorado; Children's National Hospital; NeuroNetwork Partners, Mayo Clinic, NYU Langone Health, Stoke Therapeutics; UCSF

Abstract DS is a severe and progressive genetic epilepsy that is generally caused by spontaneous, heterozygous loss of function mutations in the SCN1A gene, which encodes the voltage-gated sodium channel subunit type 1 α (Nav1.1). STK-001 is an investigational ASO designed to upregulate Nav1.1 protein expression in brain by leveraging the non-mutant (wild-type) copy of SCN1A to restore physiological Nav1.1 levels, thereby potentially reducing seizure frequency (SF) and non-seizure comorbidities.

Patients (N = 22) with DS were grouped by age (2–12 and 13–18 years) and STK-001 was administered intrathecally on Day 1 as a single dose (10, 20, or 30 mg) or on Day 1,

Week 4, and Week 8 as multiple doses (20 mg). Adverse events (AEs), SF, and plasma PK were monitored throughout. 91% of patients were taking ≥ 3 and 73% were taking ≥ 4 concomitant anti-seizure medicines as maintenance therapy. At data cut, 4 patients had study drug-related treatment-emergent (TE) AEs, all were ≤ Grade 3; and 5 patients had serious TEAEs, none related to study drug. SF was evaluated for 28 days (baseline) before first dose of STK-001. During pre-treatment period, patients had a high rate of convulsive seizures (median = 16 per 28 days). SF was reduced in 12 of 17 (70.6%) patients, including all 2–12 years patients, at days 29–84 following the first dose vs baseline. Dose-proportional increases in plasma exposure and CSF concentration were observed. Modelling data suggested that > 95% of patients are predicted to have pharmacologically active STK-001 brain levels with 3 monthly 30 mg doses.

In conclusion, single doses of STK-001 up to 30 mg, and three 20 mg doses of STK-001 given every four weeks, were well-tolerated with no study drug-related safety concerns observed. There was a trend toward reduced convulsive SF. The MONARCH study provides more clarity on STK-001 doses likely to be pharmacologically active in patients with DS, supporting continued development of STK-001 as the potentially first disease modifying precision medicine for DS.

29. Phase 2B Efficacy and Safety of XEN1101, a Novel Potassium Channel Modulator, In Adults with Focal Epilepsy (X-TOLE)

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Abstract This Phase 2b study was designed to assess the efficacy and safety of XEN1101 as adjunctive treatment in adults with focal onset seizures (FOS). XEN1101 is a novel, potent, selective KCNQ2/3 (Kv7.2/7.3) potassium channel positive allosteric opener being developed for FOS and major depressive disorder. Its pharmacokinetic properties support once daily oral dosing without titration. X-TOLE was a double-blind, placebo-controlled, dose-ranging study in adults. Subjects had ≥ 4 countable FOS per month, recorded with an eDiary, and stable treatment with 1–3 antiseizure medications (ASMs). A total of 325 subjects with a median baseline FOS frequency of 13.5/month were randomized to one of three treatment groups or placebo in a 2:1:1:2 ratio (25 mg: 20 mg: 10 mg: placebo). The trial met its primary and secondary endpoints with XEN1101 demonstrating a dose-dependent reduction from baseline in FOS frequency of 33.2% ($p = 0.035$, $n = 46$), 46.4% ($p < 0.001$, $n = 51$), and 52.8% ($p < 0.001$, $n = 112$) in the 10 mg, 20 mg, and 25 mg groups, respectively, compared to placebo (18.2%, $n = 114$). Responder rates of ≥ 50% reduction in FOS frequency were achieved in 28.3% ($p = 0.037$), 43.1% ($p < 0.001$) and 54.5% ($p < 0.001$) in the 10 mg, 20 mg, and 25 mg groups, respectively, compared to placebo (14.9%). Comparing CGI and PGI scores in the 25 mg and placebo groups, approximately twice as many subjects reported improvement with XEN1101: 46.4% vs 22.8% ($p < 0.001$) and 42.9% vs 21.9% ($p = 0.001$), respectively. The incidence of TEAEs was 67.4%, 68.6%, and 85.1% in the 10 mg, 20 mg, and 25 mg groups, respectively, compared to placebo (62.3%). The incidence of treatment-emergent SAEs was balanced across study arms. The overall dropout was 12.3%; 96.5% of study completers entered the open label extension. At all doses, XEN1101 demonstrated a statistically significant reduction in FOS frequency compared to placebo and there was a corresponding dose-dependent improvement in responder rates. XEN1101 demonstrated a safety profile similar to other ASMs.

