PARKINSON'S PRIORITY THERAPEUTIC CLINICAL PIPELINE REPORT

Q1 2024

The Michael J. Fox Foundation for Parkinson's Research

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REPORT OBJECTIVES AND OVERVIEW

This report tracks therapies currently in clinical development for Parkinson's disease as of late March 2024. It includes brief rationale and progress in key pipelines of therapeutic interest along with detailed listings of specific therapies, current development status and information about MJFF support (funding and/or non-funding connections).

MJFF monitors numerous sources to assess the therapeutic pipeline. These include online intelligence databases (e.g., Citeline, clinicaltrials.gov), company websites and our own direct engagement with industry sponsors. While the report is extensive, it is not comprehensive of every intervention in development for Parkinson's disease. Rather, it represents treatments identified by MJFF as important given potential significance to the Parkinson's community and for understanding MJFF role and impact.

The report primarily emphasizes pharmacological (small molecule) and biological (peptide, antibody, gene therapy, cell-based, etc.) therapies. We include a brief description of technology-enabled interventions (i.e., neuromodulation and other technological interventions) but highlight only programs reflecting areas of MJFF current funding support. Approaches such as exercise, alternative (non-pharmacological) therapies and behavioral interventions are not included given challenges in monitoring and tracking the many variations these approaches take within the clinical pipeline. The report also primarily focuses on therapies in development within the US and EU (with some exceptions) given these programs are easier to track and have more public information available.

This report is updated and distributed on an annual basis, although pipeline data are tracked regularly, and we may generate supplements to the report as needed. Information in this report is considered non-confidential, intended only as a guide for communicating pipeline progress and does not represent endorsement by MJFF of specific therapies. Any errors or omissions are not intentional.

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PROGRESS IN PARKINSON'S DISEASE

Since the late 1990s, we have seen significant advances in understanding and treatment of Parkinson's disease pointing to new opportunities across the research and drug development effort.

Importantly

+ Our understanding of the biological basis of Parkinson's disease has grown exponentially, driven in large part by advances in deciphering genetic and cellular contributors. Recent availability of tools to distinguish early biological signatures (e.g., the alpha-synuclein seeding amplification assay) are driving conversations about biological forms Parkinson's disease may take and its relationship to other diseases with shared underlying biology.

+ Many approvals of new Parkinson's disease therapies by the US FDA over the last decade offer an increasing array of symptom-treating options for people at early or more advanced stages of disease (see figure on next page). As exhibited in this report, many promising treatments, including those with potential to slow disease progression, are in human testing, and many more approaches, fueled by a wave of promising biological targets, are in earlier preclinical stages of therapeutic exploration.

+ Advances in tools to measure Parkinson's biology (such as the seeding assay mentioned above), as well as continued efforts to develop and refine methods to assess more sensitively patient-relevant clinical function, are enabling new clinical trial designs and testing paradigms. Ultimately, this may lead to faster and more informative clinical trials.

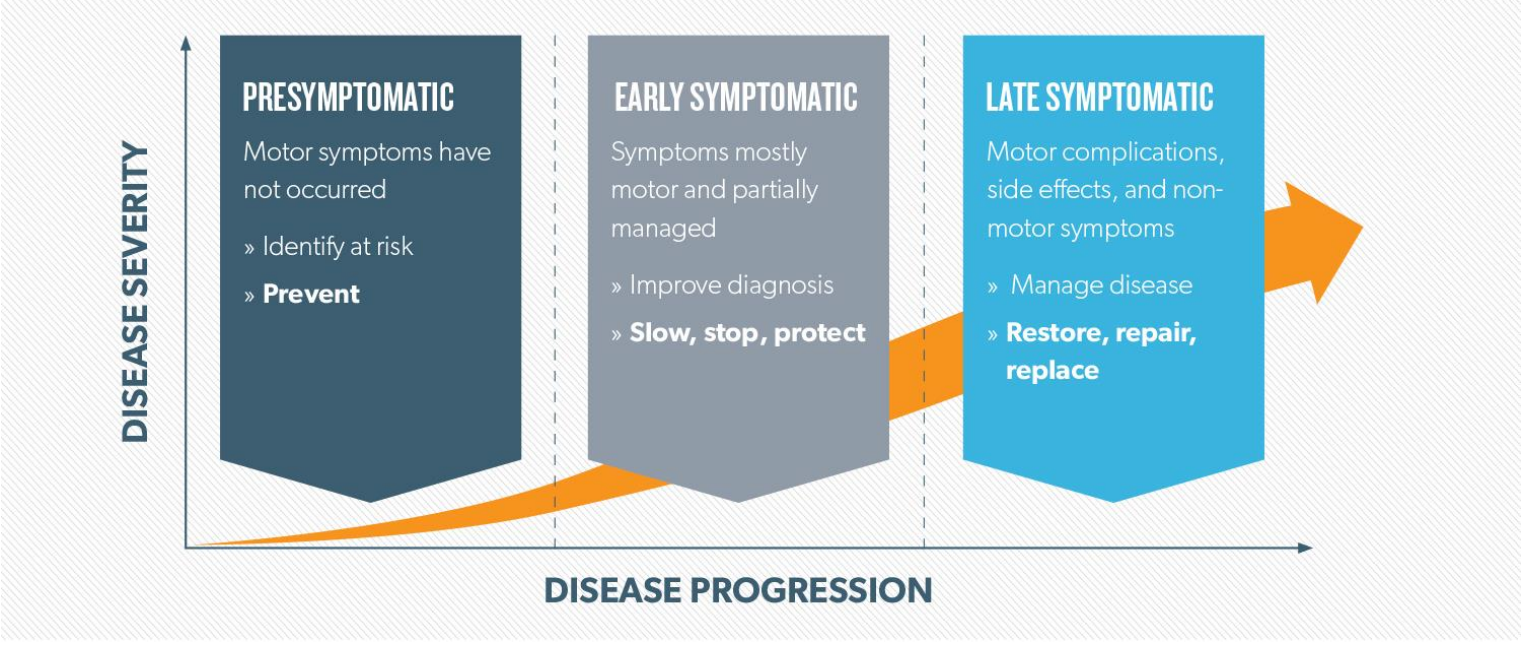
+ Increased awareness of Parkinson's disease and its impact on those living with the disease and the communities in which they live, are elevating advocacy to address policies and public priorities needed to support more robust research and improved healthcare.

