Alzheimer's Disease Preclinical Landscape - DRAFT

Organization Name	Project Leader	Project Title	OniX Summary
DARTMOUTH COLLEGE	SENTMAN, CHARLES L.	Immunomodulatory and behavioral effects of CAR T regulatory cell therapy for Alzheimer's Disease".	**Research Question:** Can T regulatory cells (Tregs) engineered to target amyloid-beta (Aβ) improve cognitive function in a murine Alzheimer's disease model? **Stage:** In vivo with animals (using 5xFAD B6 mice, a murine AD model). **Methods:** The study will investigate the effects of Tregs engineered to express chimeric antigen receptors (CARs) specific to Aβ. **Drug Development:** This research is exploring a novel therapeutic approach and is not developing a specific drug at this stage. The data will be used to evaluate the potential of CAR-Tregs as a future treatment for Alzheimer's disease.
NATIONAL INSTITUTE ON AGING	GREIG, NIGEL H.	Alzheimer's disease drug development	**Research Question:** Can targeting TNF with a new library of thalidomide analogs mitigate neuroinflammation and Alzheimer's disease progression? **Stage:** Not directly mentioned in the abstract, but likely in vivo with animals (based on mention of mouse models). **Methods:** • The study will evaluate a library of novel thalidomide analogs for their ability to lower TNF levels. • They will assess the effects of these analogs on neuroinflammation, neuronal loss, and behavioral deficits in mouse models of AD. **Drug Development:** This research is developing a new class of drugs (thalidomide analogs) that target TNF to treat Alzheimer's disease.
MAYO CLINIC JACKSONVILLE	LI, YONGHE	Discovery of apoE4 modulators for Alzheimer's disease therapy	**Research Question:** Can small molecule compounds be identified that reduce apolipoprotein E (APOE4) levels and/or aggregation to treat Alzheimer's disease (AD)? **Stage:** In vitro with human induced pluripotent stem cells (iPSCs)-derived cerebral organoids.

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			Methods: • Develop and utilize a high-throughput screening (HTS) assay to identify candidate molecules. • Evaluate the potency and mechanisms of action (MOA) of candidate molecules in cell-based assays and human iPSC-derived cellular models. • Perform medicinal chemistry to optimize lead compounds for potency and efficacy. • Assess the therapeutic efficacy of the most promising compounds in 3D human cerebral organoid models. **Drug Development:** This research aims to identify novel drug leads that target apoE4 for the treatment of AD. The project is focused on in vitro and cellular studies, but promising compounds will be evaluated for their potential for future preclinical animal studies.
DUKE UNIVERSITY	LA SPADA, ALBERT R	Molecular genetic regulation of autophagy in health and neurodegenerative disease	**Research Question:** Can an antisense oligonucleotide (ASO) targeting MAP4K3 improve Alzheimer's disease (AD) by enhancing autophagy? **Stage:** In vivo with animals (using a P301S tau x ApoE4 knock-in mouse model) and in vitro with neurons derived from late-onset AD patients. **Methods:** • The study will investigate the effects of an ASO targeting MAP4K3 on AD phenotypes in a mouse model. • They will also assess the effects on neurons derived from AD patients. **Drug Development:** This research is developing a new therapeutic approach using an ASO to target MAP4K3 for the treatment of AD. The project utilizes established ASO technology with the potential for future clinical development if successful in these preclinical stages.
UNIVERSITY OF COLORADO DENVER	ECKEL, ROBERT H	Microglial Lipoprotein Lipase; a novel	**Research Question:**

