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 ef)-6 (0F)-4 ()2 efo, (n)-2 (s a)-4 (sso)-8 (c21v- (

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2021 Award Recipient

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- † 1 û| ü 1 Š — • ' ‹ ˜ • ' Ž œ 1 ' Š Ÿ Ž 1 › Ž ™ ˜ › • Ž • 1 œ ' • — '
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disappointing results may reflect a therapeutic approach that assumes that all
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inert and non-toxic property(ies) of amyloid-β from 8 to 10 (d23105 2n (a)-1 (tNi)5 (a)4 (c)8 ((i)5 o(n)6 .
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tuOPsd(e)-.12 (s)3 (t)-2 (r)-3 (u)2 cst(o-5 in)1 a cr20.9 ottvre maretTf-2 (h)1 (se)3 ()>TJ-0.0
oroes bf14.9)f-2 (iin)1 d(u)-8 cst(o)-5 in(o)-5 (f)2 (a)-1 mf14
a41 n--

a41 thn-6 og(e)3 nn-6 io-5 cr81 (OPs)8 Ni
nea41 ma130.9 (t(a41 r)96 gee)3 tsr81 (OPs)8 Ni52 (n)TJ-18.8

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2021 Award Recipient

Se Hoon Choi, Ph.D.

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

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

"Precision Dosing of CSF1R Inhibitors to Selectively Temper Tauopathy-
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pathology.

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

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2021 Award Recipient

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

"

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2021 Award Recipient

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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2021 Award Recipient

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

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

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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.

rofessor of Neuroscience
Brown University

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Scientific Abstract
Alzheimer's Disease (AD) is a complex disorder that is devastating for patients, their familie s and, if unchecked, for the medical economies in the developed world. With the recent failure of aducanumab and many other amyloid-d irected therapies, it is clear that novel therapeutic targets must be explored. The hippocampus is one of the earliest and most affected brain regions in AD and its atrophy is a hallmark of disease progression. Importantly, it is now firmly established that adult hippoca mpal neurogenesis (AHN), which plays a major role in learning, memory and mood disorders, occurs throughout li fe in humans and is reduced in AD patients. Thus, promoting AHN could preser ve hippocampal function and counter AD. The accumulation of negative signals that degrade the neurogenic niche are thought to be important contributors to the reduction in newborn n eurons in aging and AD. BMPs negatively regulate neurogenesis and are upregulated in AD and APP transgeni c mice. We recently reported that full length Mu SK is a BMP co-receptor that augments and shapes BMP signaling. We have developed a mouse model that selectively perturbs Mu SK-BMP signaling and thus re duces BMP 'drive'. Remarkably, these mice show enhanced AHN and improved cognition. In the proposed we will also ini tiate development of a candidate therapeutic th at could lead to a readily translatable agent to promote AHN and improve cognition in AD patients.

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2019 Award Recipient

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 CO_2 to bicarbonate and protons. CA-VA and CA-

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2019 Award Recipient

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
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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 i(6T)7.08l(n)-2adaptohyaibo8ayTincl0O8g77au misfolding and in--c6.1am(c)1.165(e)2.917(s)]Tau

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2017Award Recipient

David Holtzman, M.D.
Andrew B. and Gretchen P. Jones Professor and Chairman of the Department of Neurology
Washington University in St. Louis

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The high-profile failure of numerous amyloid-t argeting therapies in tri als of symptomatic AD patients i ndicates the needto treat individuals in the early, pre-clinical phase of t

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2017 Award Recipient

Kenneth Kosik, M.D.
Harriman Professor of Neuroscience Research
University of Californi a Santa Barbara

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The aims proposed herewill lay the groundwork for   advancing the very
promising preliminary data toward a clinical trail to treat the primary
tauopathies. Farnesyl transferase inhibition using the drug lonafar nib via a
target identified as the farnesylated protein Rhes, amember of the Ras-GTPase
family has stri king effects on tau pathology.
Inhibition of Rhes can prevent behavi oral changes, brain shrinkage, frainshw (ia)Tj clus 0 -0.0480.26 t

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2017 Award Recipient

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Program in Alzheimer's Disease Drug Discovery Research
2017 Award Recipient

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

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Mounting e vidence indicates that glutamate dyshomeostasis plays a crucial role in the pathogenesis of Alzheimer's disease (AD). Glutamate transporter EAAT2 plays a critical role in the homeostatic regulation of extracellular glutamate levels. EAAT2 also plays an essential role in cognitive memory functions. However, loss of EAAT2 protein and function a re commonly found in AD patients and are an early event in disease pathology. We have discovered a series of novel compounds that can increase EAAT2 protein expression via a novel translational activation mechanism. We have demonstrated that our compounds can significantly improve cognitive functions and restore synaptic integrity in both APP a nd tau mouse models of AD. This project is currently at the clinical candidate selection phase. The goal of this study is to determine a clinical candidate and then move forward to IND-e nabling studies.