PARKINSON'S PIPELINES WE MONITOR

Delivering better treatments to people with PD requires developing diverse therapies targeting critical disease stages and symptoms. Given the many approaches needed, MJFF actively monitors therapeutic programs within the following key areas:

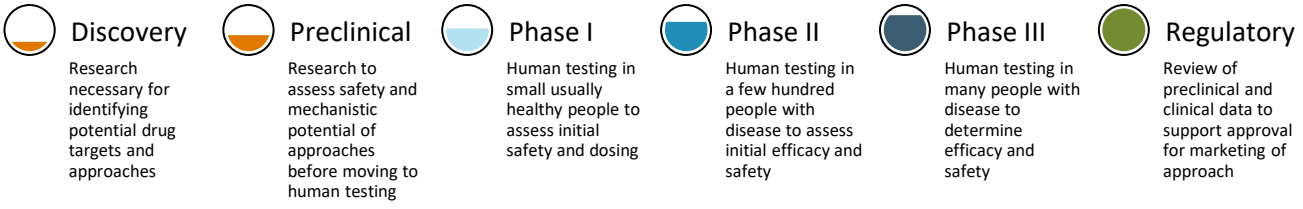
+ Therapies targeting underlying Parkinson's disease biology that may over time slow, stop, prevent or reverse the degenerative process and resulting symptom progression
+ Therapies targeting brain signaling and neural activity that may provide daily relief from disabling PD motor as well as non-motor symptoms, including cognitive impairment and gait/balance issues which are critical unmet needs for people with PD.

Disease Biology	Brain Chemistry and Activity
• Alpha-Synuclein • LRRK2 • GBA1 • Mitochondrial Impairment • Oxidative Stress • Autophagy • Inflammation • Microbiome • Cellular Repair and Replacement • Other biological targets	• Acetylcholine • Dopamine • Endocannabinoids • Epinephrine/Norepinephrine • GABA • Glutamate • Serotonin • Other neurochemical targets



THE DRUG DEVELOPMENT PROCESS

Moving an idea from disease understanding toward treatments for people with Parkinson's disease is a multi-step process, with each step adding additional data and confidence that an approach is safe and can offer meaningful benefit



Types of approaches in development for Parkinson's disease

- **Small Molecule Therapy**: small chemical compounds designed to bind or interact with specific biological targets (usually proteins) to alter their function.
- **Antibody Therapy**: therapeutic immune proteins that specifically bind cellular targets (often targets that may be challenging to modulate with small molecules) and delivered either directly (passive therapy) or generated by the body through a vaccine (active therapy).
- **Peptide Therapy**: a protein or protein fragment that can mimic the effects of or alter the function of other proteins.
- **Gene Therapy**: an approach to deliver a therapeutic gene via a modified virus into cells which then use the delivered gene to produce a therapeutic protein.
- **Antisense Oligonucleotide Therapy**: A small nucleotide that targets and inhibits specific RNA molecules usually to reduce production of a specific protein.
- **Cell/Tissue Therapy**: Transplanted or infused cells or tissues that may be used to replace damaged or lost cells (e.g., dopamine neurons) or that may support existing cells by secreting modulatory or protective factors.
- **Neuromodulation Therapy**: Approaches involving implanted or wearable stimulators or surgical lesioning to alter neural activity

HOW MJFF ENABLES THE PARKINSON'S PIPELINE

MJFF offers a range of programs to support development of innovative treatments for people living with Parkinson's disease. Strategies seek to address key financial and non-financial barriers sponsors face when moving a program through the risky development process.

Funding to de-risk and accelerate key preclinical and clinical development steps for promising therapeutic approaches

Data, biosamples and other MJFF-distributed resources to support therapy development

Clinical trial protocol input and recruitment strategies

Endpoint consensus and regulatory path

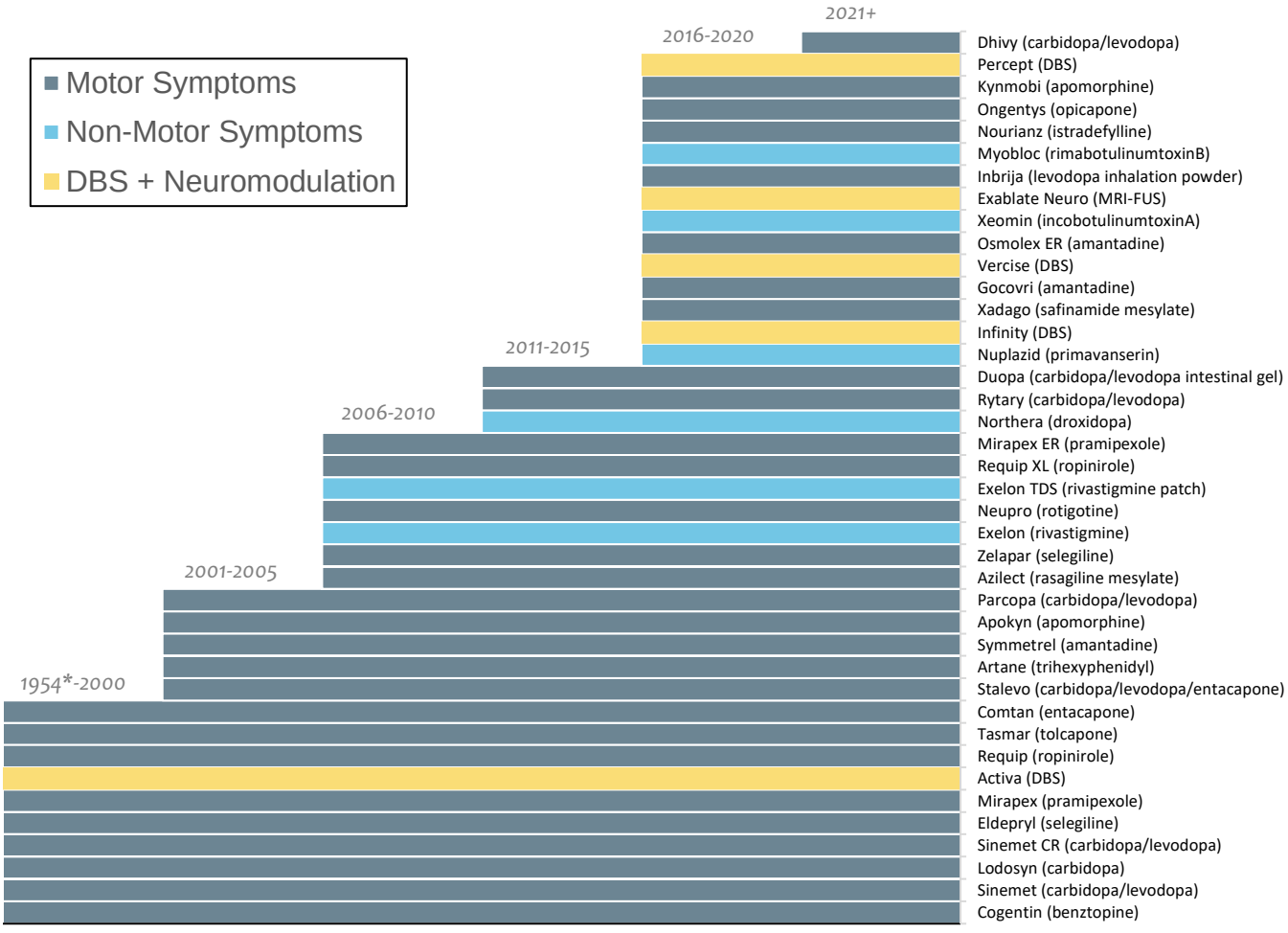
Patient lived experience and preferences insight