30. The Impact of Disease Severity on Efficacy from a Phase 2b Study of XEN1101, A Novel Potassium Channel Opener, in Adults With Focal Epilepsy (X-TOLE)

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Abstract X-TOLE was a randomized, double-blind, placebo-controlled, study to assess the efficacy and safety of XEN1101 in adults with focal onset seizures (FOS). A total of 325 subjects were randomized and treated across three treatment groups or placebo in a 2:1:1:2 ratio (25 mg: 20 mg: 10 mg: placebo). Overall, XEN1101 demonstrated a dose-dependent reduction from baseline in median monthly FOS frequency of 33.2% ($p = 0.035$, $n = 46$), 46.4% ($p < 0.001$,

n = 51), and 52.8% ($p < 0.001$, n = 112) in the 10 mg, 20 mg, and 25 mg groups, respectively, compared to placebo (18.2%, n = 114). X-TOLE included a "difficult-to-treat" patient population given baseline seizure burden, number of prior failed antiseizure medications (ASMs), and number of concomitant ASMs during the study. The median seizure frequency was 13.5/month at baseline; 50.8% study subjects were taking 3 concomitant ASMs; and median number of ASMs taken prior to study entry was 6. Additional analyses to assess the role of disease severity were performed in patients with differing baseline characteristics, namely number of prior failed ASMs, concomitant ASMs during the study, and baseline seizure burden. The following post hoc analyses pertain to the 25 mg treatment group. Compared with baseline, subjects with ≤ 8.5 seizures/month at baseline experienced a 70.6% reduction compared to 50.8% for those with > 8.5 seizures/month. Median monthly FOS reduction was 58% in subjects who failed ≤ 6 ASMs at baseline and 43% in subjects who failed > 6 ASMs. Median monthly FOS reduction was 60.9% for subjects with 1–2 concomitant ASMs and 50.8% for subjects with 3 concomitant ASMs. X-TOLE met the primary and key secondary efficacy endpoints with XEN1101 demonstrating a statistically significant, dose-dependent reduction from baseline in monthly FOS frequency compared to placebo in a difficult-to-treat population. These post hoc analyses suggest that efficacy may be more robust in patients with less severe disease, which mirrors likely use of XEN1101 if approved.

31. GM6 Attenuates Activated Cofilin and Beta-arrestin2 Impact On Pathological Tau and Decreasing Tau Aggregates in Alzheimer's Disease (AD) and Frontotemporal Lobar Degeneration (FTLD)

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Abstract Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) are major causes of dementia in the elderly. Recent studies have implicated both activated-cofiliin and beta-arrestin2 in the pathogenesis of AD and FTLD. The deposition of amyloid β (Aβ) peptide into amyloid fibrils and hyperphosphorylated tau into neurofibrillary tangles (NFTs) are key processes in the pathogenesis of the diseases. Recent studies have shown that activated cofilin and beta-arrestin2 are increased in the brains of patients with AD and FTLD, associating them in the disease process. In addition, studies have shown that reduction in cofilin and beta-arrestin2 in vitro and in vivo reduces the impact on AD and FTLD. GM6 is a derivative of motoneuronotrophic factor (MNTF) which functions as a regulator of key biomarkers, acts upon multiple extracellular receptors to modulate a series of signaling pathways. GM6 has been tested in various clinical trials and shown to be safe with favorable shifts in blood biomarkers of Abeta, tau, TDP-43, and SOD1 as well as positive signals of clinical outcomes. APP/PS-1 and tau transgenic mice were treated with GM6 daily for up to 3 months and examined for changes in Aβ peptide levels, plaques, inflammation, tau (p-tau), activated cofilin and beta-arrestin2, as well as behavioral changes associated with disease progression. As previously shown, GM6 reduced the pathology in both animal models (APP and tau) and improved outcomes. In addition, in the APP and tau mice, activated cofilin and beta-arrestin2 were elevated and treatment with GM6 reduced both by greater than 60% and 70%, respectively. In conclusion, these findings suggest that GM6 may be a feasible approach to attenuate AD and FTLD pathology as a combination therapy by concurrently reducing inflammation, activated cofilin, beta-arrestin2, Abeta and hyperphosphorylated tau.

