ASENT2020 Annual Meeting Abstracts

Poster 1

Effects of Viloxazine on Central Neurotransmitter Systems: A Microdialysis Study in Freely Moving Rats

Chungping Yu, PhD; Jennie Garcia-Olivares, PhD; Stefan Schwabe, MD, PhD; Supernus Pharmaceuticals

SPN-812 (viloxazine extended release) is currently under investigation as a treatment for ADHD. In recently completed Phase 3 trials, SPN-812 was effective in reducing symptoms of hyperactivity, impulsivity, and inattention in ADHD. Historical data has shown that viloxazine has an inhibitory effect on norepinephrine uptake. Recently, we had used microdialysis to further elucidate the activity of viloxazine in central neurotransmitter systems. In this study, extracellular levels of neurotransmitters were measured in the prefrontal cortex (PFC), nucleus accumbens (NAcc), and amygdala (AMG) of freely moving rats before and after a single administration of viloxazine (50 mg/kg, IP) or vehicle. Dialysate concentrations of norepinephrine (NE), dopamine (DA), serotonin (5-HT), gamma-aminobutyric acid (GABA), glutamate (Glu), histamine (His), and acetylcholine (ACh) were measured using LC-MS. Results indicated that viloxazine increased 5-HT, NE, and DA levels up to 506, 650, and 670% of baseline levels, respectively, in the PFC. No significant changes in the levels of GABA, Glu, His, or ACh were observed in the PFC. In the NAcc, an increase in 5-HT levels up to 365% of baseline were observed. An approximate 190% increase in NE and DA were also noted in the NAcc. Viloxazine also increased NE up to 571% in the AMG, along with increased levels of 5-HT (312%) and DA (254%). Vehicle injection produced no significant effects on the levels of all evaluated neurotransmitters in PFC, NAcc, and AMG. The observed upregulation of extracellular 5-HT in PFC, an established target area associated with ADHD pathophysiology, demonstrates viloxazine's modulatory effect on serotonergic system. The ability of viloxazine to increase NE and DA in PFC confirms its inhibitory activity on the norepinephrine transporter. Minimal increases of DA in the NAcc indicates that viloxazine presents a low risk for substance abuse disorders. SPN-812 has recently been submitted to the FDA for approval.

Poster 2

Neuronal Protection by AAV2-mediated shRNA to Human Endogenous Retrovirus-K in a Transgenic Mouse Model of Amyotrophic Lateral Sclerosis

Myounghwa Lee, PhD; Wenxue Li, PhD; Kevon Sampson, MSc.; Deborah Choi, BS; Avindra Nath, MD; National Institutes of Health

Sporadic amyotrophic lateral sclerosis (sALS) is a fatal neurodegenerative disease of unknown etiology due to the progressive loss of cortical and spinal motor neurons which often leads to paralysis and death within three to five years after onset. Our laboratory has shown that human endogenous retrovirus-K (HERV-K) is activated in brain and spinal cord of a subpopulation of ALS patients and may contribute to disease pathogenesis. We have developed a transgenic mouse model in which the HERV-K envelope (env) protein is expressed under a neuronal promoter. Expression of HERV-K env in mouse neurons resulted in neuropathology as seen in ALS patients. Neurodegeneration, including reduced dendritic spines and significant cell loss was found in corticospinal motor and anterior horn cell neurons. Damage to motor neurons caused muscle atrophy and muscle fiber type grouping, leading to progressive motor dysfunction. The mice had a shortened lifespan. Thus, HERV-K env transgenic mice recapitulated the main features of ALS, suggesting that HERV-K viral proteins can be a therapeutic target for ALS. In this study, we determined the effects of administration of recombinant adeno-associated virus serotype 2 (rAAV2) vectors to deliver small hairpin RNA (shRNA) targeting the HERV-K env transcripts in HERV-K env transgenic mice. Mice received a single intracerebroventricular (ICV) injection with AAV2-ctrl shRNA (a control vector) (n=13) or AAV2-env shRNA (a shRNA vector targeting the

env mRNA transcript) vector (n=14) at postnatal day 1 (P1). Persistent viral transgene expression was observed in the cortex and spinal cord 4 weeks after the injection. Injection of the AAV2-env shRNA vector into the brain of HERV-K transgenic mice significantly (p=0.03) reduced the expression of HERV-K env positive cells by 35% as determined by quantification of immunohistochemical staining. Concomitant with these reductions was protection of neuronal loss in the motor cortex of HERV-K transgenic mice; there was 37% neuronal loss in ctrl shRNA-injected mice, whereas there was 11% loss in env shRNA-injected mice. However, no obvious prevention of muscle atrophy and motor deficits occurred likely due to lack of effect on anterior horn cells. These findings are encouraging in that it may be feasible to target HERV-K env expression therapeutically in ALS.

Poster 3

Brain Derived Neurotrophic Factor Rescues Amyloid Induced Memory Deficit Mice by Anti-apoptotic and Proliferative Activity

Akshay Anand, PhD; Parul Bali; Bimla Nehru, Post Graduate Institute of Medical Education and Research

Neurotrophic factors have protective roles in neuronal survival and its proper functioning. Various post-mortem studies showed decline in neurotrophic factors expression i.e. GDNF and BDNF in Alzheimer's disease patient brains. Hence, it suggests that neurotrophic factors have crucial role in brain function and its related disorders. Therefore, in our study we tested the efficacy of recombinant brain derived neurotrophic factor (rBDNF) in amelioration of amyloid $\hat{I}^2$-42 (A$\hat{I}^2$-42) induced memory loss in mouse model. Our purpose was to investigate the role of rBDNF therapy in reversal of A$\hat{I}^2$-42 induced memory loss in mouse model. We established memory loss in Swiss albino mouse model using oligomeric form of A$\hat{I}^2$-42. rBDNF was administered into intra-hippocampal region of mice brains after 21 days of A$\hat{I}^2$-42 injury. Neurobehavioral analysis was done to assess spatial and fear-based memory by Morris water maze (MWM) and passive avoidance, respectively at 31st day time-point. Swimming behavior of mice was tracked using Anymaze software connected to camera. Further, molecular analysis was done by mRNA expression using real-time PCR of BDNF, GDNF, CNTF, Ki67, Bcl2, Capase3 and GFAP. The MWM results showed that mice injected with A$\hat{I}^2$-42 and TrkB inhibitor significantly increases in escape latency time (ELT) in comparison to vehicle control group. Quadrant time spent was significantly increased after rBDNF administration when compared with A$\hat{I}^2$-42 injury group. Mean distance travelled by mice from platform was less in rBDNF group, which was comparable to control mice. Passive avoidance results showed

significant increase in latency time in mice with rBDNF therapy in comparison to A$\hat{I}^2$-42 injury as well as TrkB inhibitor injected groups. Real-time analysis depicts significant escalation of BDNF, GDNF and CNTF after rBDNF administration and enhancement of ki67 and anti-apoptotic activity. In conclusion, rBDNF is effective in amelioration of A$\hat{I}^2$-42 induced memory loss via proliferative as well as anti-apoptotic activity by modulating neurotrophic effects.