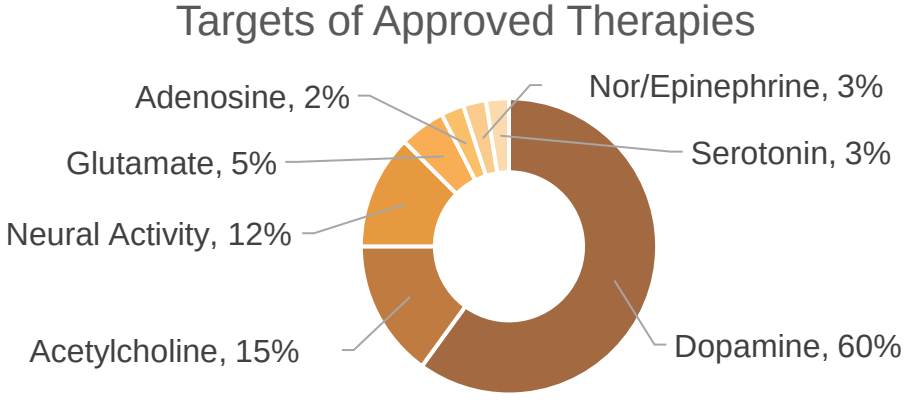
Research and drug development workshops and consortia

For more information about the many ways MJFF is accelerating advances in PD, go to www.michaeljfox.org.

APPROVED THERAPIES FOR PARKINSON'S DISEASE

Diverse and meaningful therapies reaching the hands of people with Parkinson's disease is an ultimate barometer of progress. Below highlights Parkinson's treatment approvals over time in the United States as well as important symptoms and brain pathways targeted by these approaches.





STATE OF THE PARKINSON'S DISEASE PIPELINE

As of Q1 2024, we are currently monitoring 151 priority treatments in clinical testing for Parkinson's disease[1]

[1]includes treatments MJFF has identified as important and where a trial is active or has recently completed but remains in active development with commercial potential in US/EU. Different programs testing the same therapy (e.g., exenatide) are counted once, unless a reformulation. Includes programs expected to enter the clinic soon (see Appendix).

Over the past year, we saw

- 4 programs in regulatory discussions with the US FDA, including:
  - ABBV-951 (AbbVie)
  - IPX-203 (Amneal Biosciences)
  - ND-0612 (NeuroDerm/Mitsubishi Tanabe Pharma Group)
  - SPN-830 (Supernus Pharmaceuticals)

- 8 novel programs enter initial clinical testing, including:
  - ATH-399A (NurrOn Pharmaceuticals)
  - BHV-8000 (Biohaven)
  - GT-02287 (GAIN Therapeutics)
  - HER-096 (Herantis Pharma)
  - NEU-411 (Neuron23)
  - TED-A9 (S. Biomedics)
  - VENT-02 (Ventus Therapeutics)
  - VTX-3232 (Ventyx Biosciences)

