# Parkinson's Disease 3.0 Preclinical Landscape - DRAFT

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| UNIVERSITY OF MICHIGAN AT ANN ARBOR | WANG, WENJING | Design and characterization of Nanobodies to dementia-related α-synuclein strains in Parkinson's disease | **Research question:**<br>Do different strains of alpha-synuclein (α-syn) contribute to the progression of Parkinson's disease (PD) to Parkinson's disease dementia (PDD)?<br>**Stage:**<br>In vitro (using cells)<br>**Methods:**<br>• Amplified α-syn from PD and PDD patient samples using PMCA (protein misfolding cyclic amplification).<br>• Developed and characterized a new library of synthetic nanobodies that target α-syn preformed fibrils (PFF).<br>• Tested the ability of these nanobodies to distinguish between PD and PDD strains of α-syn.<br>**Drug development:**<br>This study focuses on developing nanobodies as potential therapeutic tools, not traditional drugs. These nanobodies could target and potentially prevent the spread of α-syn PFF, thereby halting disease progression. |
| HARRY S. TRUMAN MEMORIAL VA HOSPITAL | ZAHEER, ASGAR | Glia maturation factor dependent mast cell activation in Parkinson's disease | **Research question:**<br>Does Glia Maturation Factor (GMF) play a role in activating mast cells and neuroinflammation in Parkinson's disease (PD)?<br>**Stage:**<br>This research proposes a two-stage approach:<br>1. **In vitro:** Using human and mouse mast cells, the study will investigate if GMF is required for activation and proinflammatory mediator secretion.<br>2. **In vivo:** Using MPTP-induced mouse models of PD, the study will explore the impact of GMF on mast cell function and dopaminergic neuron degeneration.<br>**Methods:**<br>• Analyze the effect of GMF on mast cell activation and proinflammatory mediator secretion in human and mouse primary mast cells.<br>• Investigate the mechanisms of GMF-induced mast cell activation.<br>• Utilize MPTP-induced acute and chronic PD mouse models. |

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| | | | • Reconstitute mast cell deficient mice with bone marrow-derived mast cells from GMF-deficient or wild-type mice.<br>• Analyze MPTP-induced neuroinflammation, neurochemical deficits, and nigrostriatal degeneration in these models.<br>• Correlate behavioral parameters with the observed pathology.<br>**Drug development:**<br>This study focuses on understanding the role of GMF, not directly developing a drug. However, by investigating GMF's influence on neuroinflammation, the research aims to identify GMF as a potential target for future therapeutic development in PD. |
| SOUTH TEXAS VETERANS HEALTH CARE SYSTEM | STRONG, RANDY | Detoxification of Biogeneic Aldehydes in Parkinson's Disease | **Research question:**<br>Does impaired aldehyde detoxification contribute to dopaminergic dysfunction in Parkinson's disease (PD)?<br>**Stage:**<br>In vivo (using animals)<br>**Methods:**<br>• Created two lines of mice:<br>  ○ Mice with mutations in Aldh1a1 and Aldh2 (important for aldehyde detoxification in dopamine neurons)<br>  ○ Wild-type control mice<br>• Examined the effects of impaired aldehyde detoxification on:<br>  ○ Motor function<br>  ○ Dopamine levels and metabolites<br>  ○ Loss of midbrain dopamine neurons<br>**Drug development:**<br>This research investigates the potential role of aldehydes as a therapeutic target in PD. The study explores:<br>• The link between impaired aldehyde detoxification and dopaminergic dysfunction.<br>• The potential of "aldehyde trapping agents" for neuroprotection.<br>These findings could lead to the development of new therapeutic strategies for PD. |