Poster 4

AlzPED: A New Data Resource for Improving the Rigor, Reproducibility, Transparency and Translation of Alzheimer's Disease Preclinical Research

Shreaya Chakroborty, PhD; Ali Sharma, PhD; Katerina Mancevska, BS; Zane Martin, PhD; Jean Yuan, PhD; Cindy Sheffield, MBA; Suzana Petanceska, PhD; Lorenzo Refolo, PhD; National Institute on Aging, National Institutes of Health

AlzPED is a publicly available database created by the National Institute on Aging to address key factors contributing to poor translation of preclinical efficacy from animal models to the clinic in Alzheimer's disease (AD) therapeutic development. Specifically, AlzPED is designed to identify critical experimental design elements and methodology missing from studies that make them susceptible to misinterpretation and reduce their reproducibility and translational value. Through this capability, AlzPED is intended to guide the development and implementation of strategies and recommendations for standardized best practices for the rigorous preclinical testing of AD candidate therapeutics. Using key word-driven literature searches published studies are acquired and curated by two experts for data on authors, funding source, AD animal models, therapeutic targets and agents, study design, and outcome measures. AlzPED currently houses curated summaries from over 900 published studies. Summaries are searchable by author, funding source, animal model, therapeutic target and therapeutic agent and elements of experimental rigor and design. At present, the database contains data on 186 animal models, 175 therapeutic targets, 804 therapeutic agents and, more than 1500 AD-related outcome measures. Analysis of curated studies demonstrates serious deficiencies in reporting critical elements of methodology such as power calculation, blinding for treatment/outcomes, randomization, sex of animal used and balancing for sex, animal genetic background and others. These deficiencies diminish the scientific rigor, reproducibility and translational value of the preclinical studies. Thus, it is evident that a standardized set of best practices is required for successful translation of therapeutic efficacy in AD research.

Poster 5

Applying Machine Learning Techniques to Discover Molecules for Alzheimer's Targets

Patricia A. Vignaux, PhD; Ana C. Puhl, PhD; Eni Minerali, MS; Sean Ekins, PhD, DSc; Collaborations Pharmaceuticals, Inc.

Alzheimer's disease (AD) is the most common cause of dementia, affecting approximately 35 million people worldwide. The current treatment options for people with AD consist of drugs designed to slow the rate of decline of memory and cognition, but these treatments are not curative and patients eventually suffer complete cognitive injury. The purpose of this study is to use our proprietary machine learning software, Assay Central, to find novel small molecule treatments for Alzheimer's disease that can supplement or replace the AD drugs currently on the market. In order to do this, we use publicly available data in ChEMBL, PubChem BindingDB and other databases to build validated Bayesian machine learning models for AD target proteins. The first target we have modeled with this method is the serine-threonine kinase Glycogen synthase kinase 3 beta (GSK3β), which is a proline-directed serine-threonine kinase that phosphorylates the microtubule-stabilizing protein tau. This phosphorylation prompts tau to dissociate from the microtubule and form insoluble oligomers called paired helical filaments (PHFs), which are one of the components of the neurofibrillary tangles (NFTs) found in AD brains. Using our machine learning model for GSK3β, we have identified a small molecule inhibitor of the kinase not previously found in the literature. We validated this finding with an in vitro assay for GSK3β activity and found the inhibitor to be effective at nanomolar concentrations. This finding demonstrates that our machine learning model is capable of predicting novel inhibitors for AD-related targets. We are now applying this approach to additional AD targets and our goal is to identify already approved drugs which can be either repurposed as AD therapeutics.

Poster 6

A Drug Discovery Platform to Identify Chaperones for Lysosomal Storage Diseases

Ana C. Puhl, PhD; Jennifer J. Klein, MS; Patricia A. Vignaux, PhD; Eni Minerali, MS; Daniel Foil, BS; Kimberley M. Zorn, MS; Sean Ekins, PhD, DSc; Collaborations Pharmaceuticals, Inc.

Lysosomal storage diseases (LSD) cause severe disability and have a devastating effect on quality of life. LSD are caused by mutations in ~50 genes encoding proteins necessary for lysosomal function. The current standard of care for the majority of LSD is enzyme replacement therapy (ERT) while gene therapies are under development. Neurodegenerative changes in the central nervous system are a major problem in several LSDs and cause severe disability and behavioral disturbances. The future of LSD therapy may lie in small molecules acting as agents for enzyme-enhancement therapy (EET). EET employs small molecules as 'pharmacological chaperones' to rescue misfolded and/or unstable mutant enzymes or proteins that have residual function. EET also offers the possibility of treating neurodegenerative lysosomal disorders since these small therapeutic molecules may cross the blood-brain barrier. We have developed a platform approach for small molecule drug discovery for LSD targets including CLN1 and CLN10 Batten Disease, and Sialidosis. Our approach involves employing machine learning techniques to build Bayesian machine learning models using data publicly available (CHEMBL, PUBCHEM) with our own in-house software Assay Central. This software can be used to find new molecules that may bind to these targets. We validated the molecules tested in vitro using enzymatic assays, isothermal titration calorimetry, differential scanning fluorimetry (DSF) and microscale thermophoresis (MST). These techniques are complimentary to each other, since EETs could bind to allosteric sites. Using this approach, we have identified 10 molecules for CLN1 and 3 molecules for Sialidosis, including inhibitors at nanomolar concentrations. These compounds are currently being tested in patient cell lines. These findings demonstrate that we have a developed a platform to rapidly identify and validate molecules for LSDs. This approach could be employed to accelerate drug discovery for other LSDs.

Poster 7

Development of a Neutral Sphingomyelinase 2 Inhibitor for the Treatment of Alzheimer's Disease

Carolyn Tallon[1,3], Kristen R. Hollinger[1,2,3], Benjamin J. Bell[1,3], Michal Sala[8], Ranjeet P. Dash[1], Ajit G. Thomas[1], Amrita Datta Chaudhuri[3], Asit Kumar[3], Lyndah Lovell[1], Ying Wu[1], Rana Rais[1,3], Norman Haughey[3], Radim Nencka[8], Camilo Rojas[1,4], Barbara S. Slusher[1,2,3,5,6,7]

Johns Hopkins Drug Discovery[1], Departments of Psychiatry and Behavioral Science[2], Neurology[3], Molecular and Comparative Pathobiology[4], Oncology[5], Medicine[6], Pharmacology[7], Johns Hopkins University School of Medicine, Baltimore, MD, United States, Institute of Organic Chemistry and Biochemistry[8], Academy of Sciences of the Czech Republic, Prague, Czech Republic

Alzheimer's disease (AD) is characterized by progressive cognitive impairment with increased amyloid and tau deposition along connectivity pathways. Growing evidence supports that extracellular vesicles (EVs) may serve as putative vectors for

this "prion-like" transmission. Pharmacological or genetic inhibition of neutral sphingomyelinase 2 (nSMase2) reduces EV release and improves cognition in AD mouse models. Unfortunately, there are no clinically available nSMase2 inhibitors. Our group conducted a high-throughput screening campaign against human nSMase2 followed by extensive structure-activity relationship studies and identified phenyl (R)-(1-(3-(3,4-dimethoxyphenyl)-2,6-dimethylimidazo[1,2-b] pyridazin-8-yl) pyrrolidin-3-yl) carbamate (PDDC) as a lead inhibitor. PDDC was found to be a selective, potent nSMase2 inhibitor (IC50 = 300nM), with excellent oral bio-availability (%F = 88) and brain penetration (AUCbrain/AUCplasma = 0.60) in mice. PDDC was also shown to dose-dependently inhibit EV release in both serum-deprived cells in culture and when administered to mice following brain injury; a closest related inactive analog had no effect. PDDC efficacy was tested in the 5XFAD mouse model of AD. While 5XFAD mice experienced significant impairments in fear memory versus age-matched wild type controls, chronic PDDC dosing completely restored cognitive performance to control levels. PDDC was subsequently incorporated into mouse chow at doses designed to deliver up to 100mg/kg per day. The mouse chow provided sustained brain exposures of PDDC (197 nmol/g*h) which stayed above the IC50 throughout the 24-hour testing period. This dosing regimen is now being evaluated in models of tau propagation in PS19 and 3xTg mice. Preliminary data suggests nSMase2 inhibition with PDDC improves cognition in the 5XFAD AD mouse model and, if confirmed, these findings support PDDC as a novel compound for the treatment of progressive cognitive decline in AD.

