Tauopathies Preclinical Landscape - DRAFT

Organization Name	Contact PI / Project Leader	Project Title	OniX Summary
UNIVERSITY OF IOWA	LIU, GUANGHAO	Tau-Fyn interaction in normal and diseased states of the brain	**Research question**: Does the interaction between Fyn and Tau protein contribute to neurodegeneration in Frontotemporal dementia linked to chromosome 17 (FTDP-17)? **Stage**: Animal models (mice) using genetic manipulation and viral vector injection. **Methods**: • Create a double knockout mouse lacking both Fyn and Tau proteins. • Inject a virus carrying the mutant Tau gene (TauP301L) into the brains of these mice and control groups. • Analyze behavior, brain biochemistry, and tissue samples to compare the effects of Tau pathology with and without Fyn. **Drug development:** While not the main focus, understanding the role of Fyn-Tau interaction might lead to future therapeutic development for slowing or halting neurodegeneration.
Columbia University Irving Medical Center	Joseph B. Rayman	Development of Small Molecule Inhibitors of Tau Oligomerization	**Research question:** Can we develop new drugs that block the formation of oligomeric tau protein to treat Progressive Supranuclear Palsy (PSP) and other tauopathies? **Scientific background:** • Tauopathies are neurodegenerative diseases characterized by the abnormal accumulation of tau protein in the brain. • Oligomeric tau, a specific form of tau, is believed to be particularly damaging to neurons. • Currently, there are no effective drugs targeting oligomeric tau for treating tauopathies like PSP. **Previous research by this team:** • They designed compounds that block oligomeric tau formation in mouse models of neurodegenerative disease. • These compounds prevented neuronal loss and improved cognitive and motor function in the mice. **Current project goals:** • Expand the range of chemical structures with potential anti-tau activity beyond the initial successful compounds.

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			• Use established screening methods to identify new compounds that prevent tau oligomerization. • Develop the most promising new compounds as potential drug candidates for advanced preclinical testing and potentially human clinical trials. **Significance:** • PSP and other tauopathies currently have no disease-modifying treatments available. • This research aims to develop first-in-class drugs targeting oligomeric tau, offering a novel approach to treating these diseases. • By expanding their existing research, they hope to translate their discoveries into effective therapies for patients.

J. DAVID GLADSTONE INSTITUTES	MUCKE, LENNART	Mouse Models with Regulatable Cell Type-specific Expression of Anti-Tau shRNAs	**Research question:**
			• How does Tau reduction in adult brains affect Alzheimer's disease (AD) pathology and epilepsy in animal models?
			• In which specific brain regions and cell types is Tau reduction most effective?
			Stage: Animal models (mice) using viral vectors and transgenic manipulation.
			Methods:
			• Develop methods to reduce Tau levels in the brains of adult mice using:
			  ○ Viral vectors expressing anti-Tau molecules (shRNA).
			  ○ Genetically modified mice with regulatable Tau reduction.
			• Analyze the effects of Tau reduction in these models, including:
			  ○ Behavior (learning and memory, seizure resistance).
			  ○ Brain anatomy.
			  ○ Biochemical changes.
			Drug development: This research aims to evaluate the safety and efficacy of Tau reduction as a potential therapeutic strategy for AD and potentially other neurological disorders. Understanding the mechanisms involved could lead to future drug development.

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INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS	TATE, MASON DOUGLAS	The role of micro-RNA-33 in Tau pathology	**Research question:** Can targeting micro-RNA-33 (miR-33) reduce tau pathology in Alzheimer's Disease (AD)?
			
			Stage: Likely a combination of animal models (mice) and cell cultures.
			
			Methods:
			• Inject mice lacking miR-33 with a virus expressing a human tau protein linked to AD.
			• Compare the extent of tau pathology in these mice with controls.
			• Generate cell cultures with and without miR-33 and introduce the human tau protein to create an in vitro model.
			• Analyze the effects of miR-33 deletion on:
			  ○ Tau hyperphosphorylation and tangle formation.
			  ○ Inflammatory response in the brain.
			  ○ Anxiety-like behavior and learning/memory deficits in mice.
			• Identify changes in protein expression patterns with and without miR-33 to understand the mechanisms involved.
			
			Drug development: This research aims to understand how miR-33 affects tau pathology and identify it as a potential therapeutic target for AD. By targeting a pathway influencing both amyloid-beta, tau, and inflammation, it might offer a more comprehensive approach than targeting single hallmarks.