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| UNIVERSITY OF GEORGIA | KANTHASAMY, ANUMANTHA GOUNDER | Novel Re-engineered L DOPA Probiotic Therapy for Parkinson's Disease | **Research question:**<br>Can genetically engineered probiotic bacteria producing L-DOPA provide sustained symptomatic relief for Parkinson's disease (PD) without causing L-DOPA-induced dyskinesia (LID)?<br>**Stage:**<br>In vivo (using animals)<br>**Methods:**<br>• Engineered a probiotic strain of E. coli Nissle 1917 (EcNrhaL-DOPA) to produce L-DOPA.<br>• Compared the L-DOPA production efficiency of EcNrhaL-DOPA to older methods.<br>• Evaluated gut colonization, pharmacokinetics, and adaptation profiles of EcNrhaL-DOPA in mice.<br>• Tested the therapeutic efficacy of EcNrhaL-DOPA in mouse models of PD.<br>• Investigated whether EcNrhaL-DOPA prevents LID in mouse models.<br>**Drug development:**<br>This research proposes a novel drug development approach using genetically engineered probiotic bacteria to continuously produce L-DOPA in the gut. This method aims to:<br>• Provide sustained and consistent L-DOPA delivery to the brain.<br>• Reduce L-DOPA fluctuations associated with traditional oral L-DOPA therapy.<br>• Potentially alleviate motor symptoms of PD without causing LID.<br>This could lead to a new therapeutic strategy for PD management. |
| PK BIOSCIENCES CORPORATION | ANANTHARAM, VELLAREDDY | Development of Novel Neuroprotective Agents for Parkinson?s Disease | **Research question:**<br>Can PKC4, a specific protein kinase, be a target for developing neuroprotective drugs for Parkinson's disease (PD)?<br>**Stage:**<br>This research is transitioning from the bench to early drug development (SBIR Phase I).<br>• Previous research identified PKC4 as a key protein involved in the death of dopaminergic neurons in PD models. |

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| | | | • This project proposes developing new drugs to inhibit PKC4 activity.<br>**Methods:**<br>• Design and synthesize new molecules that inhibit PKC4.<br>• Test the selectivity and potency of these new PKC4 inhibitors.<br>• Evaluate the neuroprotective effects of these inhibitors in cell culture models of PD.<br>**Drug development:**<br>This research aims to develop small molecule inhibitors of PKC4 as a new therapeutic approach for PD. By inhibiting PKC4, the researchers hope to protect dopaminergic neurons and slow the progression of PD.<br>**Public health relevance:** This project focuses on finding a disease-modifying treatment for PD, which would be a significant advancement in PD therapy. |
| UNIVERSITY OF COLORADO DENVER | BOYSON, SALLY J | COMPLEX I IN PARKINSON'S DISEASE | **Research question:**<br>Can a mitochondrial enzyme defect in platelets be a biomarker for Parkinson's disease (PD)?<br>**Stage:**<br>In vitro (using human platelets)<br>**Methods:**<br>• Measure the activity of complex I, a mitochondrial enzyme, in platelets from:<br>  ○ Patients with typical PD<br>  ○ Patients with "parkinson-plus" disorders<br>  ○ First-degree relatives of PD patients<br>  ○ Healthy controls<br>• Analyze platelet function in PD patients.<br>**Drug development:**<br>This research is not directly developing a drug. However, by investigating a potential mitochondrial enzyme defect, it aims to:<br>• Establish complex I activity as a biomarker for PD diagnosis.<br>• Identify potential therapeutic strategies for PD based on correcting the enzyme defect (e.g., replacing or stimulating the enzyme). |