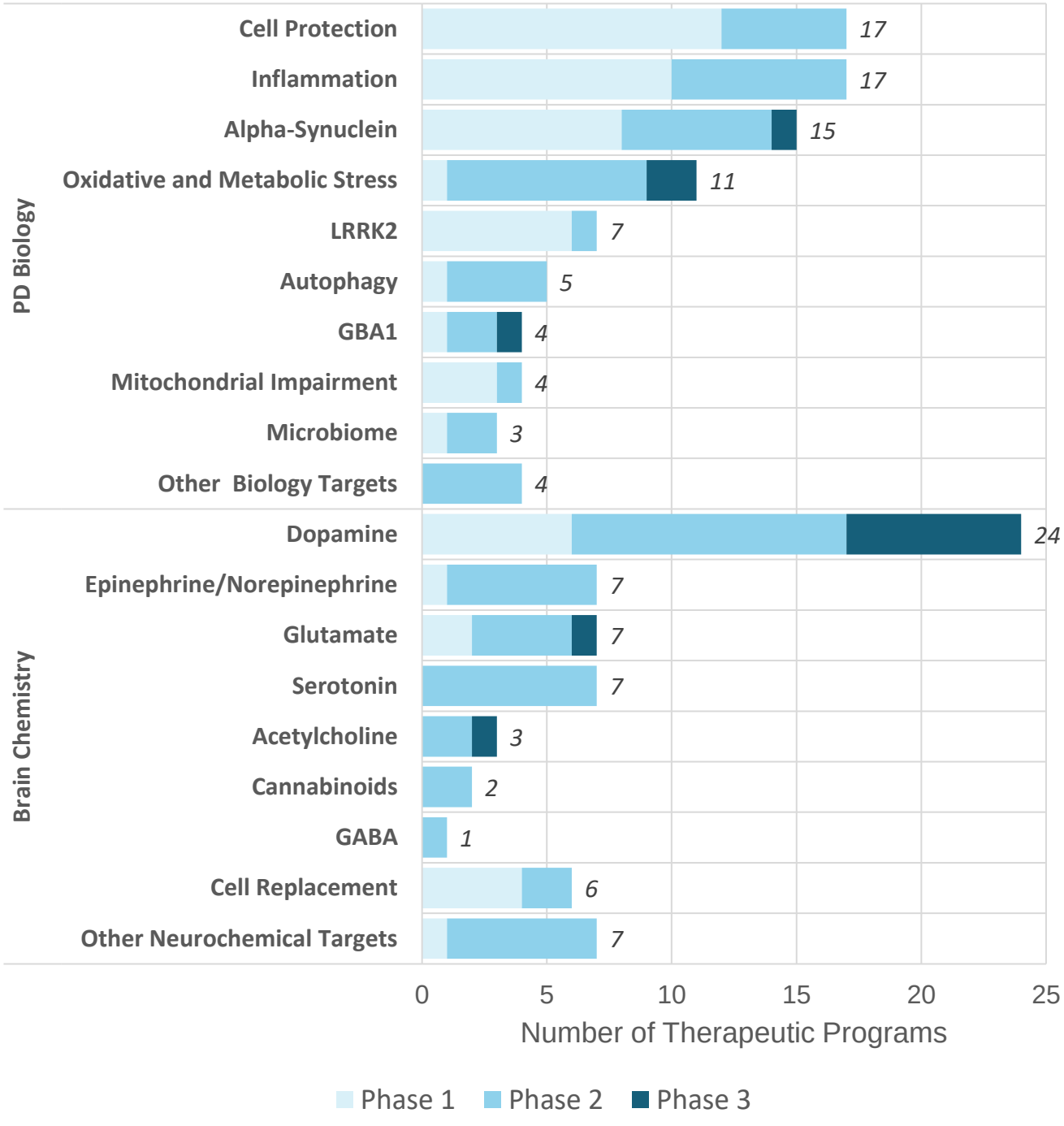
- 4 programs advance clinical phases, including:
  - ACI-7104 (AC Immune)
  - BIA 28-6156 (Bial)
  - NT-0796 (NodThera)
  - UCB-0022 (UCB)

- 2 clinical-stage programs entered partnership agreements, including:
  - AbbVie will acquire Cerevel Therapeutics who recently reported positive Phase III trial results for its dopamine receptor agonist tavapadon
  - Daewoong Pharmeceutical and HanAll Biopharma entered licensing agreement with NurrOn Pharmaceuticals for development of ATH-399A

STATE OF THE PARKINSON'S DISEASE PIPELINE

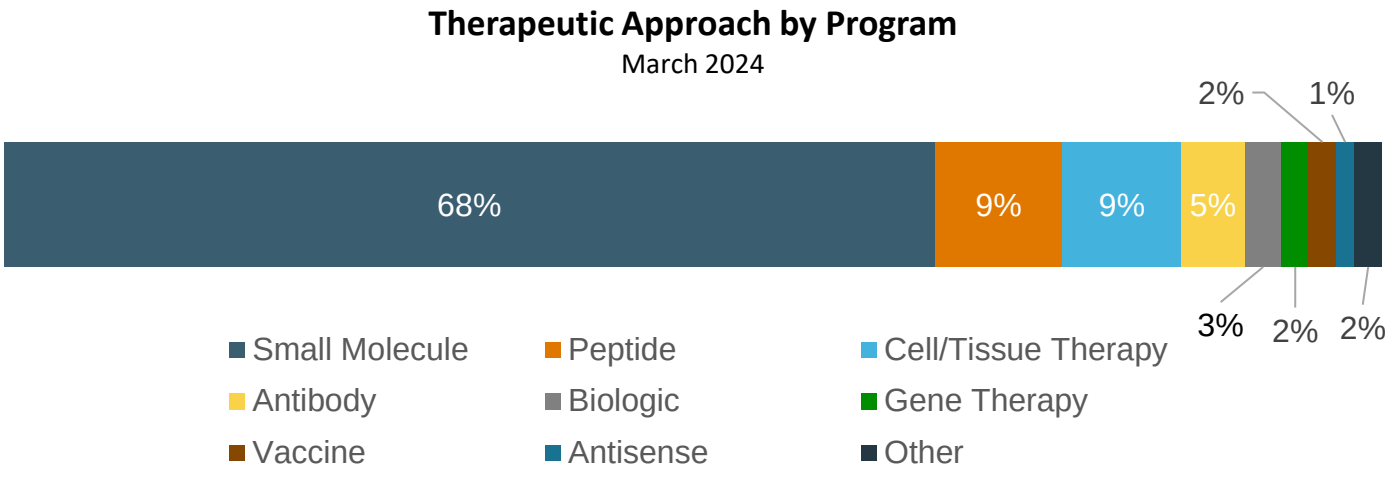
Treatments we are following in this report[1] target a range of biological pathways with potential for disease slowing or modulate brain chemistry to address motor and non-motor symptoms. While later stage pipelines are dominated by attempts to optimize dopamine-directed therapy, we also see a rising wave of novel approaches moving through clinical testing.

