The Edward N. & Della L. Thome Memorial Foundation Awards Program in Alzheimer's Disease Drug Discovery Research
2021 Award Recipient

Joseph Arboleda-Velasquez, M.D., Ph.D.
Assistant Professor
Schepens Eye Research Institute

"Fostering Resistance to Alzheimer's Disease Using Antibodies that Mimic the Effect of the Christchurch Variant in APOE"

Scientific Abstract
We previously reported on the characterization of a subject that resisted cognitive decline for over 30 years despite carrying the PSEN1 E280A mutation known to cause early-onset Alzheimer's. This subject was homozygote for the R136S mutation in APOE3 (Christchurch) and had lower than expected tau pathology in the presence of abundant amyloid pathology. ApoE3 Christchurch protein failed to bind to glycosaminoglycans (GAGs), a carbohydrate known to play critical roles in multiple steps of Alzheimer's pathology including amyloid formation and tau spreading. In a proof of concept experiment, a mouse monoclonal antibody raised against an APOE epitope centered around position R136 effectively blocked ApoE binding to GAGs in vitro and APOE-mediated tau pathology in mouse retinas. We hypothesize that inhibition of APOE-GAG interactions may be an effective therapy to blunt neurodegeneration in Alzheimer's disease. We propose to humanize our lead mouse monoclonal antibody as a first step towards the development of a therapeutic leveraging our discovery of the role of APOE3 Christchurch in the resistance to Alzheimer's disease. We propose the following research aims: Aim 1: To generate a panel of ApoE-GAG inhibitor human monoclonal antibodies (humAbs). Aim 2: To rank order the candidate antibodies using in vitro assays. Aim 3: To test the preclinical efficacy of two lead humAbs in mouse models of tauopathy. Completion of the proposed research is a necessary step towards future work for IND-enabling steps in the process of therapeutic antibody development.

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Michelle Arkin, Ph.D.
T. William and F. J. MacWilliam Distinguished Professor and Chair of Pharmaceutical Chemistry
University Of California San Francisco Foundation

"Pharmacokinetic and Pharmacodynamic Studies of Highly Selective Caspase-6 Inhibitors in AD Models"

Scientific Abstract

Human and animal studies have implicated the protease caspase-6 (aCasp6) in the development of Alzheimer's Disease (AD). We have developed covalent Casp6 inhibitors (SU110 and SU134) that target a noncatalytic cysteine residue in aCasp6. Compounds show low nM potency in iPSC-derived neurons and high brain exposure in pharmacokinetic (PK) studies. Our current goals are to establish PK/pharmacodynamic (PD) relationships in animal models of disease. Accordingly, this 2-year project will accomplish the following aims: Aim 1. Establish biomarkers and activity of SU110 and SU134 in iPSC-derived models of familial AD. Neurons bearing TauV337M mutation express aCasp6 and caspase-cleaved Tau; inhibition of aCasp6 by SU134 reverses cell death and loss of neuronal processes. We hypothesize that mutations associated with AD, including TauP301S and APPV717I, will similarly show time-dependent expression of aCasp6 and cleaved Tau, and reversal of cell damage by treatment with SU110 and SU134. These data will inform in vivo model selection. Aim 2. Measure PK and brain exposure of Casp6 inhibitors in selected mouse model(s). We will evaluate serum and brain concentrations of SU110 and SU134 dosed PO in 5xFAD and/or PS19 mice at 4-, 7-m (c)4 (e)-1 (4 (an)2 e[)-6 (0F)-4 ()2 e[o, (n)-2 (s a)-4 (sso)-8 (c21v- (

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Harvey Cantor, M.D.
Baruj Benacerraf Professor of Immunology
Dana-Farber Cancer Institute

"Development of Engineered Brain-Penetrating Monoclonal Antibody (mAb) Targeting Osteopontin (OPN) for Alzheimer's Disease Therapy"

Scientific Abstract

Recent clinical trials of anti-amyloid-

disappointing results may reflect a therapeutic approach that assumes that all studies indicate that

inert and non-toxic products of microglial processing and compaction. Both are indiscriminately targeted by current therapies.

Marked elevation of the Spp1 gene, encoding Osteopontin (OPN), by microglia is a hallmark of both animal models of AD and the human disease. Genetic deletion of OPN in 5XFAD mice substantially reduces inflammatory microglia and diffuse

the human disease using clinically and neuropathologically characterized brain tissue from AD patients and controls (Mt. Sinai Brain Bank): increasing numbers of OPN-producing microglia from AD patients directly correlate with progressive dementia, according to Clinical Dementia Rating (CDR) scores.

These findings have indicated that microglial OPN drives deposition of toxic ing to neuritic destruction and cognitive impairment. This reflects a two-pronged OPN-dependent mechanism: through a) inhibition of amyloid processing and b) induction of a microglial pro-inflammatory phenotype. These considerations suggest that, in contrast to antibody-based

pathogenic OPN-dependent mechanism that drives cognitive decline in the 5XFAD murine model and human AD brains and 2) to define the potential therapeutic impact of an engineered brain-penetrating antibody that targets OPN in the 5XFAD mouse model.