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| | | | This could lead to the development of a diagnostic test and novel therapeutic approaches for PD. |
| UNIVERSITY OF HOUSTON | LEE, BEOM CHAN | Systematic evaluations of a new smartphone-based wearable telerehabilitation system for use by people with Parkinson's disease | **Research question:**<br>Can a smartphone-based telerehabilitation system (called Smarter Balance System - SBS) improve long-term balance performance and reduce the fear of falling in people with Parkinson's disease (PD) compared to a paper-based exercise regimen?<br>**Stage:**<br>In vivo (with humans)<br>**Methods:**<br>• Compare two groups:<br>  ○ Participants with PD using SBS for in-home balance training<br>  ○ Participants with PD using a paper-based exercise regimen for in-home training<br>• Evaluate participants on:<br>  ○ Long-term static and dynamic balance performance<br>  ○ Retention of balance improvements<br>  ○ Daily physical activity levels<br>  ○ Confidence in performing activities and fear of falling<br>**Drug development:**<br>This study is not developing a drug. It is evaluating a smartphone-based telerehabilitation system (SBS) as a potential therapeutic tool for improving balance and reducing fall risk in PD patients.<br>**Expected benefits of SBS:**<br>• Improved long-term balance performance<br>• Increased confidence in daily activities<br>• Reduced fear of falling<br>• Reduced need for in-home assistance with balance training<br>• Improved monitoring and guidance by physical therapists through remote data tracking |

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| UNIVERSITY OF KENTUCKY | BING, GUOYING | Cox-2 deficient mice are resistant to MPTP neurotoxicity | **Research question:**<br>Does COX-2 play a role in worsening MPTP-induced neurotoxicity in a Parkinson's disease (PD) model by activating microglia and oxidative stress?<br>**Stage:**<br>In vivo (using animals)<br>**Methods:**<br>• Use two groups of mice:<br>  ○ Mice deficient in COX-2 gene<br>  ○ Wild-type mice<br>• Treat both groups with MPTP, a neurotoxin that mimics PD symptoms.<br>• In the wild-type group, also administer COX-2 inhibitors before MPTP treatment.<br>• Analyze:<br>  ○ Dopamine neuron survival<br>  ○ Microglial activation<br>  ○ Striatal dopamine levels<br>  ○ Functional recovery in mice<br>• Investigate the molecular mechanisms involved, including:<br>  ○ Protein modification<br>  ○ Reactive oxygen species generation<br>  ○ Inflammatory cytokine expression<br>  ○ Apoptosis-related gene expression<br>  ○ Signaling molecule activation<br>**Drug development:**<br>This research does not directly develop a drug, but investigates COX-2 as a potential therapeutic target for PD. By understanding how COX-2 contributes to MPTP neurotoxicity, researchers aim to develop:<br>• Novel therapeutic treatments for PD<br>• Treatments for other neurodegenerative diseases |
| GEORGETOWN UNIVERSITY | FEDEROFF, HOWARD J. | Dopamine, mutant synuclein, oxidative | **Research question:**<br>Does alpha-synuclein (SYN) overexpression, particularly mutant forms, trigger Parkinson's disease (PD) by activating microglia and causing oxidative stress? |

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| | | stress and inflammation | **Stage:**<br>In vivo (using animals)<br>**Methods:**<br>• Use transgenic mice models:<br>  ○ Wild-type SYN overexpression (wtSYN+/+)<br>  ○ Double-mutant SYN overexpression (dmSYN+/+)<br>• Analyze:<br>  ○ Microglial activation<br>  ○ Presynaptic function<br>  ○ Proinflammatory response<br>  ○ Quinone-mediated oxidative stress<br>• Use additional models to track quinone stress response.<br>**Drug development:**<br>This research does not directly develop a drug. It investigates the role of alpha-synuclein and microglia in the initiation of PD. By understanding how SYN overexpression triggers microglial activation and oxidative stress, researchers aim to identify potential therapeutic targets for PD, particularly focusing on early disease stages. |
| EMORY UNIVERSITY | MCKEON, JEANNE ELIZABETH | Role of UCH-L1 Oxidative Modification in Parkinson's Disease Pathogenesis | **Research question:**<br>Does oxidative stress from environmental toxins damage a protein called UCH-L1, contributing to Parkinson's disease (PD) by impairing protein degradation pathways in dopamine neurons?<br>**Stage:**<br>Not directly mentioned, but likely a combination of in vitro (using cells) and in vivo (using animal models) studies.<br>**Methods:**<br>• Analyze brain tissue from PD patients to see if UCH-L1 is modified by oxidation.<br>• Investigate how oxidative stress affects UCH-L1 function in cell models.<br>• Examine how UCH-L1 modifications impact protein degradation pathways and dopamine neuron health.<br>**Drug development:** |