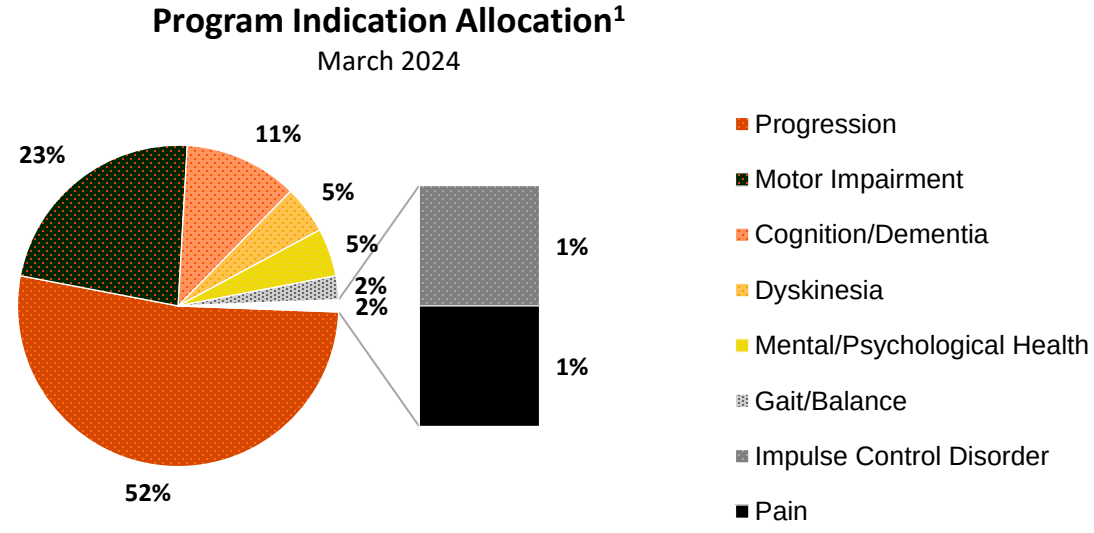
[1]Excludes technology-enabled medical devices and neuromodulation approaches.



STATE OF THE PARKINSON'S DISEASE PIPELINE

The current PD pipeline is testing a range of different approaches targeting many critical needs. Disease slowing is indicated by more than half of the programs, offering promising hope for the future.





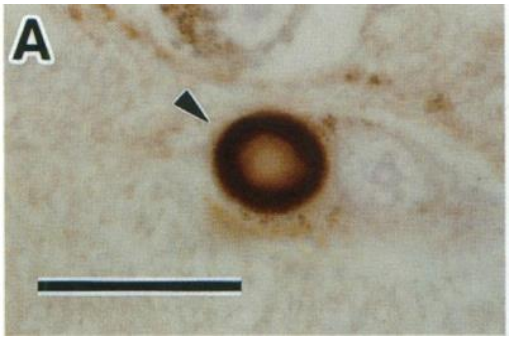
[1]Programs testing multiple indications are counted once for each indication. Multiple programs testing the same therapy for the same indication (e.g., ambroxol, exenatide) are counted once. Medical devices/neuromodulation and other non-biomedical therapies are not included in these counts.

PARKINSON'S PRIORITY THERAPEUTIC PIPELINES

TARGETING ALPHA-SYNUCLEIN

Therapeutic Rationale

Genetic and pathological evidence strongly supports a role of the alpha-synuclein (aSyn) protein in PD. Mutations in SNCA, the gene that encodes the aSyn protein, were some of the first genetic links to PD identified. Later detection of aSyn protein aggregates (see image) within certain neurons of almost all people with PD—and evidence that this pathology may spread from cell to cell—provided strong rationale for seeking treatments that can target the production, spread and/or clearance of this potentially toxic form of the aSyn protein.



One of the first images published from the brain of a Parkinson's patient of aggregated alpha-synuclein protein (Baba et al., American Journal of Pathology 1998)

Current Landscape

Treatments in development target aSyn pathology in multiple ways. Some leverage antibodies and the immune system to specifically remove aSyn. Others target cellular mechanisms involved in clearing aSyn or seek to slow spread of aSyn pathology from cell to cell.

Pipeline progress highlights include:

- Results from Roche suggesting their aSyn-directed monoclonal antibody prasinezumab may be slowing PD motor decline in some people although more data are needed from their ongoing clinical trial before meaningful conclusions can be drawn.
- Additional clinical data from Vaxxinity showing apparent ability of its aSyn vaccine UB-312 to reduce aggregated aSyn levels detected in spinal fluid, a possible measure of target engagement
- Statements from Annovis that its Phase 3 trial results testing buntanetap are delayed due to data cleaning requirements.
- Awareness that many sponsors are making strategic decisions to prioritize initial or parallel testing of aSyn therapies in multiple system atrophy (MSA), a neurological disorder also associated with accumulation of aSyn primarily in glial cells (vs neuronal accumulation seen in PD). Given its faster progression, some sponsors feel that MSA may provide quicker read-outs for aSyn-directed therapy that could then inform testing in PD.

MJFF Perspective and Role

Strong rationale remains for targeting aSyn therapeutically. MJFF continues to support a range of efforts to enable this pipeline, including fostering a diverse range of aSyn-directed therapies, developing biomarkers and imaging methods for measuring aSyn, and leveraging an expanded understanding of diseases linked to neuronal aSyn pathology (such as Dementia with Lewy Bodies) to propose new ways of categorizing, defining and staging these diseases based on their related biology.

PROGRAMS TARGETING ALPHA-SYNUCLEIN

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
ABL Bio & Sanofi	ABL-301	aSyn pathology inhibitor	Antibody	Progression	**1**	-	Phase 1 results pending H1 2025
MODAG & Teva	Emrusolmin (Anle-138b/ TEV-56286)	aSyn pathology inhibitor	Small molecule	Progression	**1**	$	**PD:** Phase 1 results Publication **MSA:** Phase 2 trial pending
Bioarctic	Exidavnemab (BAN-0805)	aSyn pathology inhibitor	Antibody	Progression	**1**	-	Phase 2 trial pending H2 2024
Vaxxinity	UB-312	aSyn pathology inhibitor	Vaccine	Progression	**1**	$	**PD & MSA:** Phase 1 results Press release
UCB	UCB-7853	aSyn pathology inhibitor	Antibody	Progression	**1**	-	Phase 1 results pending
Janssen Pharmaceutical	YTX-7739	aSyn pathology inhibitor	Small molecule	Progression	**1**	$	Pending update
Biogen & Ionis	BIIB-101/ ION-464	aSyn reduction	Antisense	Progression	**1**	-	**MSA:** Phase 1 results pending 2027
AC Immune	ACI-7104	aSyn pathology inhibitor	Vaccine	Progression	**2**	$	Phase 2 results pending 2028
Alterity Therapeutics	ATH-434	aSyn pathology inhibitor	Small Molecule	Progression	**2**	$	**MSA**: Phase 2 results pending H1 2025
Lundbeck	Lu-AF82422	aSyn pathology inhibitor	Antibody	Progression	**2**	-	**MSA:** Phase 2 interim results Press release
AstraZeneca & Takeda	MEDI-1341/ TAK-341	aSyn pathology inhibitor	Antibody	Progression	**2**	Other	**PD:** Phase 1 results Publication **MSA:** Phase 2 results pending Q2-Q3 2025
Novartis & UCB	Minzasolmin (UCB-0599/ DLX-313)	aSyn pathology inhibitor	Small molecule	Progression	**2**	$, Other	Phase 2 topline results pending H2 2024
Prothena & Roche	Prasinezumab	aSyn pathology inhibitor	Antibody	Progression	**2**	Other	Phase 2 topline results pending 2024
University of Tübingen	Prasinezumab	aSyn pathology inhibitor	Antibody	Cognition/ Dementia	**2**	$	Phase 2 trial launch pending H2 2024
Annovis Bio	Buntanetap (ANVS-401)	aSyn reduction	Small molecule	Progression	**3**	$	Phase 3 results pending