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Se Hoon Choi, Ph.D.
Assistant Professor of Neurology
Massachusetts General Hospital

"Developing Resilient Drugs Targeting Neurogenesis and BDNF for Alzheimer's Disease"

Scientific Abstract

Alzheimer's disease (AD) destroys brain cells and synapses irreversibly, leading
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proven effective in halting the disease progression. Adult hippocampal neurogenesis (AHN), a relatively novel form of brain plasticity that refers to the birth of new neurons in the adult hippocampus, remains strong in healthy human brain but drops steeply in AD patients. Yet, adult-born neurons are significantly more abundant in non-demented individuals with AD neuropathology. We
previously found that inducing AHN along with elevating brain-derived neurotrophic factor (BDNF) levels provides cognitive benefits in the presence of

natural compounds that increase AHN and BDNF (pro-AHN-BDNF compounds) might have a benefit in AD. The objective of this grant is to test the therapeutic potential of pro-AHN-BDNF compounds that we will screen and identify and that have already been reported from various animal models, using in vitro neurospheres and primary hippocampal cell cultures and in vivo AD mouse models. A successful therapy would ideally both remove the pathological

we will test whether co-treatment of the select pro-AHN-BDNF compounds with
- - -antibody
treatment can have a synergistic effect greater than either treatment alone. Successful completion of this proposal will generate a new therapeutic target for AD using endogenous stem cells. Leveraging the therapeutic potential of stimulating AHN and BDNF could be a new frontier and alternative for preventing or slowing down cognitive decline in AD.

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Carlo Condello, Ph.D.
Assistant Professor of Neurology
University of California San Francisco

"Precision Dosing of CSF1R Inhibitors to Selectively Temper Tauopathy-Activated Microglia as a Novel Alzheimer's Disease Therapy"

Scientific Abstract

Microglia are central to Alzheimer's disease (AD) pathogenesis and have multifaceted roles in neurodegenerative processes. Drugs targeting colony-stimulating factor-

pathology.

Aim 3: Deep molecular phenotyping of drug-resistant microglia and tau-laden neurons in CSF1R inhibitor studies.

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Paul Greer, Ph.D.
Assistant Professor of Molecular Medicine
Eunice Kennedy Shriver Center, University of Massachusetts Medical School

“Identification of Inhibitors etts1]H[illegible]” genes whose mutation is linked to altered susceptibility to AD. Among the most compelling of these newly identified AD-associated genes are members of the Ms4a gene family, whose polymorphisms have repeatedly been shown through genome wide association studies (GWAS) to be strongly and reproducibly linked with AD. In fact, current genetic data suggest that up to 10% of all AD cases may be associated with Ms4a polymorphisms. We have recently generated exciting data showing that deletion of Ms4a genes is sufficient to rescue all behavioral and cellular phenotypes that we have examined in two different mouse models of AD. These results suggest that inhibiting Ms4a gene function is an attractive new avenue to pursue in the development of new candidate AD therapeutic strategies. Here, we propose to use two approaches to identify means of inhibiting Ms4a genes. In the first part of our proposal, we will identify small molecule chemical inhibitors of MS4A proteins using a novel, in vitro assay that we have developed. In parallel, we will take advantage of our expertise using antisense oligonucleotides (ASO) to develop ASOs that effectively inhibit Ms4a genes. Together, the two approaches described here will identify new inhibitors of Ms4a genes that can be advanced as potential therapeutic strategies for treating AD.

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Daniel Lee, Ph.D.
Associate Professor
University of Kentucky

"Nutrient Sensor Modulators as Therapeutics for Alzheimer's Disease"

Scientific Abstract
To date only one disease modifying therapy for Alzheimer's disease (AD) has been approved targeting beta amyloid however treatment modalities for other phenotypes and hallmarks such as tau remain unmet in the clinic. Dysregulation of brain metabolism and slowed protein clearance increases with age and chronic conditions. Amino acid signaling impacts proteostasis but remains largely ignored as an intervention. Nutrient-sensing dysfunction offers a novel entry po

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Chien-liang Lin, Ph.D.
Associate Professor
The Ohio State University

"Restoration of Synapses as a Therapeutic Strategy for Alzheimer's Disease"

Scientific Abstract

Studies indicate that loss of tripartite glutamatergic synapses is the major

glutamatergic synapsesi4 (se(a)4 ()] W)3d (f)2 ()-1 i (fg(n)6 (i)5 ff.2 (T)5 (c)8 (a)4)3 (o l(ti)y) Tm(i)5dve

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Michael Welsh, M.D.
Professor, Internal Medicine
University of Iowa

"Developing Novel Agents that Enhance Energy Metabolism for Alzheimer's Disease"

Scientific Abstract

Alzheimer's disease (AD) is an enormous personal and public health challenge that lacks therapies that prevent progressive neurodegeneration. Identification of decreased glycolysis as a key pathogenic mechanism beginning years before symptom onset suggested that enhancing energy metabolism would be therapeutic.