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| | | | This research indirectly contributes to drug development by investigating a potential mechanism of PD progression. By understanding how oxidative stress damages UCH-L1 and disrupts protein degradation, researchers may:<br>• Identify UCH-L1 as a target for protective therapies against PD.<br>• Develop treatments to prevent oxidative damage to UCH-L1 or restore its function.<br>• Gain insights into potential environmental risk factors for PD. |
| STANFORD UNIVERSITY | DING, JUN | Dopamine Degradation Pathway and Alpha-synuclein Aggregation | **Research question:**<br>• How does alpha-synuclein (α-syn) aggregation spread in the brain, and can targeting the enzyme aldehyde dehydrogenase 1a1 (ALDH1a1) help reduce α-synuclein burden and slow Parkinson's disease (PD) progression?<br>**Stage:**<br>In vivo (using animals)<br>**Methods:**<br>• Investigate the impact of:<br>  ○ Reduced ALDH1a1 function on α-synuclein aggregation.<br>  ○ Inhibiting monoamine oxidase (MAO, an enzyme upstream of ALDH1a1) on α-synuclein aggregation and spread.<br>  ○ Increased ALDH1a1 function on protecting dopamine neurons from α-synuclein aggregation.<br>**Drug development:**<br>This research investigates ALDH1a1 as a potential target for PD treatment. By understanding how it affects α-synuclein aggregation, researchers aim to:<br>• Validate ALDH1a1 as a therapeutic target for PD.<br>• Gain insights into α-synuclein transmission and aggregation in the brain.<br>• Potentially develop drugs that increase ALDH1a1 activity to slow PD progression. |
| RESEARCH TRIANGLE INSTITUTE | DECKER, ANN M | Development of hTAAR1 antagonists | **Research question:**<br>Develop potent and drug-like antagonists targeting the human Trace Amine-Associated Receptor 1 (hTAAR1) for potential treatment of Parkinson's disease (PD). |

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| | | | **Stage:**<br>Not directly mentioned, but likely in vitro (using cells) with the potential for future in vivo studies.<br>**Methods:**<br>• Medicinal chemistry to design and synthesize novel hTAAR1 antagonists based on an existing lead compound (TAR-44).<br>• Pharmacology to evaluate the potency, selectivity, and drug-like properties of the synthesized compounds.<br>**Drug development:**<br>This research directly aims to develop a new drug for PD. By creating potent hTAAR1 antagonists, researchers hope to:<br>• Increase dopaminergic signaling and neuronal firing in the brain.<br>• Improve the efficacy of L-DOPA, a current PD medication.<br>• Reduce neurodegeneration and potentially slow disease progression. |
| NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE | WALTERS, JUDITH RICHMOND | Thalamo-Cortical Plasticity: Pain, Executive Function and Loss of Dopamine | **Research question 1: Pain mechanisms in Parkinson's disease (PD)**<br>**Stage:**<br>In vivo (using rats)<br>**Methods:**<br>• Lesion dopamine neurons in one hemisphere of rats to create a PD model.<br>• Implant electrodes in specific brain regions (subthalamic nucleus, anterior cingulate cortex, and ventromedial thalamic nucleus).<br>• Inject formalin into the rat's paw to induce pain.<br>• Analyze behavioral pain responses and electrical activity in the brain regions.<br>**Drug development:**<br>This research indirectly contributes to drug development by investigating the mechanisms of pain in PD. By understanding how pain processing is disrupted in the parkinsonian brain, researchers may develop better pain management strategies for PD patients.<br>**Research question 2: Cognitive function in PD**<br>**Stage:** |