[a]MJFF roles include direct funding at any stage of development ($) or additional support (Other) such as recruitment or protocol advice. MJFF continuously engages with companies to understand challenges and opportunities and this may not be fully reflected in this report.
[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.

Development Stage

1 2 3 Reg.

LEADING PROGRAM DETAILS: ALPHA-SYNUCLEIN

Buntanetap (Annovis)

Investigational oral small molecule drug believed to target production of pathological proteins like alpha-synuclein and slow progression of PD. Initial trial results support safety and tolerability and reveal possible effects on exploratory biomarkers and clinical measures in both PD and Alzheimer's disease. A Phase 3 trial to assess the drug's effectiveness in people with early PD recently completed but announcement of results has been delayed by the company (as of March 2024) due to ongoing data cleaning. MJFF supported earlier preclinical work of this drug.

Minzasolmin (UCB & Novartis)

Investigational oral small molecule targeting alpha-synuclein aggregation in the brain to slow progression of PD. Phase 1b results have confirmed minzasolmin's safety and tolerability while an ongoing Phase 2a trial (called Orchestra) is assessing the drug's potential to alter disease progression. MJFF funded earlier preclinical development of the drug with the company Neuropore before it was licensed to UCB in 2014.

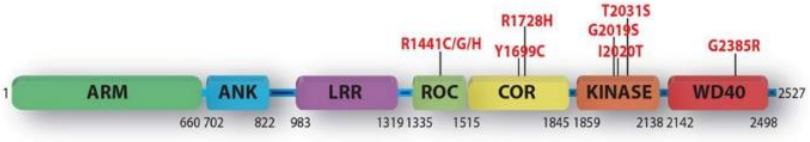
Prasinezumab (Roche)

Investigational monoclonal antibody delivered through intravenous infusions to block alpha-synuclein spread between nerve cells. Results from a Phase 2 trial (the PASADENA trial) revealed that while the drug did not meet its primary objective of slowing overall clinical progression, secondary tests suggested possible slowing of motor decline. A Phase 2b trial (called PADOVA) is ongoing with results expected in late 2024. Separately, MJFF is supporting an investigator-initiated study testing prasinezumab's potential in slowing cognitive decline in people with PD who carry a mutation in the GBA gene.

TARGETING LRRK2

Therapeutic Rationale

Mutations in the gene leucine-rich repeat kinase 2 (LRRK2) explain 1-40% of cases of PD depending on the ethnic population studied. LRRK2 is a 'kinase': a protein that chemically modifies other proteins to regulate cellular processes, such as the endolysosomal pathway, a system critical for transporting, recycling and degrading cellular components. PD-associated mutations appear to increase this activity, although how this causes neurodegeneration is not fully known. Whether abnormal LRRK2 activity may explain cases of PD in people without mutations is an area of active investigation.



A schematic of the LRRK2 protein showing some of the most important mutations linked to PD (Image from Steger et al., eLife 2016.)

Current Landscape

Programs in clinical testing seek to reduce LRRK2's pathological function either by inhibiting its kinase activity or reducing production of the LRRK2 protein itself. Drug makers are testing benefits of inhibiting LRRK2 in people both with and without genetic mutations in the hope of exploring wider use of such approaches.

Pipeline progress highlights include:

- An expanding pipeline with new companies Neuron23 (NEU-411), Arvinas (ARV-102) and 1st Biotherapeutics (FB-418) initiating trials of additional LRRK2-directed therapies.
- Consolidation of Denali and Biogen's Phase 2 and Phase 3 trials testing DNL-151/BIIB-122 in people with and without LRRK2 mutations based on a desire to accelerate trial readouts. Denali has also indicated it hopes to launch a separate Phase 2 trial in LRRK2 mutation carriers.

MJFF Perspective and Role

With strong genetic links to PD and compelling therapeutic rationale, MJFF has been a consistent supporter and funder of studies to facilitate translation of LRRK2 research into treatments for people with PD. MJFF uses highly collaborative models to support work around key challenges and barriers to progress (e.g., biomarkers, safety assessments, patient recruitment challenges) which have been instrumental in fueling the growing number of LRRK2 therapeutic programs in development.

PROGRAMS TARGETING LRRK2

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Neuron23	NEU-411	LRRK2 kinase inhibitor	Small Molecule	Progression	**1**	-	Phase 1 results pending H1 2024
Neuron23	NEU-723[1]	LRRK2 kinase inhibitor	Small molecule	Progression	**1**	-	Pending update
Arvinas	ARV-102	LRRK2 protein degrader	Small Molecule	Progression	**1**	-	Phase 1 trial ongoing
Biogen	BIIB-094	LRRK2 reduction	Antisense	Progression	**1**	$, Other	Phase 1 results pending H1 2025
Denali & Biogen	DNL-151/ BIIB-122[2]	LRRK2 kinase inhibitor	Small molecule	Progression	**2**	Other	Ongoing phase 2 trial

[1]Phase 1 study terminated due to business decision.
[2]Mid-2023, Biogen stopped the Ph3 LIGHTHOUSE study in favor of prioritizing LUMA, the Ph2 recruiting idiopathic PD. In a February 2024 financial update, Denali indicated plans to launch a new Phase 2 trial of DNL-151/BIIB-122 in people carrying LRRK2 mutations.