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		therapeutic Target for Alzheimer's disease	Can activating lipoprotein lipase (LPL) in microglia with NO-1886 improve Alzheimer's disease (AD) by enhancing clearance of amyloid-beta (Aβ) and ApoE-containing lipoproteins? **Stage:** In vivo with animals (using a 5XFAD mouse model of AD). **Methods:** • The study will investigate the effects of NO-1886, an LPL activator, on AD progression in a mouse model. • They will assess biochemical and behavioral changes in the mice. **Drug Development:** This research is exploring a novel therapeutic approach targeting LPL in microglia for the treatment of AD. The project is focused on preclinical studies using an activator drug (NO-1886), but the findings aim to inform the development of future AD treatments.
NATIONAL INSTITUTE ON AGING	KAPOGIANNIS, DIMITRIOS	Clinical and biomarker studies in Alzheimer's disease and related disorders	**Research question:** This abstract does not focus on a single research question, but rather highlights the application of **Exosome biomarkers** and **Magnetic Resonance Spectroscopy (MRS)** for various neurological and psychiatric diseases, including Alzheimer's Disease (AD). **Stage:** The research is in multiple stages, including: • Retrospective analysis of existing samples from large cohorts. • Longitudinal studies following participants over time. • Clinical trials of interventions for AD and other diseases. **Methods:** • **Exosome biomarker analysis:** Isolating neuronal and astrocytic exosomes from blood samples and measuring levels of various proteins. • **Magnetic Resonance Spectroscopy (MRS):** Measuring brain metabolites and neurotransmitters using a special MRI technique. **Drug development:**

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			This research is not directly developing drugs, but is focused on developing and validating biomarkers that can be used to assess disease progression, treatment response, and potentially identify preclinical AD.
UNIVERSITY OF COLORADO DENVER	DOOLING, BREANNA	Individual Predoctoral Fellowship	**Research Question:** • How does the APOE4 genotype contribute to the development of Alzheimer's disease (AD) in people with Down syndrome (DS)? • Can small molecule inhibitors targeting apoE or amyloid beta (Aβ) be used to treat DS-AD? **Stage:** In vitro with human induced pluripotent stem cell (hiPSC)-based models of DS-AD. **Methods:** • Develop hiPSC models of DS-AD carrying the APOE4 genotype. • Generate various human neural cell types and cerebral organoids (COs) from the hiPSCs. • Evaluate the effects of APOE4 on these DS-AD models. • Test the efficacy of small molecule drugs that inhibit apoE and/or Aβ fibrilization in the CO model system. **Drug Development:** This research aims to identify therapeutic targets by investigating the role of APOE4 in DS-AD. The project utilizes hiPSC models to assess the potential of existing small molecule drugs for treating DS-AD.
WASHINGTON UNIVERSITY	CHAND, GANESH	Characterizing Alzheimer's disease molecular and anatomical imaging markers and their relationships with cognition and genetics using machine learning	**Research Question:** This research question is not focused on a single question, but rather aims to understand the relationships between various factors in Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI). Here are the specific relationships they aim to investigate: • How do in vivo amyloid-beta, tau, and neurodegeneration relate to cognitive, clinical, and genetic markers in AD/MCI patients? • How does the regional distribution of amyloid-beta, tau, and neurodegeneration on brain scans relate to cognitive and clinical markers in AD/MCI patients?

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			• Are there subgroups of AD/MCI patients with distinct patterns of amyloid-beta, tau, and neurodegeneration?
			• How do these potential subgroups differ in terms of cognition and genetics?
			Stage:
			In silico, using existing patient data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and Washington University's Knight Alzheimer Disease Research Center (Knight ADRC).
			Methods:
			• Machine learning analysis of patient data, including:
			  ○ In-vivo amyloid-beta and tau PET scans
			  ○ Structural magnetic resonance imaging (sMRI) scans
			  ○ Cognitive test scores (Mini-mental state examination)
			  ○ Clinical assessments (CDR-SB and CDR)
			  ○ Genetic data (polygenic risk scores and APOE)
			Drug Development:
			This research is not directly developing drugs, but focuses on using machine learning to improve understanding of AD/MCI heterogeneity. This improved understanding may inform future drug development efforts by identifying more precise targets and subgroups of patients.

UNIVERSITY OF TENNESSEE HEALTH SCI CTR	VAITHIANATHAN, THIRUMALINI	Dynamics of calcium signals control neurotransmitter release in retinal ribbon synapses.	**Research Question:**
			How do Alzheimer's disease (AD) histopathology markers in the retina contribute to visual impairment?
			Stage:
			In vivo with adult zebrafish treated with okadaic acid (OKA) - a model that replicates AD hallmarks and memory deficiencies.
			Methods:
			• Utilize a combination of techniques including:
			  ○ Fluorescence imaging
			  ○ Electrophysiology
			  ○ Computational modeling
			  ○ Electron microscopy
			  ○ Pharmacological tools

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			• Analyze synaptic vesicle dynamics and mitochondrial function in retinal bipolar cells of the zebrafish model. • Investigate calcium signaling at ribbon synapses in the OKA-treated zebrafish. **Drug Development:** This research is not directly developing drugs, but focuses on understanding the mechanisms of visual impairment in AD. By understanding how AD pathology affects the retina, this research may inform future therapeutic development for AD.