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| | | | In vivo (using rats)<br>**Methods:**<br>• Lesion dopamine neurons in one hemisphere of rats to create a PD model.<br>• Train rats on a cognitive task and analyze electrical activity in brain regions involved in decision-making.<br>**Drug development:**<br>Similar to research question 1, this research aims to identify potential biomarkers for cognitive decline in PD, which could guide future therapeutic development.<br>**Research question 3: Role of parafascicular thalamic nucleus (Pf) in PD motor function**<br>**Stage:**<br>In vivo (using rats)<br>**Methods:**<br>• Lesion dopamine neurons in one hemisphere of rats to create a PD model.<br>• Implant electrodes in brain regions involved in motor control.<br>• Analyze motor function and electrical activity in these regions before and after manipulating Pf activity using drugs.<br>**Drug development:**<br>This research investigates the Pf nucleus as a potential target for deep brain stimulation (DBS) to improve motor function in PD. By understanding how manipulating Pf activity affects motor circuits, researchers may explore DBS as a treatment approach.<br>**Research question 4: Medial dorsal thalamus and schizophrenia**<br>**Note:** This research question is not directly related to Parkinson's disease.<br>**Stage:**<br>In vivo (using rats)<br>**Methods:**<br>• Administer drugs that affect dopamine D4 receptors to rats. |

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| | | | • Analyze electrical activity in the medial prefrontal cortex and mediodorsal thalamus.<br>**Drug development:**<br>This research investigates the effects of drugs targeting dopamine D4 receptors on brain activity. By understanding how these drugs modulate brain circuits, researchers may develop new medications for schizophrenia. |
| UNIVERSITY OF PENNSYLVANIA | BONINI, NANCY M | Molecular Genetic Insight into Neurodegenerative Disease from Drosophila | **Research question:**<br>This research program investigates the genes and mechanisms underlying neurodegenerative diseases like amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Parkinson's disease (PD) using the fruit fly (Drosophila melanogaster) as a model organism.<br>**Stage:**<br>In vivo (using fruit flies) with potential extension to human patient tissue, mammalian cells, and primary neurons in culture.<br>**Methods:**<br>• Conduct genetic screens in fruit flies to identify genes that modify the toxicity of ALS/FTD-causing factors.<br>• Analyze the identified pathways in human patient tissue, mammalian cells, and primary neurons.<br>• Use the fruit fly model to investigate the impact of risk factors like traumatic brain injury and gut microbiota on neurodegenerative disease.<br>**Drug development:**<br>This research does not directly develop a drug. It utilizes the fruit fly as a model to understand the biological mechanisms of neurodegenerative diseases. By identifying genes and pathways involved, researchers aim to:<br>• Gain insights into the underlying causes of ALS, FTD, and PD.<br>• Provide a foundation for developing future therapeutic strategies for these diseases. |
| EMORY UNIVERSITY | MAO, ZIXU | Oxidation-dependent Regulation of MEF2D in Neuronal Stress | **Research question:**<br>Does oxidative stress impair the function of a neuronal survival protein (MEF2D) in multiple cellular compartments, contributing to neurodegenerative diseases like Parkinson's disease (PD)? |