MAYO CLINIC ROCHESTER	PETRUCELLI, LEONARD	Project 2	**Research question:** Can inhibiting a specific enzyme (cytosolic histone deacetylase 6, HDAC6) reduce hyperphosphorylated tau accumulation and potentially slow Alzheimer's disease (AD) and related tauopathies? **Stage:** Likely a combination of cell studies and animal models based on existing evidence of HDAC6 effects on tau. **Methods:** • Utilize a novel blood-brain-barrier permeable inhibitor to target HDAC6.

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			• Analyze the effects of HDAC6 inhibition on tau protein:
			  ○ Hyperacetylation levels.
			  ○ Degradation rates.
			  ○ Binding to microtubules (using specific antibodies).
			• Investigate the potential for HDAC6 inhibition to:
			  ○ Prevent neurofibrillary tangle formation.
			  ○ Delay disease progression in animal models.
			Drug development: This research proposes HDAC6 inhibition as a novel therapeutic strategy for AD and tauopathies. The project highlights the potential benefits and low toxicity of this approach compared to other targets. They aim to provide data supporting further clinical development of HDAC6 inhibitors.

UNIVERSITY OF PENNSYLVANIA	KUNG, HANK F	In vivo imaging agents targeting Tau aggregates	**Research question:** Can novel F-18 and I-123 radiotracers be developed to image tau aggregates (tangles) in the brain for diagnosing Alzheimer's disease (AD) and other tauopathies? **Stage:** Preclinical development using postmortem brain tissue, cell cultures, and potentially normal mice. **Methods:** • Develop and test new F-18 and I-123 labeled compounds for binding specifically to tau aggregates. • Utilize binding assays and autoradiography to evaluate compound effectiveness in cell cultures and brain tissue sections. • Conduct initial biodistribution studies in normal mice to assess the properties of promising compounds. **Drug development:** This project is not directly developing drugs but aims to create imaging agents for diagnosing AD and tauopathies. Successful tau imaging agents could improve patient diagnosis, track disease progression, and aid in developing future therapies.

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STATE UNIVERSITY OF NEW YORK AT BUFFALO	WILLIAMS, JAMAL	Exploration of a Novel Therapeutic for Alzheimer's Disease and Related Disorders	**Research question:** Can selectively reducing a specific E3 ubiquitin ligase enzyme in the brain rescue synaptic and cognitive decline in a tauopathy model of Alzheimer's disease (AD)?
			Stage: Likely animal models (mice) using viral vector injection for targeted gene knockdown.
			Methods:
			• Utilize a transgenic mouse model (P301S) known to overexpress hyperphosphorylated tau and exhibit cognitive decline.
			• Knock down a specific E3 ubiquitin ligase enzyme in the prefrontal cortex of these mice using an in vivo gene transfer method.
			• Analyze the effects of E3 ligase reduction on:
			  ○ Cognitive function through behavioral tests.
			  ○ Synaptic protein levels (biochemical and immunocytochemical analysis).
			  ○ NMDAR receptor function using electrophysiological recordings.
			Drug development: This research is not directly developing a drug, but investigates a potential therapeutic target (E3 ligase) for future drug development. Understanding how this enzyme influences tau-induced cognitive decline could inform future strategies to prevent or slow disease progression.

TRANSLATIONAL GENOMICS RESEARCH INST	DUNCKLEY, TRAVIS L	Neurofibrillary Tangle-Induced Dementia in AD	**Research question:** What are the key molecular mechanisms leading to neurofibrillary tangle (NFT) formation in Alzheimer's disease (AD) and related tauopathies? **Stage:** Likely a combination of human tissue analysis and cell culture studies. **Methods:** • Analyze gene expression profiles in neurons with and without NFTs from AD patients and controls. • Investigate the CD47 signaling pathway as a potential contributor to NFT formation using: ○ Analysis of messenger RNA (mRNA) and protein levels.