[a]MJFF roles include direct funding at any stage of development ($) or additional support (Other) such as recruitment or protocol advice. MJFF continuously engages with companies to understand challenges and opportunities and this may not be fully reflected in this report.
[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.

LEADING PROGRAM DETAILS: LRRK2

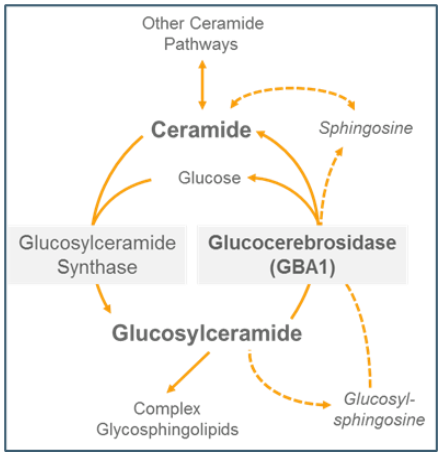
DNL-141/ BIIB-112 (Denali & Biogen)

Investigational oral small molecule inhibitor of LRRK2 hypothesized to improve lysosomal dysfunction and possibly slow PD progression. Phase 1b trial results support the drug's safety and tolerability, as well as demonstrate ability of the drug to reduce LRRK2 activity. Recently, sponsors decided to terminate a Phase 3 trial (LIGHTHOUSE) in people with LRRK2 genetic mutations and add these participants to an ongoing Phase 2 trial in early-stage PD patients without genetic mutations (LUMA) in order to get a faster readout on efficacy in early-stage idiopathic Parkinson's disease while gaining further clinical data from people with and without a LRRK2 mutation.

TARGETING GBA1

Therapeutic Rationale

Certain variants in the gene GBA1 increase risk for PD. GBA1 encodes the protein glucocerebrosidase ("GCase") which regulates metabolism of important lipids in cells (see graphic) and when dysfunctional may lead to toxic accumulation of these lipids. PD patients with certain GBA1-associated gene changes often have an earlier age of disease onset, can exhibit more cognitive issues and may progress more rapidly. Whether altered GCase activity explains PD cases without GBA1 mutations is an area of active study.



Schematic of the complex lipid pathway in which GBA1 functions. Impaired GBA1 can lead to accumulation of glucosylceramide which may underlie toxicity in Parkinson's disease in people with this impairment.

Current Landscape

Drug makers primarily seek to enhance GCase activity or reduce accumulated lipids as potential ways of treating this form of PD. Approaches include using gene therapy to deliver functional copies of the gene or using small molecule drugs to enhance GCase activity.

Pipeline progress highlights include:

- Initiation of a Phase 1 trial of GAIN Therapeutics' GT-02287 GCase enhancer. Results of the study in healthy participants are expected later in 2024.
- Expanded and continued testing of repurposed mucolytic drug ambroxol through multiple, mostly academic, investigator-led trials.

MJFF Perspective and Role

GBA1 variation contributes to some of the most common genetic forms of PD and represent a major therapeutic area of focus. MJFF has supported work to identify factors that may influence GCase protein function and its impact on the lysosomal pathway which may point to additional therapeutic targets and ways of identifying people at-risk for this form of PD.

PROGRAMS TARGETING GBA1

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Gain Therapeutics	GT-02287	GCase enhancer	Small Molecule	Progression	**1**	-	Phase 1 interim results Publication
Agyany Pharmaceuticals	Ambroxol	GCase enhancer	Small Molecule	Progression	**2**	-	Phase 2 results pending Q2-Q3 2025
IRCCS National Neurological Institute	Ambroxol	GCase enhancer	Small molecule	Progression	**2**	-	Phase 2 results pending H1 2025
Lawson Health Research Institute	Ambroxol	GCase enhancer	Small molecule	Progression	**2**	-	Phase 2 interim results Press release
University College, London	Ambroxol	GCase enhancer	Small molecule	Progression	**2**	-	Phase 3 trial launch pending
Bial Biotech	BIA 28-6156/ LTI-291	GCase enhancer	Small molecule	Progression	**2**	$, Other	Phase 2 results pending H1 2026
Prevail Therapeutics (Eli Lilly) & Regenxbio	PR-001	GCase restoration	Gene Therapy	Progression	**2**	Other	Phase 2 results pending 2029
University Medical Center Groningen	Ambroxol	Gcase enhancer	Small Molecule	Cognition/ Dementia, Progression	**3**	-	Phase 3 results pending H2 2025

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[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.

LEADING PROGRAM DETAILS: GBA1

Ambroxol (multiple sponsors)

Oral small molecule therapy being repurposed for possible treatment of PD. Approved as a mucolytic agent for treatment of respiratory illnesses, laboratory screening of cells from people with Gaucher disease, a disorder also associated with GBA1 mutations, identified ambroxol as a possible GCase enhancer. This led to interest in testing ambroxol also in people with GBA1-associated PD. An earlier open-label trial led by researchers at University College London reported that ambroxol could target and elevate GCase levels in people with PD both with and without GBA1 mutations. These findings have supported launch of a larger Phase 3 trial of ambroxol by the same group. In parallel, several other academic centers (and at least one company) are exploring ambroxol for PD.

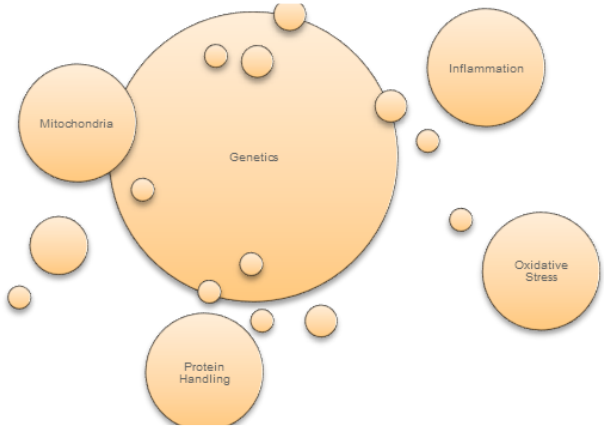
BIA 28-6156 (Bial)

Investigational oral small molecule allosteric modulator of the GBA1 gene-encoded glucocerebrosidase protein. MJFF supported preclinical work with earlier versions of this drug through its prior company owner, Lysosomal Therapeutics. An initial Phase 1 trial of the drug demonstrated sufficient safety and tolerability in healthy volunteers which was followed by a successful Phase 1b safety trial in people with GBA1-associated PD. Currently, the drug is being assessed in a Phase 2 trial (ACTIVATE) in people with PD carrying GBA1 mutations with results anticipated by end of 2025.