We discovered that terazosin binds and activates phosphoglycerate kinase 1 (PGK1), the first ATP-generating enzyme in glycolysis. Terazosin increases ATP levels in cultured cells, mouse brain, and in preliminary studies, human brain. Stimulating PGK1 with terazosin also attenuates neurodegeneration in spinal muscular atrophy and Parkinson's disease. Preliminary epidemiologic data suggest that use of terazosin may slow AD progression in humans and may reduce tau aggregation in an AD mouse model.

Although these findings suggest that glycolytic dysfunction may be a common pathway for neurodegeneration and that enhancing PGK1 activity may have

vivo tests in rodents for evaluations of safety and efficacy.

We believe this exciting strategy offers a tremendous opportunity to improve the lives of people with AD.

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Silvia Fossati, Ph.D.
Associate Professor of Pharmacology
Associate Director Alzheimer's Center at Temple
Temple University School of Medicine

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Scientific Abstract
Mitochondria represent the energy source for brain cells, and mitochondrial damage is one of the earliest events in the development of Alzheimer’s disease (AD). Preserving mitochondrial function can be a key strategy to prevent the progression of AD pathology. Carbonic anhydrases (CAs) are a family of enzymes catalyzing the conversion of CO2 to bicarbonate and protons. CA-VA and CA-

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Jie Gao, Ph.D.
Assistant Professor of Neuroscience
The Ohio State University

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Scientific Abstract
ApoE genotype is the strongest genetic risk factor for Alzheimer's disease (AD), and has been shown to independently influence several key factors that drive ™ Š • ‘ ˜ • Ž — ˜ • Ž 1 œ ð ’ d e – 1 Œ • ž • ’ Š — • ¢ 1 • ˜ ’ • 1 û • Ž Ì ™ Ï 1 œ ’ • ’ ˜ — ð 1 • Š ž ˜ ™ Š • ‘ ¢ ð 1 Š — • 1 synaptic dysfunction. In the brain, ApoE functions as a ligand for members of lipoprotein receptor family, including low-density lipoprotein receptor (LDLR), very low-density lipoprotein receptor (VLDLR), and ApoE Receptor 2 (ApoER2). Brain ApoE receptors not only regulate the p08(l)-1.833(i)]TJ -0.0313Tw (A)of

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Dianne Perez, Ph.D.
Professor
Cleveland Clinic Lerner Research Institute

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Scientific Abstract
Alpha1-adrenergic receptors (ARs) rs.912 Tw <0 r l

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Stephen Strittmatter, M.D., Ph.D.
Vincent Coates Professor of Neurology and Neuroscience
Yale School of Medicine

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Scientific Abstract
Disease-modifying therapy for Alzheimer's disease (AD) is a massive and urgent unmet medical need. Genetic and biomarker studies demonstrate that Amyloid-ß (Aß) peptide accumulates early in AD and triggers a decades-long pathophysiology including Tau misfolding and in-

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David Holtzman, M.D.

Development and testing of novel TREM2 - targeted therapeutics

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2017 Award Recipient

Kenneth Kosik, M.D.

Farnesyltransferase inhibitors to Treat Neurofibrillary Pathology of Alzheimer's Disease

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2017 Award Recipient STj E120 0 142 2 688856 7m [.6(1 2.164

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Chien-liang Lin, Ph.D.

Restoration of tripartite glutamaterigic synapse as a therapeutic strategy for Alzheimer's disease

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2017 Award Recipient

Thomas Wisniewski, M.D.

Developing Peptoid Inhibitors to Target the ApTargtorsA ep ŕ ⁄ ˥ ˦ ˦ ˩ TG a ˥ TG

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Awards Program in Alzheimer s Disease Drug Discovery Research
2015 Award R ecipient

Karen Ashe, M.D.

Discovery of Caspase - 2

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2015 Award R ecipient

Yueming Li, Ph.D.

Development of TFEB ettargeted smallmolecules for Alzheimer ' s disease therapy

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2015 Award R ecipient

Development of Novel Targeted Therapy for Alzheimer ' S Disease

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2012 Award Recipient

P. Jeffrey Conn, Ph.D.

I*n vivo characterization of metabotropic glutamate receptor subtype 5 positive allosteric modulators in a mouse model of Alzheimer's disease*

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2012 Award Recipient

Philip De Jager, M.D., Ph.D.

Identification of small molecules that modify CD33 expression

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2012 Award Recipient

Susan Lindquist, Ph.D.

A Yeast Model of Abeta Toxicity for Drug Discovery

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2012 Award Recipient

David Morgan, Ph.D.

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2012 Award Recipient

Luigi Puglielli, M.D., Ph.D.

ATase1/ATase2 inhibitors for the prevention of Alzheimer's disease

ATase1 1