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			○ Functional assays to understand the pathway's role. • Validate the involvement of other dysregulated genes identified in the initial analysis. **Drug development:** This research aims to identify novel therapeutic targets for preventing or reducing NFT formation in AD and related diseases. By understanding the molecular mechanisms involved, they hope to discover pathways for future drug development. This approach focuses on tau pathology, which can occur even without the presence of amyloid plaques, suggesting its independent role in neurodegeneration.
INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS	VIDAL, RUBEN	Identification of novel four repeat tauopathies through analysis of network vulnerability, tau structure and propagation.	**Research question:** • How prevalent is a newly identified tauopathy named "limbic-predominant neuronal inclusion body 4R tauopathy" (LNT) within existing collections of progressive supranuclear palsy (PSP) cases? • What are the defining characteristics of LNT compared to PSP? • Are there other previously undiagnosed tauopathy variants within the PSP collections? **Stage:** Analysis of existing human brain tissue collections and potentially using established in vitro and in vivo models for tau aggregation. **Methods:** • Analyze a large set of PSP brain tissue samples (Indiana and Toronto cohorts) using: ○ Neuropathological examination. ○ Genetic analysis. ○ Cryo-electron microscopy (cryo-EM) to determine tau filament structure. • Investigate the molecular changes associated with tau protein in LNT-I and LNT-II variants. • Utilize in vitro methods to assess the "seeding ability" and potency of tau from LNT cases. • Develop microfluidic devices and potentially a mouse model to study the propagation of tau filaments from PSP and LNT cases.

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			○ Compare the structure of tau filaments obtained from these models with the original human brain samples. **Drug development:** This research focuses on understanding different tau pathologies and their underlying mechanisms. It lays the groundwork for future therapeutic development by: • Identifying a new tauopathy (LNT). • Characterizing LNT and potentially other novel tau variants. • Establishing models to study tau filament propagation. • Understanding these factors could inform the development of drugs targeting specific tau conformations or inhibiting their spread.
UNIVERSITY OF CALIFORNIA SANTA CRUZ	HOLMAN, THEODORE R	Discovery of 12/15-lipoxygenase therapeutics for Alzheimer's disease	**Research question**: Can inhibiting a specific enzyme (12/15-Lipoxygenase) restore autophagy and reduce Alzheimer's disease (AD) pathology? **Stage**: Animal models (mice) based on existing findings of genetic manipulation and pharmacological blockade. **Methods**: • Assess a new, selective 12/15-LOX inhibitor (ML351) in mice models of AD and tauopathy. • Identify additional candidate molecules for drug development through screening libraries. • Evaluate the effectiveness of ML351 and other inhibitor candidates in cell studies and animal models. **Drug development**: This research aims to develop selective and potent inhibitors of 12/15-LOX as a novel therapeutic approach for AD and related tauopathies. The project focuses on a specific inhibitor (ML351) with promising properties for further development.
UNIVERSITY OF IOWA	LEE, GLORIA	Tyrosine phosphorylation in Alzheimer's disease	**Research question:** How does tyrosine phosphorylation of tau protein contribute to Alzheimer's disease (AD) and other tauopathies? **Stage:** Likely a combination of cell culture studies and animal models (mice). **Methods:** • Investigate the role of Fyn, a Src-family tyrosine kinase, in tauopathy:

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			○ Use a mouse model lacking Fyn and analyze tau pathology, neuronal health, and behavior. • Examine the function of abnormally phosphorylated tau, specifically: ○ Its interaction with the protein tyrosine phosphatase SHP2. ○ The functional significance of this interaction. • Analyze SHP2 activation in AD brain tissue and a mouse tauopathy model. • Monitor activity of the MAPK pathway in these models. **Drug development:** This research aims to understand how tau phosphorylation contributes to AD and identify potential targets for therapeutic intervention. By elucidating the mechanisms involved, they hope to discover new targets for drugs that could:
WEILL MEDICAL COLL OF CORNELL UNIV	NIXON, DOUGLAS F	The Role of Transposable Elements in Healthy Aging and in Alzheimer's Disease	**Research question:** Do transposable elements (TEs), specifically human endogenous retroviruses (HERVs), contribute to Alzheimer's disease (AD) through the cGAS-STING pathway? **Stage:** This research combines bioinformatic analysis, human cell cultures, and animal models. **Methods:** • Analyze HERV expression patterns in: ○ Brain tissue samples across the lifespan and from AD patients. ○ Single-nucleus RNA sequencing data from human neurons. ○ Induced neuron (iN) cell models derived from young and elderly individuals. • Investigate the cGAS-STING pathway in a tauopathy mouse model of AD: ○ Analyze the effects of a cGAS inhibitor on TE expression and cognitive function. ○ Determine if cGAS deletion affects TE expression and protects against tauopathy.

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			Drug development: This research aims to identify TEs and the cGAS-STING pathway as potential therapeutic targets for AD. By understanding how TEs might influence tauopathy, they could inform the development of drugs to: • Suppress TE expression. • Inhibit cGAS activity. **Biomarkers:** While not explicitly stated, identifying TE expression patterns associated with AD could potentially lead to the development of biomarkers for earlier disease detection.