COLUMBIA UNIV NEW YORK MORNINGSIDE	WELLMAN, STEVEN	Deciphering the Role of Noradrenergic Receptors during Neuromodulation in Alzheimer's Disease	**Research Question:**
			How does stimulation of the locus coeruleus (LC) and subsequent norepinephrine (NE) release improve Alzheimer's disease (AD) pathology and cognitive function? This research will investigate the specific cell types and receptor subtypes involved in this therapeutic effect.
			Stage:
			In vivo with two different rodent models of AD.
			Methods:
			• Long-term stimulation of the locus coeruleus (LC).
			• Assessment of:
			  ○ Neuroinflammation
			  ○ Amyloid/tau burden
			  ○ Cognitive impairment
			• Genetic editing to interfere with specific noradrenergic receptor subtypes in astrocytes and microglia.
			• Single-cell RNA sequencing to assess neuroinflammatory profiles.
			• Two-photon microscopy to track morphological and functional changes.
			• Electrophysiology to measure changes in neuronal activity.
			• Behavioral training to assess cognitive performance.
			Drug Development:
			This research is not directly developing drugs, but investigates the mechanisms by which LC stimulation improves AD. This knowledge

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			may inform the development of future neuromodulatory drugs or devices for AD therapy.
NOVORON BIOSCIENCE, INC.	STILES, TRAVIS LEE	A novel approach to restricting the spread of neurofibrillary tau	**Research Question:** Can a drug targeting LRP1, called NOVO-118, slow the progression of Alzheimer's disease (AD) by restricting the spread of tau protein in the brain? **Stage:** In vivo with rodent models. **Methods:** • Evaluate the ability of NOVO-118 to restrict tau spread in the rodent brain. • Assess two aspects: 1. Proof of concept: Does NOVO-118 effectively reduce tau spread? 2. Translational feasibility: Can the drug be delivered effectively and show benefit in a way that is relevant to clinical use in humans (considering factors like route of administration)? **Drug Development:** This research is directly developing a new drug (NOVO-118) that targets LRP1 to treat AD. The project is focused on preclinical studies in animals to assess proof of concept and translational feasibility.
HARVARD MEDICAL SCHOOL	AUGUR, ZACHARY MARK	Selective neuronal autophagy in phosphorylated tau degradation and Alzheimer's disease	**Research Question:** • How do deficiencies in protein degradation systems (autophagy and UPS) contribute to tau accumulation in Alzheimer's disease (AD)? • Can modulation of autophagy adaptor protein OPTN and chaperone protein BAG3 be used to improve tau clearance and neuronal function in AD? **Stage:** In vitro with human induced pluripotent stem cell (iPSC)-derived neuronal system (iNs) from the ROSMAP cohort. **Methods:** • Utilize iNs representing a spectrum of late-onset AD.

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			• Measure:
			  ○ Basal autophagic flux and UPS capacity.
			  ○ Levels of various tau species and proteins involved in aggrephagy.
			  ○ Neuronal firing activity.
			• Investigate the effects of:
			  ○ Brain extract containing neurotoxic proteins on tau levels and neuronal function.
			  ○ Modulating OPTN and BAG3 expression on tau accumulation, neuronal firing, and protein turnover.
			Drug Development:
			This research is not directly developing drugs, but focuses on understanding the role of protein degradation systems in tau clearance. By identifying mechanisms involving OPTN and BAG3, this research may inform the development of future therapeutic strategies for AD.