Poster 8

GM6 Effects in h-tau Animals

Mark S. Kindy, PhD; Dorothy Ko; Genervon Biopharmaceuticals LLC

Transgenic mice that express all 6 isoforms of human microtubule-associated protein tau (MAPT) were tested for effect in Alzheimer's disease pathogenesis with GM6 treatment. Animals were randomly assigned to a GM6-treatment group (‰=‰20) receiving a daily intravenous injection of a 6-mer active fragment of MNTF (GM6) or a reversed-GM6 peptide control group (a peptide with reversed GM6 sequence) at a dose of 5 mg/kg. Four months after treatment the right brain hemispheres were frozen in OCT medium and sectioned with a cryostat to obtain 30-Î¼m frozen sections for immunohistochemical analysis. The left brain hemispheres were frozen as quickly as possible and used to quantitate the levels of inflammatory markers. Immunohistochemical staining showed the pT231 tau level in the GM6-treated group is 10% that of the control group

(p<0.05). Quantitative analysis of cytokines levels by ELISA for control group compared to GM6 -treated group for TNF-Î± are 60 vs 10 pg/mg protein (p<0.05); for IL-1Î² are 180 vs 20 pg/mg protein (p<0.05); for IL-6 are 120 vs 20 pg/mg protein (p<0.05). All behavioral testing was performed in groups by an observer blinded to the treatment of the mice. The open field was used as a standard test of general activity. The behavioral testing results comparing the control group to GM6 -treated group are as follows: for latency to gait initiation (sec) was 38 vs 4 percent time, in central zone (%) was 23 vs 7, the distance traveled (cm) was 1500 vs 2200. In the passive avoidance model control vs GM6-treated group the step-through (sec) was 30 vs 230 (P<0.05). In the novel object recognition model, the discrimination ratio (DR) was used. DR is defined as the time exploring the novel object minus the time spent with the familiar divided by the combined time spent exploring both novel and familiar objects memory. The DR in the control group compared to the GM6 - treated group was 0.14 vs 0.25, suggesting the GM6-treated group has better memory (p<0.05).

Poster 9

GM6 can Block tau hyperphosphorylation Induced by AGEs and AÎ²

Mark S. Kindy, PhD; Dorothy Ko; Genervon Biopharmaceuticals LLC

Genervon Biopharmaceuticals has discovered a novel peptide GM6 as a potential novel therapy for targeting Alzheimer's disease (AD). We have a better understanding now that inefficient insulin receptors can lead to insulin resistance and downstream activation of AÎ² and tau which results in AD. Our recent studies suggest that GM6 would allosterically bind to insulin receptors, increase their efficiency, decrease insulin resistance, and, in turn, decrease AÎ² and tau or p-tau in AD. Bioinformatics data also showed that GM6 increases the expression of genes that reduce insulin resistance, upregulates genes for AÎ² catabolism, and downregulates mitochondria genes including MAPT. Previously, GM6 was shown to attenuates AD pathology in APP mice. In this in vitro model, SK-N-SH cells were treated with AGE-BSA or with AÎ²1-42 and showed a dose-dependent increase in tau hyperphosphorylation as determined by western blot analysis of pT231, pS396, and pS404. Tau1 and Tau5 were controls to show that Tau levels did not change. In addition, actin was used as a control. These results validated that AGE-BSA or AÎ²1-42 induced tau hyperphosphorylation. SK-N-SH cells induced with tau hyperphosphorylation were treated with GM6 or a control with reversed GM6 sequence. Tau hyperphosphorylation was determined by western blot analysis of pT231. In this validated in vitro model, SK-N-SH cells with AGE-BSA or AÎ²1-42-induced tau

hyperphosphorylation treated with GM6 showed a dose-dependent decrease in tau hyperphosphorylation. Treatment with GM6 at a 3uM concentration showed a decrease in tau hyperphosphorylation by >70% (p<0.01) which is like the effect of RAGE antibodies, while treatment with control did not. Based on the data presented, we have demonstrated in the present study that exogenously added AGEs and AÎ²1-42 can induce tau hyperphosphorylation and that this can be blocked by GM6, like the blocking by RAGE antagonist. Additional GM6 treatment effects in h-Tau animals to follow.

Poster 11

2DG for Treatment of Status Epilepticus, Acute Repetitive Seizures, and Prevention of Post-Traumatic Epilepsy and Delayed Consequences of TBI

Thomas P. Sutula, MD, PhD, University of Wisconsin – Madison; Nathan Fountain, MD, University of Virginia

2DG (2-deoxy-D-glucose) is a reversible inhibitor of glycolysis. 2DG has acute anticonvulsant actions in multiple in vivo and in vitro seizure models, and chronic antiepileptic "disease-modifying" actions in rodent epilepsy models consisting of 2-fold slowing of kindling progression, initially suggesting potential for development as an anticonvulsant for chronic treatment of epilepsy. The acute anticonvulsant actions of 2DG involve glycolytic regulation of synaptic vesicle by presynaptic mechanisms, and the chronic antiepileptic "disease-modifying" actions involve glycolytic metabolic regulation of seizure-induced and injury-induced gene expression by the transcriptional repressor Neuron Restrictive Silencing Factor (NRSF) and its redox sensor Carboxy-terminal Binding Protein (CtBP). These unique acute and chronic mechanisms distinguish 2DG from all currently available anticonvulsants. Following observations in preclinical toxicological studies that 2DG induces dose-dependent cardiac myocyte vacuolation with features of reversible autophagy at high doses in rats, we now present additional toxicological studies that have precisely characterized doses and treatment durations inducing cardiac vacuolation, and have demonstrated complete reversibility across all examined dose ranges. Cardiac toxicity does not occur in rats treated for less than 14 days even at the highest doses. Safety and tolerability of 2DG (45 mg/kg/day) has been demonstrated in humans with repeated daily dosing for 3 weeks in cancer clinical trials, supporting the potential for safe use of limited repeated dosing of 2DG in humans. With this safety profile and the unique property of neurovascular coupling that focally delivers 2DG into local brain circuits with increased energy demand for as long as 15 minutes after seizures and brain injury, limited repetitive dosing of 2DG is currently being pursued for treatment of status epilepticus and acute repetitive seizures. Limited repetitive dosing after TBI may also prevent and protect against delayed consequences of TBI demonstrated in rodent models of post-traumatic epilepsy and PTSD. Initial human clinical trials to assess safety, tolerability, and pharmacokinetics acute administration of 2DG in patients with established epilepsy will be underway during 2020.