CLEVELAND CLINIC LERNER COM-CWRU	CHENG, FEIXIONG	TREM2 Genotype-Informed Drug Repurposing and Combination Therapy Design for Alzheimer's Disease	**Research question:** Can microglia-targeted therapies, specifically repurposed anti-inflammatory drugs or drugs targeting the TREM2 receptor, be effective treatments for Alzheimer's disease (AD)?
			Stage: This research combines human genetic data, electronic health records (EHR) analysis, cell culture models (iPSCs and cerebral organoids), and potentially animal models.
			Methods:
			• Analyze the TREM2R47H variant:
			  ○ Use single-nucleus RNA sequencing (snRNAseq) data to identify molecular changes in microglia associated with this risk factor.
			  ○ Investigate the Akt signaling pathway as a potential target for TREM2R47H-related inflammation.
			• Identify repurposable drugs using EHR data and deep learning:
			  ○ Analyze EHR data from millions of patients to find existing anti-inflammatory drugs associated with a reduced risk of AD.
			  ○ Utilize deep learning to identify potential drug combinations for targeting microglia.
			• Validate promising drug candidates using:
			  ○ Patient-derived iPSCs carrying the TREM2R47H variant.
			  ○ Cerebral organoids (3D brain cell cultures).
			  ○ Potentially mouse models of AD.
			Drug development: This research focuses on repurposing existing anti-inflammatory drugs and developing new drugs targeting the TREM2

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			receptor pathway in microglia. Microglia are immune cells in the brain and their malfunction is believed to contribute to AD progression. By understanding how TREM2 mutations and inflammation influence microglia function, they hope to discover: • Repurposed anti-inflammatory drugs for treating AD. • Novel drugs targeting the TREM2 pathway to modulate microglia activity. **Biomarkers:** While not the main focus, identifying microglial gene expression patterns associated with AD risk factors (like TREM2R47H) could potentially lead to the development of biomarkers for earlier disease detection.

STATE UNIVERSITY OF NEW YORK AT BUFFALO	CLARK, STEWART DONALDSON	Tau accumulation in the pedunculopontine tegmentum as an early node in Progressive Supranuclear Palsy pathogenesis	**Research question:** Does the accumulation of tau protein in a specific region of the brain (cholinergic pedunculopontine tegmentum, PPT) initiate and drive the pathology and symptoms of Progressive Supranuclear Palsy (PSP)?
			Stage: Animal model development using genetically engineered viruses and behavioral testing.
			Methods:
			• Develop a rat model of PSP by:
			  ○ Injecting a virus that overexpresses the specific tau protein isoform (1N4R) associated with PSP into cholinergic PPT neurons.
			  ○ Comparing these animals to controls receiving a benign protein at regular intervals.
			• Analyze the model over time using:
			  ○ Postmortem analysis of brain tissue to assess tau pathology and neuronal loss.
			  ○ Magnetic Resonance Imaging (MRI) to visualize brain changes.
			  ○ Recordings of REM sleep patterns.
			  ○ Behavioral tests to evaluate cognitive and motor function.
			Expected outcome: Establish a model where tau accumulation in PPT neurons leads to PSP-like pathology and symptoms.

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			Future directions (not covered in this proposal but implied): • Develop therapeutic strategies to target tau accumulation or other disease mechanisms in the established model. • Identify early biomarkers for PSP diagnosis based on the model's disease progression. • Conduct further mechanistic studies to understand the molecular pathways involved. **Significance:** • This research could improve the accuracy of PSP diagnosis and lead to the development of new treatments. • The model could also be used to identify early signs of the disease before symptoms appear.

BOSTON UNIVERSITY MEDICAL CAMPUS	MCKEE, ANN C.	Tau Pathology in CTE vs. Alzheimer's Disease: Microvasculopathy and Neuroinflammation	**Research question:** How do microvascular dysfunction, neuroinflammation, and repetitive head impacts (RHI) contribute to tau protein deposition and spread in Alzheimer's disease (AD) and Chronic Traumatic Encephalopathy (CTE)?
			Stage: Analysis of existing brain tissue collections and clinical data.
			Subjects:
			• Large cohorts with neuropathological confirmation:
			  ○ CTE cases (N=250)
			  ○ AD cases (N=800)
			• Controls with and without RHI exposure from the VA and Framingham Heart Study (N=120 total)
			Methods:
			• Analyze brain tissue samples to assess:
			  ○ Tau pathology (distribution and amount)
			  ○ Microvascular dysfunction
			  ○ Neuroinflammation
			  ○ Accumulation of other proteins associated with neurodegeneration (Aβ, α-synuclein, TDP-43)
			• Analyze clinical data to assess:
			  ○ RHI exposure