32. Treatment with Selective Inhibitors of Nuclear Export (SINE) Compounds Attenuates Dystrophic Symptoms in Zebrafish and Mouse Models of Duchenne Muscular Dystrophy

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Abstract The overall purpose was to evaluate the effectiveness of Selective Inhibitor of Nuclear Export (SINE) compounds in zebrafish and mouse models of Duchenne muscular dystrophy (DMD). DMD is an X-linked disorder that affects approximately 1:5000 boys, who develop muscle weakness, cardiac arrhythmias, respiratory weakness, and loss of ambulation. The nuclear export protein XPO1/CRM1 is a promising target for treatment of neuromuscular disorders with inflammatory pathology such as DMD. XPO1 regulates the function of > 200 cargo proteins, including transcription factors that regulate inflammation and neurotoxicity. SINE compounds are orally available small molecules that inhibit XPO1 nuclear export function. Treatment with SINE compounds have been shown to improve phenotypes in other rodent models of neuromuscular disease, such as ALS and Huntington's via reducing fibrosis and inflammation in the skeletal muscles. To ascertain the short-term and long-term effects of SINE compound treatment on dystrophic disease pathologies in sapje zebrafish (severe model

of DMD), embryos were treated for either 5 days post-fertilization (dpf) or 3x/week for 24 h for 21 dpf with either vehicle, SINE compound, or aminophylline (positive control). Furthermore, we tested SINE compound (5 mg/kg) in adult mdx (DBA2J) and WT mice 3x/week for 8 weeks in a double-blinded protocol. In all studies, SINE compound-treated sapje zebrafish showed significant prevention of the muscle degeneration pathology associated with dystrophin-deficiency and improved overall muscle architecture. Consistent with this, SINE compound treatment in mdx (DBA2J) mice blocked muscle inflammation, improved mobility, and reduced overall dystrophic symptoms compared to vehicle controls. Our studies demonstrated that SINE compounds are a promising therapeutic that can attenuate the symptoms in relevant animal models of DMD.

33. Oral Small Molecule Hepatocyte Growth Factor/MET Positive Modulator ATH-1020 Reduces Depression-like Behaviors and Normalizes Pathological EEG Mismatch Negativity in Preclinical Models

Andrée-Anne Berthiaume, Jewel Johnston, Robert Taylor, Kevin Church; Athira Pharma, Inc

Abstract The purpose of this study is to identify and develop a small molecule capable of augmenting the neurotrophic hepatocyte growth factor (HGF)/MET signaling pathway for the treatment of neuropsychiatric disorders. Positive modulation of the HGF/MET system may represent a novel, safe, and effective therapeutic strategy for a variety of neuropsychiatric indications, as reduced HGF levels are implicated in depression, bipolar disorder, and schizophrenia. HGF/MET activity may also regulate the glutamatergic signaling disruptions commonly seen in neuropsychiatric disorders, by influencing the activity and synaptic localization of NMDA receptors. We identified a novel small molecule HGF/MET positive modulator, ATH-1020, and characterized its potential in treating neuropsychiatric indications in preclinical models. In in vitro biochemical activity screens, we confirm that ATH-1020 augments HGF-dependent activation of MET and its downstream signaling target, extracellular signal-regulated kinase (ERK). In pharmacokinetic studies, we demonstrate that ATH-1020 is orally bioavailable and crosses the blood–brain barrier. Toxicology studies in both rats and beagle dogs indicate a favorable safety profile for ATH-1020. To explore its potential as a treatment for neuropsychiatric diseases, ATH-1020 was tested in models of depression and schizophrenia. In the forced swim test, healthy rats are less prone to behavioral despair as measured by reduced immobility when treated with ATH-1020. When stress-induced depression is modeled using a chronic unpredictable stress paradigm, ATH-1020 treatment reduces stress-related hyperactivity in an open field test. Additionally, ATH-1020 treatment effects on mismatch negativity (MMN), a measure of sensory processing derived from electroencephalogram (EEG) recordings of auditory event-related potentials, were evaluated in the MK-801 schizophrenia rat model. MK-801 pathologically reduces the MMN signal, which is restored by ATH-1020 treatment. MMN is a pharmacodynamic biomarker that has been shown to translate to clinical schizophrenia. Based on our initial findings, ATH-1020 may be well-suited as a therapeutic for neuropsychiatric disorders. We plan to pursue further preclinical and clinical development towards these indications.