Poster 12

Efficacy and Safety of Selinexor in Recurrent Glioblastoma

A. B. Lassman, MD[1]; P. Y. Wen, MD[2]; M. van den Bent, MD[3]; S. R. Plotkin, MD[4]; A. Walenkamp, MD, PhD[5]; A. Green, MD[6,7]; X. Huang, PhD[8]; K. Karla Rodriguez-Lopez, MD[8]; M. G. Kauffman, MD, PhD[8]; S. Shacham, PhD[8]; M. Mau-Soerensen, MD, PhD[9]

[1]Columbia University Irving Medical Center, New York, NY, United States, [2]Dana Farber Cancer Institute, Boston, MA, United States, [3]Erasmus MC Cancer Center, Rotterdam, Netherlands, [4]Massachusetts General Hospital, Boston, MA, United States, [5]University of Groningen, Groningen, Netherlands, [6]Dana Faber Cancer Institute, Boston, MA, United States, [7]Current affliation: University of Colorado Cancer Center, Aurora, CO, United States, [8]Karyopharm Therapeutics, Inc., Newton, MA, United States, [9]Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

New treatment modalities are needed for recurrent glioblastoma (rGBM). Selinexor is a novel, oral selective inhibitor of nuclear export which forces nuclear retention of tumor suppressor proteins including p53 and p27, leading to apoptosis. We previously reported interim results showing tolerability, preliminary efficacy, and blood-brain barrier penetration in a surgical cohort (N=8). We now report updated results following completion of accrual to non-surgical cohorts (N=68). Materials and Methods: This is an open-label, multicenter, ph-2 study of selinexor monotherapy. Patients (pts) not undergoing surgery for measurable rGBM per response assessment neuro-oncology criteria (RANO) were enrolled in one of 3 arms encompassing different dosing schedules of selinexor (50 mg/m2 [~ 85 mg] BIW, 60 mg BIW, and 80 mg QW). Treatment was continuous, although cycles were defined as 28 days and response was assessed every other cycle by MRI. Prior treatment with radiotherapy and temozolomide was required and prior bevacizumab was exclusionary. The primary endpoint was 6-month progression free survival (6mPFS) rate, calculated by the Kaplan-Meier method.
Results: 76 pts were enrolled; 24, 14 and 30 pts on doses of ~85 mg BIW, 60 mg BIW, and 80 mg QW, respectively.

Median age was 56 years (range 21-78). Median number of prior treatments was 2 (range 1-7). At the end of the 6 cycles, 30.2% pts on 80 mg QW were free from progression. The 6mPFS rate on 80 mg QW was 18.9%. Best RANO-defined responses (assessed locally) among 26 evaluable pts on 80 mg QW included 1 complete response, 2 partial responses, 7 stable disease, and 16 with progressive disease. Complete and partial responses were durable: the complete and a partial responder remain on selinexor for 393 and 1093 days respectively, as of the cut-off date. Median duration of response was 10.8 months. The most common related adverse events (all grades) in pts on ~85 mg BIW/60 mg BIW/80 mg QW were nausea (42%/64%/63%), leukopenia (38%/7%/43%), fatigue (71%/71%/47%), neutropenia (29%/14%/33%), decreased appetite (46%/71%/27%), and thrombocytopenia (67%/29%/23%).

Conclusion: Selinexor demonstrated efficacy, with durable responses and disease stabilization in rGBM. Based on the favorable efficacy and safety profile, selinexor at a dose of 80 mg QW is recommended for further development in rGBM.

Poster 14

GLP-1 Analogs for Therapy of Multiple Sclerosis (MSGLP): Design, Methods and Rationale of Randomized, Controlled Clinical Trial

Richard Imrich, MD, PhD[1]; Adela Penesova, MD, PhD[1]; Miroslav Vlcek, DrSc[1]; Zofia Radikova, MD, PhD[1]; Andrea Havranova[1]; Pavol Siarnik, MD, PhD[2]; Monika Sivakova, MD[2]; Branislav Kollar, PhD[2]; Peter Turcani, PhD[2]

[1]Biomedical Research Centre, Slovak Academy of Sciences, Bratislava, Slovakia
[2]1st Department of Neurology, Faculty of Medicine, Comenius University, Bratislava, Slovakia

Background: Multiple sclerosis (MS) is an inflammatory disease of the central nervous system leading to demyelinization and neurodegeneration. Impairments in glucose metabolism and signs of insulin resistance were found in non-obese MS patients suggesting a presence of mutual mechanisms responsible for neurodegeneration and metabolic dysfunction. Glucagon-like peptide 1 (GLP-1) is one of the main incretin hormones secreted in response to ingested nutrients. Metabolic functions of GLP-1 in periphery include regulation of glucose-dependent insulin secretion and re-sensitization of insulin signaling leading to improvement of insulin resistance. GLP-1 receptor agonists have been successfully used in Type 2 diabetes treatment. In addition to the metabolic effects, incretins were found to play a role in neurogenesis, synaptic plasticity, neurotransmission and neuromodulation in the central nervous system. GLP-1 analogue dulaglutide was found to modulate the differentiation of Th1/Th17 cells and pathogenicity of antigen presenting Th1 cells in murine model of MS. Thus, GLP-1 analogue treatment has emerged as a potentially viable therapeutic approach for disease modification in MS. Methods and Design: The MSGLP study has been designed as an exploratory, unblinded ,randomized, single center clinical trial in relapsing-remitting MS patients with EDSS score less than five on treatment with natalizumab. The primary goal of MSGLP is to evaluate effects of one year treatment with GLP-1 analogue dulaglutide (Trulicity 0.75 mg subcutaneously once weekly) on chronic axonal damage and neurodegeneration in patients with MS. Secondary goals are aimed at evaluating effects of GLP-1 analogue dulaglutide on insulin resistance and cognitive function in MS. The primary endpoints are (1) brain and grey matter atrophy quantified by MRI volumetry and (2) serum levels of neurofilament L, secondary endpoints include insulin sensitivity indices (ISI Cederholm, ISI Matsuda, HOMA-IR a HOMA-IR2) and Symbol Digit Modalities and Stroop test scores.

Conclusions: The study addresses important knowledge gap about effects of GLP-1 analogue on chronic axonal damage, neurodegeneration, insulin resistance and cognitive function in patients with relapsing-remitting MS in patients and may provide a novel therapeutic target for disease modification.

Poster 16

Buspirone dose-response on forelimb functional recovery in cervical spinal cord injured rats

Rakib Uddin Ahmed, MSc[1]; V. Reggie Edgerton, PhD[2, 3, 4, 5, 6]; Shuai Li[1]; Hui Zhong, MD[2]; Yong-Ping Zheng, PhD[1], and Monzurul Alam, PhD[1]

[1]Department of Biomedical Engineering, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong SAR, China
[2]Department of Integrative Biology and Physiology, University of California, Los Angeles, CA 90095, United States
[3]Brain Research Institute, University of California, Los Angeles, CA 90095, United States[4]Pavlov Institute of Physiology, St. Petersburg 199034, Russia[5]Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan 420006, Russia[6]Departments of Neurosurgery, Neurobiology and Neuroscience, University of California, Los Angeles, CA 90095, United States.