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			○ Cognitive decline ○ APOE ε4 and MAPT gene variants (known risk factors for AD) **Expected outcome:** Identify how RHI, microvascular dysfunction, and neuroinflammation influence tau pathology and distinguish these processes between AD and CTE. **Future directions (not covered in this proposal but implied):** • Develop new biomarkers for AD and CTE based on the findings, particularly focusing on markers of vascular dysfunction and inflammation. • Identify potential therapeutic targets based on the distinct disease mechanisms in AD and CTE. **Significance:** • This research could improve understanding of the early events leading to AD and CTE, potentially leading to earlier diagnosis and treatment. • The identification of novel biomarkers could allow for earlier detection of these diseases. • Understanding the role of RHI in tau pathology could inform preventive strategies for athletes and military personnel.
AETON THERAPEUTICS, INC.	SINHA, ANJANA	Optimizing virtual hits of human CGAS inhibitors to treat neurodegeneration	**Company:** Aeton Therapeutics **Disease:** Alzheimer's disease (AD) **Drug target:** cGAS (cyclic GMP-AMP synthase) **Scientific rationale:** • AD is characterized by the formation of amyloid beta plaques and tau tangles in the brain. • cGAS is a protein that senses DNA in the cytosol (cell interior) and triggers an inflammatory response. • Studies suggest that cGAS is abnormally activated in AD, leading to neuroinflammation and cognitive decline. • Blocking cGAS activity (using cGAS inhibitors, cGASi) could protect against these negative effects. **Project goals:**

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			• Develop potent and specific inhibitors of human cGAS (h-cGASi).
			• Evaluate the best candidates in human cell models (microglia and organoids) derived from induced pluripotent stem cells (iPSCs).
			• Identify a lead compound that:
			  ○ Reduces key inflammatory markers in these models.
			  ○ Penetrates the brain.
			  ○ Shows no toxicity.
			  ○ Lacks off-target effects.
			Expected outcome:
			• Identify a lead h-cGASi candidate for further development as a potential treatment for AD.
			• This drug candidate could reprogram microglial responses (immune cells in the brain) and prevent tau-related cognitive decline.
			Significance:
			• This research could lead to a novel therapeutic approach for AD by targeting the cGAS-STING pathway involved in neuroinflammation.

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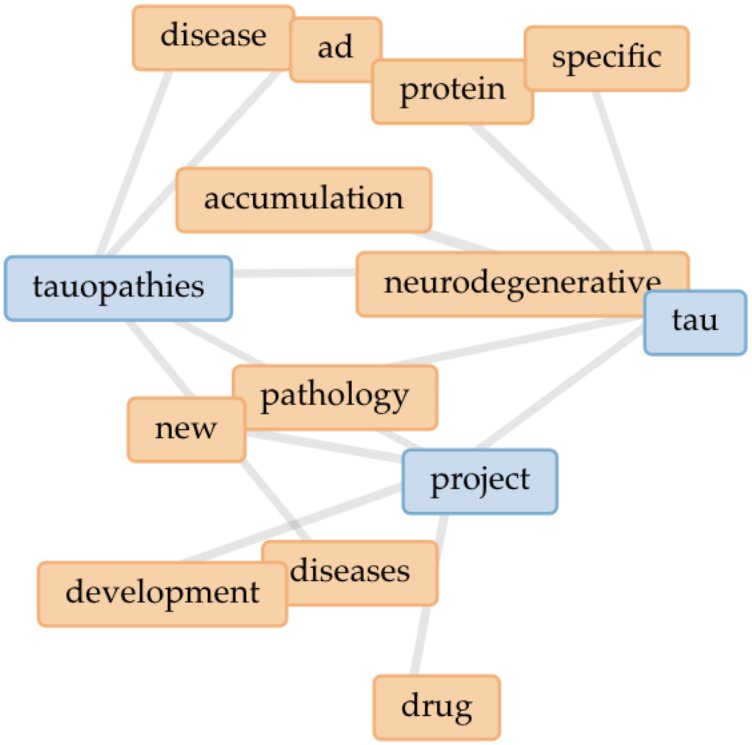

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