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| | | | **Stage:**<br>In vitro (using cells) and in vivo (using animal models)<br>**Methods:**<br>• Investigate how oxidative stress affects MEF2D in neurons.<br>• Analyze:<br>  ○ MEF2D modifications due to oxidative stress<br>  ○ Impact of these modifications on MEF2D function in different cellular compartments (nucleus and mitochondria)<br>• Use animal models of neurotoxin-induced degeneration to see if MEF2D is similarly affected.<br>• Analyze postmortem brain tissue from PD patients for MEF2D modifications.<br>**Drug development:**<br>This research does not directly develop a drug, but investigates a novel mechanism for neuronal death in PD. By understanding how oxidative stress impairs MEF2D function, researchers aim to:<br>• Establish MEF2D as a key target for oxidative stress in PD.<br>• Identify a potential therapeutic target for developing new treatments for PD and other neurodegenerative diseases. |
| VANDERBILT UNIVERSITY | ASCHNER, MICHAEL | Mechanisms of Manganese Neurotoxicity | **Research question:**<br>Do mutations in genes associated with Parkinson's disease (PD) (dj-1 and pink1) and their chaperone proteins make dopamine-producing neurons more susceptible to manganese (Mn)-induced damage?<br>**Stage:**<br>In vivo (using the nematode Caenorhabditis elegans)<br>**Methods:**<br>• Use RNA interference (RNAi), mutations, and overexpression to manipulate genes in C. elegans.<br>• Analyze:<br>  ○ Dopamine neuron degeneration<br>  ○ Alpha-synuclein aggregation<br>  ○ Markers of oxidative stress |

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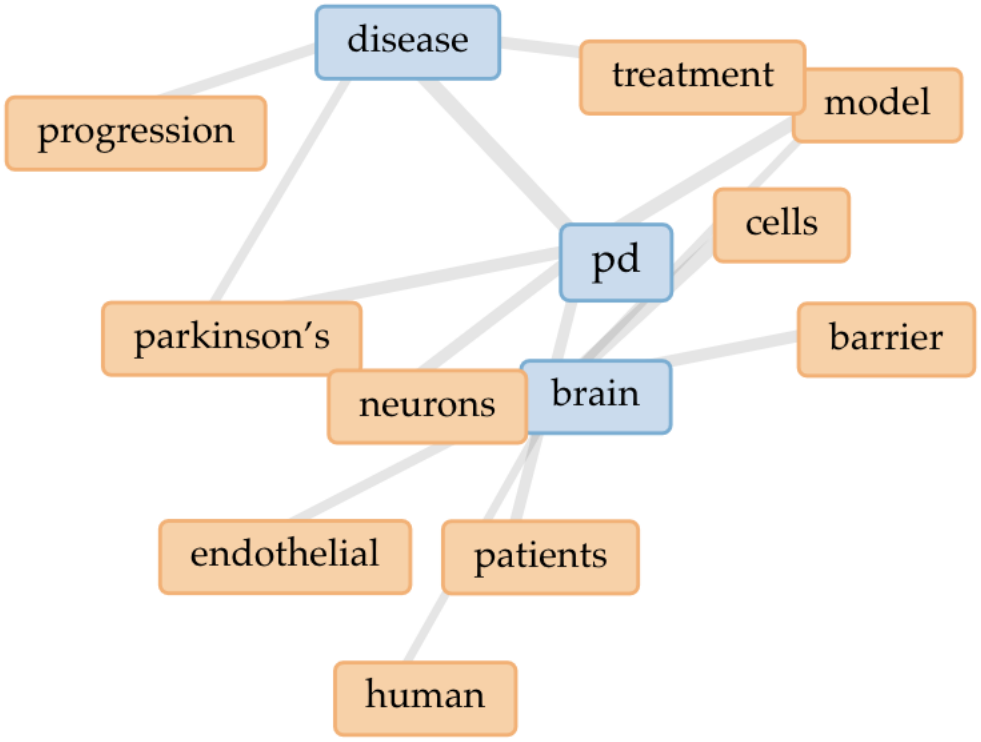
| | | | ○ Mitochondrial function<br>• Expose worms to Mn with different genetic modifications.<br>**Drug development:**<br>This research does not directly develop a drug. It investigates the link between mutations in PD-related genes and Mn exposure in a worm model. By understanding how these factors affect dopamine neurons, researchers aim to:<br>• Gain insights into the mechanisms of Mn-induced neurotoxicity in PD<br>• Identify potential therapeutic strategies to protect neurons from Mn-induced damage |



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