Buspirone, a 5-hydroxytryptamine (5-HT1A) partial agonist for the serotonin receptors, widely used as a neuropsychiatric drug, has also shown potentials for motor function recovery of spinal cord injured. In this study, we investigated the dose

response of buspirone treatment on reaching and grasping function in cervical cord injury rats. 17 adult female Sprague-Dawley rats (230Â±20 grams b.w.) were trained to reach and grasp sugar pellets before a C4 bilateral dorsal column crush injury. After 1 week of recovery, the rats were ranked based on their reaching scores and divided into 3 balanced groups to receive different dosage of buspirone (i.p., 1 dose/day): Low-dose group (1.5 mg/kg b.w.; n=5), Medium-dose group (2.5 mg/kg b.w.; n=6) and High-dose group (3.5 mg/kg b.w.; n=6). Behavior tests (forelimb reaching task and grip strength test) were recorded once per week, within 1 hour of buspirone administration, up to 12 weeks post-injury. After 9 weeks, the drug administration was ceased, and behavior scores were recorded only at week 12 post-injury. Forelimb reaching scores dropped significantly ($p < 0.001$; paired t test) after 1 week post-injury. With buspirone treatment, the reaching scores started to increase in all the rats. However, different dose groups did not show any noticeable difference in their reaching scores until 3 weeks of buspirone treatment (4 weeks post-injury). From week 4 post-injury, the reaching score was found higher in low-dose group rats compared to the other two dose group rats. However, no significant difference was found among the three groups. In addition to low-dose group, at week 4 and 5 post-injury, the reaching score was also found high in medium-dose group, but dropped to high-dose group level from week 6 and thereafter. Grip strength test was found highest in low-dose rats compared to the other dose rats. Cessation of the drug after week 9 post-injury, however, did not affect the muscle strength among all the three dose groups. Our results suggest an optimum dose of buspirone treatment is around 1.5 mg/kg/day b.w. for the facilitation of forelimb functional restoration, and also warns to limit the dose to <3.5 mg/kg/day b.w., which may not have significant beneficial effect on functional restoration after a cervical cord injury.

Poster 17

Cognitive Improvement by Deep Cerebellar Stimulation in a Traumatic Brain Injury Model of Rat

Hugh Chan, PhD; Nicole Mathews; Olivia Hogue, MPH; Cara Wyant; Joshua Hunter; Ronak Kundalia; Darlene Floden, PhD; Andre Machado, MD, PhD; Ken Baker, PhD; Cleveland Clinic

Many traumatic brain injury (TBI) survivors live with persistent chronic cognitive deficits despite contemporary rehabilitation services, underscoring the need for novel treatment. We have previously shown that deep brain stimulation (DBS) of the lateral cerebellar nucleus (LCN) can enhance post-fluid percussion injury motor recovery and increase the expression of markers of long-term potentiation in perilesional cerebral cortex. We hypothesize that a similar beneficial effect will be for cognitive deficits induced by controlled cortical impact (CCI) in rodents through long-term potentiation-based mechanisms.Twenty male Long Evans rats with a DBS macroelectrode in the LCN underwent CCI over medial frontal cortex. After 8 weeks of spontaneous recovery, DBS treatment was applied for 4 weeks, with the Barnes maze and baited Y maze used to evaluate cognitive performance. All animals were euthanized and tissue harvested for further analysis by histology and immunohistochemistry. All animals in both cohorts, with or without LCN DBS generally had the performance on Barnes maze improved. However, by analyzing the variance of performance, only the treated group demonstrated a steady performance while the untreated group displayed a fluctuated performance (p<0.01). There is also a better performance on the baited Y-maze in treated group when compared to that in untreated. The LCN DBS reversed the loss of BDNF+ cells at the perilesional area induced by the CCI lesion in the treated group, accompanying with the reversal of loss of p75NTR+ signal in the same area. Finally, CCI induced the proliferation of c-fos+ cells at the perilesional area which was further increased by the LCN DBS. The current study supports the hypothesis that LCN DBS improves the cognitive deficits by maintaining the health of perilesional neurons and their excitability.

Poster 18

Lessons Learned From Implementing Digital Health Technologies in Clinical Trials

Andrei Pikalov, MD, PhD; Todd Grinnell, BA; Suzanne Giordano, PhD; Thomas Goodin, PhD; Shahin Sanjar, PhD; Elizabeth Marble, BS; Georgia Mitsi, PhD; Sunovion

Several digital health technologies have been incorporated into clinical development programs, including external, wearable, implantable, and ingestible devices/sensors, plus health apps and software accessible via users'electronic devices (e.g. smartphones, tablets, computers). Epilepsy seizure frequency was investigated as an exploratory end point using the Empatica system[TM] a wearable watch device (Embrace) paired with an electronic seizure diary (Empatica Mate smartphone app)[TM] to continuously track and record seizures, in a 31-week, multicenter, prospective, open-label, phase 4 study (NCT03116828) of adjunctive eslicarbazepine acetate in patients with partial-onset seizures. This system, which may potentially reduce biases associated with traditional paper and electronic seizure-recording diaries, was used to assess multiple parameters, including concordance between daily seizure frequency recorded by the patient and the device. Other digital technologies evaluated in respiratory studies will also be presented. One of the greatest potential benefits of digital

technologies is the collection of subjective and/or biological data continuously or at regular intervals outside of the clinic during a patient's daily activities to provide additional efficacy and safety information versus data capture from traditional episodic, timepoint-based clinic visits. Reduced frequency of clinic visits has the potential to expand trial recruitment to patients from wider geographic, socioeconomic, and ethnic backgrounds. Many challenges encountered with digital technologies can be successfully addressed by providing training to staff and patients, ensuring availability of appropriate infrastructure support, and conducting pilot studies before scaling up to larger trials. Overall, digital health technologies have the potential to increase the amount of objective data collected in clinical trials, expand patient access to these trials, and perhaps, ultimately improve clinical outcomes.

Poster 19

Modifying the Pharmacologic Properties of Botulinum Neurotoxin Via Amino Acid Substitution

Philip Band, PhD; Luis Tenezaca; PJ Stewart Hutchinson, PhD; Justin Whitfield; Konstantin Ichtchenko, PhD; CytoDel, Inc.

We report a counter-intuitive approach to improve the safety of botulinum neurotoxin A1 (BoNT/A1). Cyto-014 is a recombinant derivative of BoNT/A1 with a single amino acid substitution (Y366>F) in the light chain (LC) protease active center that reduces protease activity. Cyto-014 was expressed and purified using previously described methods, and compared to wt BoNT/A1. The IP-LD50 potency Unit of Cyto-014 and wt BoNT/A1 was 35 pg and 4.6 pg, respectively. In primary rat cortical cultures, Cyto-014 cleaved SNAP-25 at equipotent Unit doses to wt BoNT/A1. Pharmacologic activity, measured after intra-muscular (IM) injections into the murine gastrocnemius muscle and monitored using the Digital Abduction Score (DAS) assay, found Cyto-014 had an IM-ED50 of 12 pg compared to 0.6 pg for wt BoNT/A1, and an IM-LD50 that was 240 pg compared to 6.22 pg for wt BoNT/A1. Note that although Cyto-014 was 7.6-fold less toxic by the IP route, it was ~25-fold less toxic by the IM route. The safety margin, defined as the IM-LD50/IM-ED50 ratio, was 20 for Cyto-014 compared to 13 for wt BoNT/A1. The Maximum Tolerated Dose (MTD) defined as the dose providing a maximal DAS response without systemic toxicity, was 2.14 LD50 Units for Cyto-014, compared to 0.5 LD50 Units for wt BoNT/A1, a 4-fold improvement. The immunogenicity of Cyto-014 was no different from that of wt BoNT/A1 in mice that received two IM injections over a 5-week period. Sera subsequently collected was negative for the presence of IgG or IgM antibodies reactive to BoNT/A1. Sera from these mice were also negative for BoNT/A1 neutralizing antibodies, as determined using the murine

protection assay. These data illustrate that though Cyto-014 is less potent than wt BoNT/A1, it has improved safety and no detectable immunogenicity. We suggest that the local uptake of Cyto-014 is increased because of its higher molar concentration at equipotent LD50 dose Units, and the decreased toxicity of any BoNT that escapes the injection site.