34. Positive Modulation of Hepatocyte Growth Factor/MET by a Novel Small Molecule Induces Neurotrophic and Procognitive Effects

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Abstract The purpose of this study was to evaluate the neurotrophic effects of ATH-1001, the active metabolite of fosgonimeton (ATH-1017) a novel small molecule positive modulator of the neurotrophic hepatocyte growth factor (HGF)/MET system under development for the treatment of neurodegenerative diseases including Alzheimer's and Parkinson's. Currently approved neurotransmitter-based therapies have limited efficacy that wanes over time. New treatments, especially those focused on restoring neuronal health and function, are needed. Based on extensive literature, positive modulation of the HGF/MET system may be capable of inducing beneficial neurotrophic responses, and thus may have multi-modal and lasting therapeutic potential. ATH-1001 enhancement of the HGF/MET pathway was demonstrated in HEK293 cells by ELISA for phosphorylated MET. Activation of HGF/MET leads to stimulation of a variety of intracellular signaling pathways, including phospho-activation of the signaling kinase extracellular signal-regulated kinase (ERK), which partially mediates HGF-dependent cell behaviors and neurotrophic signals. ERK activation in HEK293 cells was enhanced by treatment with ATH-1001, and this effect was blocked by the MET inhibitor Capmatinib. The neurotrophic effects of ATH-1001 were assessed in rat primary hippocampal neurons. One day old neuronal cultures were treated with ATH-1001 for 2–3 days prior to βIII-tubulin staining for neurite outgrowth or for 7–8 days prior to staining with synaptobrevin II to assess synaptogenesis. ATH-1001 treatment significantly enhanced both neurite outgrowth and synaptogenesis in primary hippocampal neurons as indicated by 1) an increase in neurite length, 2) number of new synapses, and 3) synaptic strength. Finally, the procognitive effects of ATH-1001 were evaluated in vivo using Morris water maze (MWM) in the scopolamine amnesia rat model. ATH-1001 treatment reversed spatial memory impairment as measured by reduced escape

latencies in the MWM. Together, these results suggest that ATH-1001 positively modulates the HGF/MET system thus inducing neurotrophic effects and enhancing cognition, which may be valuable in the treatment of neurodegenerative disorders. Fosgonimeton, the prodrug of ATH-1001, was developed to improve drug-like characteristics and is currently in clinical trials for Alzheimer's and Parkinson's disease dementia.

35. Pharmacologically Targeting Inducible Prostaglandin E Synthase to Counteract Neuroinflammation-associated Cognitive Impairments

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Abstract Background and hypothesis: The association between neuroinflammation and symptomatic cognitive impairments following acute brain injuries warrants more intense interrogations; Meanwhile, the relevant implications of anti-inflammation therapy by specifically targeting phospholipid metabolite prostaglandin E2 (PGE2) biosynthesis are yet to be articulated. The biosynthesis of PGE2 involves stress-inducible COX-2 and microsomal prostaglandin E synthase-1 (mPGES-1) enzymes. Targeting mPGES-1 appears to be an advantageous alternative to circumventing those side effects pertinent to the canonical inhibition of COXs. Nevertheless, the orthologue discrepancy between human and rodent mPGES-1 has remarkably compromised the translational potential of mPGES-1 inhibitors earlier developed. Now upon a series of multi-species compatible mPGES-1 inhibitors newly developed, pharmacologically targeting mPGES-1 using the lead compound MPO-0063 (N-phenyl-N'-(4-benzyloxyphenoxycarbonyl)-4-chlorophenylsulfonyl hydrazide) is expected to counteract neuroinflammation, to salvage brain tissues from injuries, and to maintain the long-term integrity of neurological and neuropsychological functions following acute cerebral ischemia.