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2017 Award Recipient

Thomas Wisniewski, M.D.
Lulu P. and David J. Levidow Professor of Neurology;Professor of Neurology,
Pathology and Psychiatry
New York University School of Medicine

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Edward N. and Della L. Thome Memorial Foundation, Bank of America, N.A. Trustee,
Awards Program in Alzheimer's Disease Drug Discovery Research
2015 Award Recipient

Karen Ashe, M.D.
Chair, Neurology and Neuroscience, University of Minnesota Medical School

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Yueming Li, Ph.D.
Associate Member/Professor, Memorial Sloan-Kettering Cancer Center

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The overall objective of this proposal is to develop small molecules that promote TFEB-
mediated clearance of misfol2(s)i.35 Td [(6 0.003 Tw [(5TJ 0u.004 Tc -0.001 Tw -1.19 -6.9[(K)-3(etp)2

Edward N. and Della L. Thome Memorial Foundation, Bank of America, N.A. Trustee,

Professor of Medicine, Beth Israel Deaconess MedicalCenter

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Prevalence of Alzheimer's disease (AD) may quadruple worldwide by 2050, but
effective treatment is not available. Tauopathy made of hyperphosphorylated tau is one
hallmark lesion in A D. Immunization against tauopathy epitopes shows promising
efficacy in mouse models. Tauopathy correlates well w ith m emory decline in AD and is
also a defining feature of other tauopathies, notably chronic tr aumatic e

P. Jeffrey Conn, Ph.D.

Lee E. Limbird Professor of Pharmacology; Director, Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center

In vivo characterization of metabotropic glutamate receptor subtype 5 positive allosteric in a mouse model of Alzheimer's disease

Alzheimer disease (AD) is the most common form of dementia and is characterized by the progressive decline in cognitive function, with the primary deficits being hippocampal, mediated learning and memory loss. Recent studies suggest the involvement of glutamate in the pathology of the disease, as levels are decreased in the hippocampus of AD patients. Glutamate modulates excitatory postsynaptic currents via metabotropic glutamate receptors (mGlus). mGlu5 is the most highly expressed mGlu in the hippocampus and a close signaling partner of the N,Methyl,D,aspartate receptor (NMDAR). The NMDAR is critical in regulating hippocampal synaptic plasticity and essential for hippocampal,dependent cognitive function. Therefore, increased activation of mGlu5 offers an exciting new therapeutic strategy to enhance cognitive function in patients suffering from AD. Recently, our group has developed a highly potent, selective series of mGlu5 positive allosteric modulators (PAMs) with enhanced pharmacokinetic properties for in vivo studies, providing an unprecedented opportunity to evaluate the potential of selective potentiation of mGlu5 as a novel target for the treatment of symptoms associated with AD. Unlik Td <0231>Tj /TT1 s1 Tf<0231>Tj /TT1 1 Tf 4.918 0 Td (Tf 0om 04 TpT1 1 T3

Philip De Jager, M.D., Ph.D.
Associate Professor
Harvard Medical School

dentification of small molecules that modify CD33 expression

With the discovery and validation of Alzheimer's disease (AD) susceptibility loci, we now have
AD risk factors that give insights into the earliest pathophysiological processes of AD.
Specifically, recent genome-wide studies have identified nine non-APOE AD susceptibility loci:
ABCA7, BIN1, CD2AP, CD33, CLU, CR1, EPHA1, MS4A1

Edward N. and Della L. Thome Memorial

Susan Lindquist, Ph.D.
Member, Whitehead Institute
Full Professor of Biology, Whitehead Institute for Biomedical Research

A Yeast Model of Toxicity for Drug Discovery

The Abeta peptide is a central player in Alzheimer's Disease (AD). Abeta is processed from the full length Amyloid Precursor Protein and populates large plaques throughout the brain. However, smaller oligomeric species are widely believed to cause cell death. Unfortunately, efforts to reduce Abeta processing or promoting clearance have largely failed. We have thus created a much simpler model of Abeta toxicity for unbiased phenotypic screens free of prejudice about mechanism. To this end, we use the budding yeast, Saccharomyces cerevisiae, to capture agents that reduced Abeta toxicity. Though lacking the complexities of a nervous system, yeast offer nearly all of the conserved cellular pathways involved in most aspects of basic eukaryotic cell biology, including the sophisticated protein homeostasis mechanisms that cope with the cellular stresses imposed by toxic neurodegenerative disease proteins. In the yeast model of Abeta toxicity, the peptide is targeted to the endoplasmic reticulum and samples the secretory pathway. A genetic screen against Abeta toxicity identified the yeast homolog of PICALM, a risk factor for AD in humans. We validated genetic modifiers in both a C. elegans model and an Abeta oligomer assay in rat neuronal cultures. For this proposal, we have one completed and one ongoing phenotypic drug screen for compounds that combat Abeta toxicity. Importantly, we identified the AD-relevant compound clioquinol (CQ), which rescues Aβ toxicity and cognition in a mouse model of AD. A close derivative of this compound has shown promise in early clinical trials. Here, we propose to enter the compounds that reduce Abeta toxicity into a pipeline of secondary screens, neuronal assays, and medicinal chemistry. We will

Edward N. and Della L. Thome Memorial Foundation, Bank of America, N.A. Trustee,
Awards Program in Alzheimer's Disease Drug Discovery Research
2012 Award Recipient

David Morgan, Ph.D.
Distinguished Professor and Executive Director
University of South Florida College of Medicine

Luigi Puglielli, M.D., Ph.D.
Associate Professor
University of Wisconsin, Madison

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

Our group has identified a novel form of post-translational regulation that affects both levels and activity of BACE1. Specifically, we discovered that nascent BACE1 is transiently acetylated in the lumen of the ER by two acetyltransferases, which we named ATase1 and ATase2. The acetylated intermediates of nascent BACE1 are able to complete is ATase4 j/C2_1 1 Tf 0 Tc 1.393 0 Td <02 Tc