Poster 20

The NIH Blueprint Neurotherapeutics Network

Charles Cywin, PhD; National Institute of Neurological Diseases and Stroke

The NIH Blueprint Neurotherapeutics Network (BPN) serves as a pipeline between the typical endpoint of NIH-funded research and the beginning of industry drug development. The BPN provides neuroscience researchers with funding for small molecule drug discovery and development through grant funding and access to a full range of industry-style drug development services and expertise while preserving intellectual property for potential licensing.

Program Goals:

Identify and support the best neuroscience projects for translation to the clinic, provide the necessary resources (grants, contracts, consultants, etc.) that are typically lacking in in academic and small business community, de-risk supported projects to the point that industry will invest in them, preserve PI/Institution's Intellectual Property to facilitate licensing. This poster will discuss the background of the program and provide information on applying for funding.

Poster 21

The NINDS Division of Translational Research

Rebecca Roof, PhD; National Institute of Neurological Diseases and Stroke

The mission of the Division of Translational Research (DTR) at the National Institute of Neurological Disorders and Stroke (NINDS) within the National Institutes of Health (NIH) is to accelerate the preclinical discovery and development of new therapeutic interventions for neurological disorders. DTR helps academic and industry researchers create a bridge through which discoveries made in the laboratory lead to new and improved medical treatments. DTR provides several funding opportunities to accelerate preclinical research and technology. These include grants, cooperative agreements, and contracts to academic and industry researchers to advance early-stage therapeutic programs.

In the earlier translational space, the Innovative Grants to Nurture Initial Translational Efforts (IGNITE) Program is a suite of funding opportunity announcements to enable grantees to build on their innovative basic science finding and initiate preclinical discovery and development. The Epilepsy Therapy Screening Program (ETSP) is a compound screening service to help investigators identify therapeutics to ameliorate the epilepsies. Current efforts emphasize unmet medical need including treatments for refractory epilepsies, epileptogenesis and disease progression.

In the later translational space, the NINDS Biomarker Program supports analytical and clinical validation of candidate biomarkers for neurological diseases. The Blueprint Neurotherapeutics Network (BPN) Program is a cooperative agreement program to support small molecule drug discovery and development. These programs are designed to maintain the grantees' intellectual property while providing non-dilutive funding. For biologics development, NINDS has the Cooperative Research to Enable and Advance Translational Enterprises (CREATE Bio). This supports the development of peptides, proteins, oligonucleotides, gene therapies and cell therapies for disorders that fall within the NINDS mission. Lastly, the Translational Neural Devices Program supports the development, validation and verification, and early clinical studies of therapeutic devices.

In addition, DTR has two programs that cut across from early to late: The Countermeasures Against Chemical Threats (CounterACT) Program and the NINDS Small Business Programs (SBIR/STTR). The mission of the NIH CounterACT Program is to understand fundamental mechanisms of toxicity caused by chemical threat agents and the application of this knowledge to develop therapeutics for reducing mortality and morbidity. The SBIR/STTR Program is a congressionally-mandated set-aside program to encourage research and development leading to commercialization.

Please see our website for more details.

Poster 23

The Use of Ultrasonic Micro-Vibration to Improve Insertion of Neural Implants in the Central and Peripheral Nervous Systems

Ryan Clement, PhD; Natasha N. Tirko, PhD; Jenna K. Greaser, BS; Roger B. Bagwell, PhD; Maureen L. Mulvihill, PhD; Actuated Medical

Implanted electrodes are critical interfaces for neuroprosthetic systems. Electrode arrays come in many form-factors to meet functional needs, but all must insert into or near delicate cortical and peripheral neural tissues. Penetrating electrodes offer the most direct and highest resolution interface, but typical forces required to insert them can apply strain and trauma to neural tissues or lead to incomplete device insertion or breakage. Bleeding and inflammation can incite a chronic foreign body response leading to neural cell death, glial scaring, and device failure. These issues have limited the use and lifetime of penetrating arrays in preclinical studies and thwarted their translation to clinical applications such as brain-machine interfacing and peripheral nerve stimulators. Actuated Medical, Inc. is developing a suite of neural implant insertion systems which utilize ultrasonic micro-vibration to reduce the forces necessary to penetrate and insert devices (www.neuralglider.com). The initial system was developed for cortical microwire arrays; data from benchtop, rodent and porcine studies reveal that vibration of arrays reduces insertion force, tissue compression and bleeding during implantation, and does not damage electrodes or neural tissues. Ongoing development has enabled the use of the insertion tool with more complex neural implants (e.g. NeuroNexus probes, polyimide arrays, ultra-fine carbon fiber arrays) for cortical applications in preclinical studies. A complementary system is under development for electrode insertion into peripheral nerves, where epineurium penetration and nerve movement pose additional challenges. Finally, future expansion will target deep brain stimulation probe implantation, with goals to reduce the size, and possibly necessity of, the duratomy and guide cannula required. Ultrasonic micro-vibration safely improves electrode insertion mechanics and could play a valuable role in future neuroprosthesis surgery.

Poster 24

The Rare Disease Cures Accelerator- Data and Analytics Platform: Value for Drug Development in Neuromuscular Diseases

Jane Larkindale, DPhil; Vanessa Boulanger, MSc; Pamela Gavin, MBA; Richard Liwski, BS; Klaus Romero, MD; Michelle Campbell, PhD; Critical Path Institute

The Rare Disease Cures Accelerator Data and Analytics Platform (RDCA-DAP) is an integrated database and analytics hub, designed to help build tools to accelerate drug development across rare diseases. It is being developed by the Critical Path Institute (C-Path) and the National Organization for Rare Disorders (NORD) through a collaborative grant from FDA. The RDCA-DAP promotes sharing of patient-level data and encourages the standardization of prospective data collection, as well as generating advanced data analysis solutions. As clinical trials have been performed in many neuromuscular diseases (NMDs) and there are high quality natural history studies, NMDs are ideal for integration

into this platform, in terms of both needs of current drug development and existence of high-quality data that can inform future studies. C-Path's work in Duchenne Muscular Dystrophy and Friedreich's Ataxia integrated over 1,000 patients' data exemplifying this opportunity. NORD's network of patient groups and natural history studies, including for Spinal Muscular Atrophy with respiratory distress type 1 and Guillain-Barre syndrome, adds an important opportunity to incorporate untapped data sources. Despite many drug targets and technologies, NMD drug development is frequently slowed by the low numbers of patients and the lack of comprehensive quantitative characterization of diseases. This means that design of clinical trials that can reliably evaluate the efficacy and safety of a potential therapy is challenging. Developing a clear understanding of how each disease progresses, as measured by defined outcome measures and/or biomarkers, and what the relevant sources of variability are, will allow development of clinical trial protocols that efficiently determine if a new therapeutic is effective or not. This would accelerate clinical development, make it less expensive, and encourage new companies to develop rare disease drugs. The RDCA-DAP launched in September 2019, and several pilots are underway to demonstrate the utility of the platform.