UNIVERSITY OF COLORADO DENVER	JOHNSON, NOAH RAY	Investigating and targeting apolipoprotein E4 in Down syndrome-associated Alzheimer's disease	**Research Question:** • How does apoE4, specifically its interaction with Aβ, contribute to Alzheimer's disease (AD) in people with Down syndrome (DS)? • Can previously identified small molecules that inhibit apoE4-Aβ interaction be used to prevent AD in DS? **Stage:** • In vitro using human iPSC-derived cerebral organoid (CO) models of DS and AD. • In vivo using a new mouse model of DS expressing human APOE4. **Methods:** • Utilize iPSC-derived CO models to study apoE-induced AD phenotypes. • Evaluate the ability of candidate apoE inhibitors to block AD development in the DS CO models. • Develop a new mouse model of DS with human APOE4 expression.

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			• Assess the ability of the same apoE inhibitors to prevent cognitive decline, cerebrovascular damage, and other AD-related pathologies in the DS mouse model. **Drug Development:** This research directly aims to develop new therapies for AD in DS. The project focuses on repurposing existing drugs that inhibit apoE4-Aβ interaction and have already been tested for safety in humans. They will investigate the effectiveness of these drugs in both human cell models and a new mouse model of DS-AD.

UNIVERSITY OF FLORIDA	ZHAO, JINYING	Brain lipids and AD	**Research Question:**
			• What is the role of lipid accumulation in Alzheimer's disease (AD) pathology?
			• Can a comprehensive analysis of brain lipids identify specific molecules associated with AD and cognitive decline?
			• Can this research provide insights into potential therapeutic targets for AD by regulating lipid metabolism?
			Stage:
			In silico, using existing data from a large-scale epidemiological study (Religious Orders Study and Rush Memory and Aging Project, ROSMAP).
			Methods:
			• Analyze brain tissue samples from 1,450 ROSMAP participants.
			• Utilize a mass spectrometry platform (Metabolon's Complex Lipid Panel) to identify and quantify a wide range of lipid species in the samples.
			• Correlate brain lipid profiles with:
			  ○ Clinical diagnoses of AD and dementia phenotypes.
			  ○ Existing data on neuropathology (amyloid-beta, tau tangles).
			  ○ Other omics data (genomics, epigenomics, transcriptomics) collected from the ROSMAP participants.
			Drug Development:

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			This research is not directly developing drugs, but focuses on understanding the role of lipid accumulation in AD. By identifying specific lipid species associated with AD, this project may inform the development of future therapies targeting lipid metabolism for AD prevention or treatment.

ST. JOSEPH'S HOSPITAL AND MEDICAL CENTER	MUFSON, ELLIOTT JAY	Default mode network dysfunction in Down Syndrome	**Research Question:**
			How does tau pathology contribute to dementia in Down syndrome (DS), specifically focusing on the vulnerability of neurons in the frontal cortex (FC) and precuneus (PreC)?
			Stage:
			In vitro, using post-mortem brain tissue samples from people with DS with and without dementia.
			Methods:
			• Analyze brain tissue samples from FC and PreC regions.
			• Investigate:
			  ○ Tau pathology in pyramidal neurons.
			  ○ Differences in gene expression between DS with and without dementia.
			  ○ Defects in splicing proteins associated with tau processing.
			• Utilize:
			  ○ Splicing antibodies to track tau progression.
			  ○ Single-cell microarray and RNA transcriptomics to analyze gene expression.
			  ○ Functional gene pathway analysis to understand the biological processes affected.
			Drug Development:
			This research is not directly developing drugs, but focuses on understanding the mechanisms of tau-related dementia in DS. By identifying the molecular pathways involved, this project may inform the development of future therapies to prevent dementia in DS, potentially with applications to AD as well.

TEXAS BIOMEDICAL	MOHAN, MAHESH	Epigenetic mechanisms underlying cannabinoid	**Research Question:**