Results: In this study, the lipopolysaccharide challenges resulted in an overproduction of PGE2 and prototypic cytokines from murine primary microglia; Likewise, the oxygen–glucose deprivation consistently induced excessive PGE2 release across neuronal and microglial cell lines. These pro-inflammatory responses can be dose-dependently counteracted by MPO-0063 (n = 4–8). In a mixed primary culture of murine neuron and glia, there were no cytotoxicity determined with MPO-0063. Instead, this lead compound showed its potent neuroprotective properties in both in vitro and in vivo models mimicking acute cerebral ischemia (n = 8–11). A battery of long-term functional studies were performed in mice subjected to a mild MCAO modeling. The early administration of MPO-0063 prevented the decline of max instantaneous velocity in the open field test at day 7. Meanwhile, it transiently disclosed an anxiolytic potential during the light/dark box test. Moreover, post-stroke long-term cognitive impairments were measured using novel object recognition test. On day 30 after MCAO, untreated mice could not tell a novel object. By contrast, the early treatment with MPO-0063 conferred a remarkable restoration of cognitive function (n = 12–13).

Conclusions: The therapeutic effects of our current lead mPGES-1 inhibitor MPO-0063 in this proof-of-concept study provide the first pharmacological evidence that mPGES-1 represents a feasible target for delayed, adjunct treatment – along with reperfusion therapies for acute brain ischemia. More importantly, pharmacologically targeting mPGS-1 might open a novel therapeutic avenue to decelerate neuroinflammation-associated neuropsychological dysfunction.

36. Preclinical Development of NRTX-1001, an Inhibitory Interneuron Cellular Therapeutic for the Treatment of Chronic Focal Epilepsy

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Abstract Rationale: About one-third of people with epilepsy have drug-resistant seizures. Anti-seizure drugs that potentiate the inhibitory neurotransmitter GABA provide potent seizure suppression, but their use is limited due to side effects, tolerance, and the potential for abuse. Surgical resection or ablation of a seizure focus can be an effective option for chronic focal-onset epilepsy, however these options are tissue-destructive and not indicated for all individuals. A cellular therapeutic delivering GABA could restore balanced neural activity and suppress chronic seizures without destruction of tissue. Development of a cellular therapeutic for clinical use requires reliable manufacturing and thorough characterization of the cell product, and comprehensive testing in preclinical models.

Methods: Clinically-compliant processes were used to consistently manufacture and cryopreserve a post-mitotic GABAergic interneuron product candidate, NRTX-1001,

derived from a human pluripotent stem cell line. NRTX-1001 was characterized for composition, sterility, viability, and the lack of adventitious agents. Preclinical studies included functional assessments in a rodent model of chronic pharmacoresistant focal seizures; extensive safety testing to assess biodistribution, toxicology and tumorigenicity; and MRI-guided delivery into non-human primates.

Results: Hippocampal administration of NRTX-1001 into mice with intrahippocampal kainic acid-induced chronic mesiotemporal seizures resulted in pronounced focal seizure reduction, hippocampal distribution and persistence of transplanted interneurons, and reduced hippocampal pathology. Approximately 75% of epileptic mice were stably seizure-free after receiving NRTX-1001, as compared to 8% of mice in the control group. Biodistribution studies with qPCR-based analyses of central and peripheral tissues confirmed that cell persistence was restricted to the hippocampus. Daily clinical observations and assessments of histopathology, hematology and clinical chemistries at multiple time points did not indicate systemic toxicities or adverse behavioral effects related to NRTX-1001. Targeted intrahippocampal delivery, engraftment, and persistence of NRTX-1001 were demonstrated in immunosuppressed non-human primates. NRTX-1001 transplantation was well tolerated in preclinical models and did not form ectopic tissues or teratomas.

Conclusions: A Phase 1/2a clinical trial to assess the safety and preliminary efficacy of NRTX-1001 in patients with drug-resistant mesiotemporal lobe epilepsy is underway.

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