Poster 25

NIH HEAL Initiative: National Institute of Neurological Disorders and Stroke's Early Phase Pain Investigation Clinical Network (EPPIC-Net)

Jennifer Beierlein, PhD; Rebecca Hommer, MD; Clinton Wright, MD; Barbara I. Karp, MD; Division of Clinical Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health

The NIH HEAL (Helping to End Addiction Long-term) Initiative seeks to focus efforts on advancing scientific solutions for the opioid crisis, improving prevention and treatment of opioid misuse/addiction and enhancing pain management. Within the HEAL Initiative, NINDS has been tasked with identifying, developing, and testing non-addictive pharmacologic and non-pharmacologic therapeutics ("assets") targeted to pain conditions of high unmet need. NINDS established the Early Phase Pain Investigation Clinical Network (EPPIC-Net) to accelerate and enhance clinical testing of novel, non-addictive pain therapies and evaluate new as well as repurposed small molecules, biologics, natural products and devices.

EPPIC-Net will conduct cutting-edge early phase clinical trials of novel pain therapeutics for pain conditions submitted by industry/academic/other partners across the age and pain condition spectrum. The EPPIC-Net infrastructure includes a Clinical Coordinating Center, a Data Coordinating Center, and

12 Specialized Clinical Sites to coordinate and conduct trials that:

- Test new pain treatments in early-stage trials
- Provide proof-of-concept testing of potential biomarkers and new non-addictive treatments
- Validate biomarkers for utility in assessing target engagement or pain outcomes
- Develop and test innovative clinical trial paradigms to engineer adaptive, ever-improving early-phase testing of new pain therapies
- Establish well-characterized pain patient cohorts for clinical trials

The goals of EPPIC-Net are to provide academic and industry investigators with access to a research network with expert infrastructure providing study design, conduct, and analysis at no cost to the asset provider AND, ultimately, to reduce reliance on opioids by accelerating early-phase clinical trials of non-addictive pain therapeutics.

EPPIC-Net is now open to applications from academic and industry researchers. Applications are accepted at any time and reviewed on a rolling basis.

Poster 26

NIH HEAL Initiative: National Institute of Neurological Disorders and Stroke Preclinical Screening Platform for Pain (PSPP)

Smriti Iyengar, PhD; Amir P. Tamiz, PhD; Sarah A. Woller, PhD; National Institute of Neurological Disorders and Stroke

NINDS has been charged with enhancing pain management and accelerating the discovery and development of new non-addictive pain therapeutics as part of the recently launched Helping to End Addiction Long-term (HEAL) Initiative, a trans-agency effort to provide scientific solutions to the opioid crisis. With HEAL support, the NINDS Preclinical Screening Platform for Pain (PSPP) has been set up to accelerate identification of novel approaches to treat both acute and chronic pain conditions, including headache.

The overall goal of the PSPP is to provide researchers from academia and industry, in the US and internationally, an efficient, rigorous, one-stop in vivo screening resource to identify and profile novel therapeutic candidates, including small molecules, biologics, devices and natural products for the treatment of pain. Under NINDS direction, preclinical testing of submitted agents is performed by contract facilities on a blinded and confidential basis at no cost to the PSPP participants. Test candidates are evaluated in a suite of in vivo pain-related assays following in vitro receptor profiling, pharmacokinetic and side-effect profile assessment. Importantly, test candidates are also evaluated in

models of abuse liability. A key feature of the PSPP is the flexibility to continuously acquire and validate innovative new models that more closely represent human pain conditions.

This presentation will elaborate on this novel pain therapeutic discovery and development program and its efforts to engage the drug discovery community.

Poster 27

Informing Natural History and Clinical Trials from Verbatim Reports of >20,000 Parkinson Patients

Ira Shoulson, MD; Lakshmi Arbatti, MS; Connie Marras, MD, PhD; David Standaert, MD, PhD; Caroline Tanner, MD, PhD; Luba Smolensky, MS; Catherine Kopil, PhD; Jamie Hamilton, PhD; Emily Flagg, BA; Monica Javidnia, PhD; Carol Christopher, PhD; Abhishek Hosamath, MS; Andrew Nguyen, PhD; University of Rochester

Purpose: We aimed to analyze the verbatim Patient Reports of Problems (PROP) from Parkinson disease (PD) patients who volunteered to answer in their own words and by priority: (1) What bothers you the most about your PD? and (2) In what way does this problem affect your daily functioning?

Methods: Using natural language processing (NLP), expert clinical curation, and machine learning (ML), we analyzed the verbatim PROP replies of consenting PD patients, 0-10 years since diagnosis, who consented to share their verbatim PROP replies by keyboard entry on the Michael J Fox Foundation (MJFF) FoxInsight.org (FI) online research platform.

Results: By July 2019, 21,649 PD FI participants reported their problems and functional consequences (averaging about four prioritized reports each) that were categorized as motor (about 50% for Tremor, Rigidity, Bradykinesia, Postural Instability) and non-motor (about 50% for Cognition, Sleep, Fatigue, Pain, Mood, Bowel) symptoms. Most frequently reported were the treatment-refractory problems of Postural Instability and Cognition. Postural Instability symptoms were classified further into sub-symptoms of Gait Disorder, Balance, Falling, Posture, and Freezing. Cognition symptoms were classified further into sub-symptoms of Word Finding, Memory, Concentration, Cognitive Slowing, and Confusion. Postural Instability was reported early within 0-3 years since diagnosis, and more common with older age and longer duration of PD. Cognition problems were more frequent with longer duration of PD.

Conclusions: NLP, clinical curation and ML methods showed utility in capturing verbatim-reported motor and non-motor problems. These data and approaches, in turn, enable a patient-reported natural history of PD, clinical trial enrichment, and fit-for-purpose clinical outcome assessments.

Poster 28

Phase 2 BRIGHT (An open-label tolerability and efficacy study of ZYN002 administered as a transdermal gel to children and adolescents with autism spectrum disorder): Baseline Characteristics

Helen Heussler, MD[1,2]; Michael Duhig, MSc [1,2]; Terry Hurst, BS[3]; Carol O'Neill, BA[4]; Wendy Agnese, PharmD[4]; Joseph M. Palumbo, MD[4]

[1] Centre for Clinical Trials in Rare Neurodevelopmental Disorders (CCTRND), Children's Health Queensland, Brisbane, Australia
[2] Centre for Child Health Research, University of Queensland, Brisbane, Australia
[3] Zynerba Pharmaceuticals, Pty., Ltd., Brisbane, Australia
[4] Zynerba Pharmaceuticals, Devon PA, USA

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by difficulties with behaviors, communication and reciprocal social interaction. ZYN002 is a pharmaceutically manufactured transdermal cannabidiol (CBD) gel currently in clinical development for the treatment of behavioral symptoms in ASD. BRIGHT is a 14 week open-label single-center study (ZYN2-CL-030) to evaluate the safety and tolerability in 37 pediatric and adolescent patients diagnosed with ASD. The efficacy assessments include the Aberrant Behavior Checklist (ABC-C), Parent Rated Anxiety Scale - Autism Spectrum Disorder (PRAS-ASD), Autism Impact Measure (AIM), the Children's Sleep Habit Questionnaire (CSHQ), Clinical Global Impression - Severity and Improvement (CGI-S, CGI-I), Autism Parenting Stress Index, and the Qualitative Caregiver Reported Behavioral Problems Survey. The Autism Diagnostic Observation Schedule Second Edition (ADOS-2) was also used to assess the severity of ASD symptoms at baseline. The majority of patients enrolled were male, n=34 (91.9%), the mean age was 9.2 years old (range 3-16 years), and 75.7% were white, while 5.4, 8.1, 10.8% were Aboriginal, Asian, or other, respectively. Ninety-four percent of enrolled patients were categorized in the moderate-to-severe symptom range as guided by the ADOS-2 criteria. Similarly, the mean baseline ABC-C Irritability subscale score was 30.0 (range: 18-41) which further describes the increased severity of the enrolled patient population. In conclusion, this study was enriched for disease severity in order to avoid floor effects on outcome measures, while still enrolling a broad and inclusive patient population with a spectrum of behavioral symptomology and an enduring high unmet need.