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RESEARCH INSTITUTE		modulation of neuroinflammation in HIV/SIV infection-supplement	• Can chronic, low-dose cannabinoid treatment reduce neuroinflammation and improve cognitive function in HIV-infected individuals at risk of Alzheimer's disease (AD) and HIV-associated neurocognitive disorder (HAND)?
			Stage:
			In vivo with SIV-infected rhesus macaques.
			Methods:
			• Analyze the effects of chronic cannabinoid treatment on:
			  ○ Proinflammatory gene expression in the basal ganglia.
			  ○ Plasma concentrations of indole-3-propionate (a metabolite with anti-inflammatory properties).
			  ○ Neurocognitive function.
			  ○ Levels of proinflammatory cytokines and other markers in blood and cerebrospinal fluid.
			  ○ Microglial activation (using PET/CT imaging).
			• Utilize spatial transcriptomics to understand how amyloid plaques affect gene expression in surrounding brain cells.
			• Investigate the effects of combining cannabinoid treatment with anti-retroviral therapy (cART).
			Drug Development:
			This research investigates the therapeutic potential of chronic, low-dose cannabinoids for reducing neuroinflammation and improving cognitive function in individuals with HIV at risk of AD and HAND.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	ENGLAND, PAMELA MICHAEL	Investigating the effect of Nurr1 ligands in Alzheimer's Disease models	**Research Question:** Can novel Nurr1 ligand drugs, specifically those that directly activate the Nurr1 receptor, be used to treat Alzheimer's disease (AD) by: • Reducing oxidative stress? • Inhibiting neuroinflammation? • Regulating amyloid-beta (Aβ) fibril formation? • Preventing tau protein hyperphosphorylation and aggregation? **Stage:** In vitro using cells treated with amyloid peptides and tau fibrils. **Methods:**

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			• Evaluate the effects of Nurr1 ligands on the expression of genes involved in:
			  ○ Oxidative stress response.
			  ○ Inflammatory signaling.
			• Investigate the effects of Nurr1 ligands on:
			  ○ Aβ fibril formation and secretion.
			  ○ Tau protein hyperphosphorylation and aggregation.
			Drug Development:
			This research directly aims to develop new AD therapeutics by investigating novel Nurr1 ligand drugs. These ligands activate the Nurr1 receptor, which in turn regulates cellular processes relevant to AD pathology.

UNIVERSITY OF CALIFORNIA AT DAVIS	SEKER, ERKIN	Interplay of Neuroinflammation and Tau Transport in a Microfluidic Primary Neural Cell Tri-Culture Model	**Research Question:**
			• How do neuroinflammation and abnormal protein transport contribute to Alzheimer's disease (AD) progression?
			• Specifically, how does amyloid-beta (Aβ) affect the spread of phosphorylated tau protein in the brain?
			Stage:
			In vitro using a microfluidic platform with a tri-culture (neurons, astrocytes, microglia) rat model of neuroinflammation.
			Methods:
			• Utilize a microfluidic platform with separate chambers connected by microchannels to mimic neuronal connections.
			• Create a tri-culture model with primary neurons, astrocytes, and microglia.
			• Investigate the effects of:
			  ○ Aβ and phosphorylated tau expression on neuroinflammation in the tri-culture model.
			  ○ Aβ addition vs Aβ-triggered neuroinflammation on tau protein propagation along axons connecting the microfluidic chambers.
			Drug Development:
			This research is not directly developing drugs, but focuses on understanding the mechanisms of how neuroinflammation and abnormal

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			protein transport worsen AD. By identifying the interplay between Aβ, tau propagation, and neuroinflammation, this project may inform the development of future therapeutic targets.

AUGUSTA UNIVERSITY	BRANN, DARRELL W	Mechanisms of Estrogen Signaling and Neuroprotection	**Research Question:**
			• How does surgical menopause increase the risk of cognitive decline and dementia?
			Stage:
			• In vitro and in vivo with animals.
			  ○ In vitro using human brain tissue samples from deceased women.
			  ○ In vivo using a forebrain-specific PELP1 knockout (KO) mouse model.
			Methods:
			• Investigate the role of 17β-estradiol (E2) loss after surgical menopause on:
			  ○ Hemoglobin-alpha (Hb-α) levels in the forebrain (Aim 1).
			  ○ Forebrain hypoxia, neuroinflammation, and oxidative stress (Aims 1 & 2).
			  ○ Amyloid-beta (Aβ) processing, tau phosphorylation, and cognitive function (Aim 2).
			• Analyze relationships between Hb-α expression, AD pathology, and cognitive function in human brain samples from women with and without surgical menopause (Aim 3).
			Drug Development:
			This research does not directly develop drugs, but focuses on understanding the mechanisms by which E2 loss after menopause increases the risk of dementia. By identifying the role of Hb-α and PELP1 in forebrain health, this project may inform the development of future therapeutic targets to protect the brain after menopause.