References

Heussler H. A phase 1/2, open-label assessment of the safety, tolerability, and efficacy of transdermal cannabidiol (ZYN002) for the treatment of pediatric fragile X syndrome. Journal of Neurodevelopmental Disorders. (2019).

Poster 29

Fragile X Syndrome Diagnosis and Patient Journey: The Caregivers' Perspective

Joseph M. Palumbo, MD[1]; Jeffrey Zhang, PhD[2]; Wendy Agnese, PharmD[1]

[1] Zynerba Pharmaceuticals, Devon PA [2]Princeton Pharmatech, Princeton Junction, NJ

Fragile X syndrome (FXS) is a rare genetic condition characterized by a variety of clinical symptoms, including anxiety (and behaviors associated with anxiety such as social avoidance, irritability, and social withdrawal), deficits in learning and cognition, sleep difficulties, and seizures. A quantitative 30-minute online survey was conducted to further understand the patient journey including diagnosis, and clinical and medical experiences. Participants were caregivers of a child with FXS. The children were 3-16 years old, confirmed full mutation FXS, and experienced social avoidance. Thirty-five caregivers participated in the quantitative assessment. Caregivers were predominantly female (80%), and the mean age was 42.6 years old. The mean age of the children with FXS was 9.1 years, and 74.3% were males. The three reasons caregivers scheduled the initial doctor visit to address FXS symptoms included: issues with speech/motor function, cognitive/intellectual development delays, and social avoidance/social unresponsiveness. The first physician seen was most often the general pediatrician or primary care physician (71.4%). The physician who most commonly diagnosed FXS was the geneticist or neurologist/pediatric neurologist (40.0% and 28.6%, respectively). The average age of the child at time of diagnosis was 3.0 years. Most caregivers rated the FXS symptoms as severe or moderate (85.7%) and 14.3% were mild or unknown. Seventy seven percent of the children were reported to have other co-morbidities, the most common being autism spectrum disorder (65.7%) and attention deficit hyperactivity disorder (25.7%). Caregivers of children with FXS often notice a variety of initial symptoms early and seek healthcare professional help; however, it is not until subsequent physician visits that a formal diagnosis is made. Further research and education is needed to help support early recognition of FXS by various stakeholders throughout the patient journey. Acknowledgements: Research Partnership Inc. for conducting the survey.

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Post-hoc Analysis - An Open-Label Study of Transdermal Cannabidiol (ZYN002) for the Treatment of Fragile X Syndrome in Children and Adolescents: Estimating Health State Utility Scores

Joseph M. Palumbo, MD[1]; Stephen O'Quinn, PharmD[2]; Nancy Tich, PhD[1]; Jeffrey Zhang, PhD[3]; Wendy Agnese, PharmD[1]

[1] Zynerba Pharmaceuticals, Devon PA
[2] Perissos Inc, Wake Forest NC
[3] Princeton Pharmatech, Princeton Junction NJ

Fragile X syndrome (FXS) is a rare genetic condition characterized by a range of developmental, neuropsychiatric, and behavioral symptoms. Due to the severity and spectrum of symptoms, patients and their families are impacted by high clinical, humanistic, and economic burden. ZYN002 is a pharmaceutically manufactured cannabidiol (CBD) gel in clinical development for the treatment of behavioral symptoms associated with FXS. Health state utility index (HUI) is a metric to assess overall health where 0 represents death and 1 represents full health. HUI is commonly considered in clinical and health economic analyses, as it can be used for meaningful comparisons of health status across disease states. For FXS, the Aberrant Behavior Checklist (ABC)-Community utility index (the ABC-UI) scoring algorithm was previously developed by mapping targeted questions from the ABC-CFXS to assess treatment impact on overall health. To further understand the potential therapeutic impact of ZYN002, a post-hoc analysis of study ZYN2-CL-009 was conducted by mapping individual patient-level data from ABC-CFXS questions used in the ABC-UI algorithm. Questions included in the algorithm assessed core symptomatology of FXS: social avoidance, irritability/aggression, socially unresponsive/lethargic, stereotypy, hyperactivity, and inappropriate speech. Twenty patients, ages 6-17 years old were enrolled in the 12 week open-label study. The mean ABC-UI was 0.57 (STD 0.159) at baseline and 0.71 (STD 0.179) end of the study (p=0.003), representing an approximate 40% proportional change. Improvements in the utility index score were observed at the first time-point (4 weeks) (p<.0001). The ABC-UI was correlated to Clinical Global Impression-Severity (CGI-S) (p=0.0017). In this post-hoc analysis, treatment with ZYN002 significantly improved the health state utility index scores in pediatric and adolescent patients with FXS, demonstrating a potential spectrum of benefit of ZYN002.

References
Kerr C. Developing a utility index for the Aberrant Behavior Checklist (ABC-C) for fragile X syndrome. Qual Life Res (2015) 24: 305-314.

Poster 31

Characterization of Ketamine's (2,6)-hydroxynorketamine Metabolites: Pharmacokinetic and Behavioral Considerations for Antidepressant Applications

Jaclyn N. Highland, BS; Patrick J. Morris; Panos Zanos, PhD; Lace M. Riggs, MA; Jacqueline Lovett, MS; Soumita Gosh, PhD; Kylie Konrath, PhD; Amy Q. Wang; Carlos A. Zarate Jr., MD; Craig J. Thomas, PhD; Ruin Moaddel, PhD; Todd D. Gould, MD; University of Maryland Baltimore

Despite numerous available treatments for major depression, most are slow to take effect and ineffective in many patients, highlighting the need for novel and more effective antidepressants. While (R,S)-ketamine (ketamine) has gained attention for rapid-acting antidepressant efficacy in previously treatment-resistant patients, its widespread antidepressant use is limited by adverse effects, abuse potential, and poor oral bioavailability (BA). The ketamine metabolite (2R,6R;2S,6S)-hydroxynorketamine (HNK), and most potently (2R,6R)-HNK, exerts antidepressant-like actions but lacks the adverse effect burden and abuse potential of ketamine in rodent studies. However, several important considerations for the antidepressant utility of HNKs had not previously been evaluated. First, the oral BA and antidepressant efficacy of oral (2R,6R)-HNK had not been studied. Further, while (2R,6R)-HNK and, with lower potency (2S,6S)-HNK, exert antidepressant-relevant actions, the biological activities of two other (2,6)-HNKs, (2R,6S)- and (2S,6R)-HNK, have not been studied; thus, it is possible that they have greater potencies or more favorable pharmacological profiles. We evaluated the oral BA, antidepressant-like behavioral actions, and adverse effect profile of orally administered (2R,6R)-HNK in mice. Additionally, we evaluated the pharmacokinetics and brain penetrance of the four (2,6)-HNKs, and screened a subset for antidepressant-like behavioral effects. (2R,6R)-HNK exhibited favorable oral BA (~50%), which was not improved by an ester prodrug strategy. Oral (2R,6R)-HNK exerted antidepressant-like behavioral actions but not overt adverse effects in mice. All (2,6)-HNKs readily penetrated the brain and were detected in the brain with brain:plasma ratios between 0.6-1.4. Preliminary data suggests that (2R,6S)-HNK may exert antidepressant-like effects at even lower doses than (2R,6R)-HNK, despite lower brain penetrance.