TARGETING OTHER DISEASE BIOLOGY

Therapeutic Rationale

Increased understanding of biological processes disrupted in PD—including data from genetic studies—points to a host of molecular targets and pathways that could offer hope for slowing disease. Cellular mechanisms linked to mitochondrial function, oxidative stress and metabolic impairment, inflammation, microbiome and processes involved in handling and degrading misfolded proteins all represent promising avenues for therapeutic development.



A range of biological factors may influence the cause and progression of PD and are areas of active research and treatment development.

Current Landscape

A robust pipeline of drugs targeting various hypothesized mechanisms contributing to PD are in active clinical testing. These approaches include company-led development of novel drugs but quite often, investigators also test repurposed therapies approved for other indications based on their potential for targeting putative PD pathogenic mechanisms. As biological understanding of PD improves, more targeted and optimized therapies may be developed.

Pipeline progress highlights include:

- Emerging approaches targeting mitochondrial health, including MTX-325 from Mission Therapeutics which seeks to enhance removal of damaged mitochondria to possibly slow PD progression.
- More data from mostly repurposed treatments targeting the GLP-1 receptor suggesting possible impact on motor decline in people with PD, although published results across trials are mixed.
- A growing pipeline of treatments targeting inflammation and immune responses, including several seeking to inhibit NLRP3, a core component of the so-called inflammasome signaling complex important for initiating key inflammatory responses in cells.

MJFF Perspective and Role

Given the complex nature of PD, no single treatment may be sufficient to address all possible underlying biology linked to the disease, so maintaining a diverse range of approaches in clinical testing is critical. MJFF supports work to expand biological understanding of PD including implementation of partner-led initiatives like the Aligning Science Across Parkinson's Collaborative Research Network and Global Parkinson's Genetics Program. Insight from these and other efforts point to targets that can be translated into future therapies. In parallel, MJFF is supporting development of pathway-specific biomarkers to inform patient stratification and therapeutic target engagement, with a goal of making interpretation of trial results more informative.

PROGRAMS TARGETING OTHER DISEASE BIOLOGY

MITOCHONDRIAL IMPAIRMENT

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Mthera Pharma	MT-101-5	aSyn inhibitor, Mitochondrial enhancer (multi-component)	Small Molecule	Progression	**1**	-	Phase 2 trial launch pending Q3 2024
Glaceum	Vutiglabridin (HSG-4112)	PON2modulator	Small Molecule	Progression	**1**	$	Phase 2 trial launch pending Q3 2024
Sheffield Teaching Hospital	Ursodiol (UDCA)	Mitochondrial enhancer	Small molecule	Progression	**2**	$	Phase 2 results Publication

OXIDATIVE AND METABOLIC STRESS

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Clene Nanomedicine	CNM-Au8	Bioenergetics, gold nanocrystals	Other	Progression	**2**	$	Pending update
Stockholm Health Care Services	Exenatide	GLP-1 agonist	Peptide	Progression	**2**	-	Phase 2 results pending
Cedars-Sinai Medical Center & Novo Nordisk	Liraglutide	GLP-1 agonist	Peptide	Progression	**2**	-	Pending update
University Hospital, Toulouse & Sanofi	Lixisenatide	GLP-1 agonist	Peptide	Progression	**2**	-	Phase 2 results Publication
Neuraly	NLY-01 (pegylated exenatide)	GLP-1 agonist	Peptide	Progression	**2**	-	Phase 2 results Publication
Invex & Peptron	PT-320 (exenatide SR)	GLP-1 agonist	Peptide	Progression	**2**	-	Phase 2 results Press release
Oslo University & Novo Nordisk	Semaglutide	GLP-1 agonist	Peptide	Progression	**2**	-	Phase 2 results pending H1 2025

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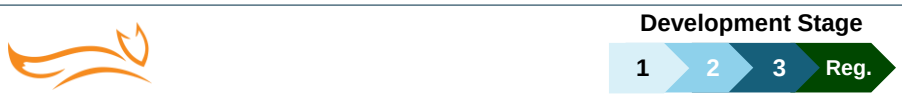
[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.



PROGRAMS TARGETING OTHER DISEASE BIOLOGY

OXIDATIVE AND METABOLIC STRESS

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Radbound University	Hypoxia Therapy	Hypoxic preconditioning	Other	Progression	2	$	Phase 2 results pending H2 2024
HealthPartners Institute	Novolin R (intranasal insulin)	Insulin receptor agonist	Peptide	Multiple Symptoms	2	-	Phase 2 results pending Q2 2024
Gateway Institute	ISN-GSH (insulin-glutathione)	Insulin receptor agonist + reducing agent	Peptide	Cognition/ Dementia	2	-	Phase 2 results pending Q3 2024
University College London	Exenatide	GLP-1 agonist	Peptide	Progression	3	$	Phase 3 results pending Q3 2024
Zhejiang University School of Medicine	Idebenone	Reducing agent	Small molecule	Progression	3	-	Phase 3 results pending

AUTOPHAGY

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
1st Biotherapeutics	1st-102 (FB-101)	c-Abl kinase inhibitor	Small molecule	Progression	1	-	Phase 1 results Press release
Inhibikase	ikT-148009	c-Abl kinase inhibitor	Small molecule	Progression	2	$, Other	Phase 2 results pending H2 2024
Il-Yang Pharmaceutical	Radotinib	c-Abl kinase inhibitor	Small molecule	Progression	2	-	Phase 2 results pending Q2-Q3 2025
SPARC	Vodobatinib (K-0706)	c-Abl kinase inhibitor	Small molecule	Progression	2	Other	Phase 2 interim results pending Q2 2024, topline results pending Q3 2024
FAScinate Therapeutics (Kainos Medicine)	KM-819	FAF1 antagonist	Small molecule	Progression	2	Other	Phase 2 results pending Q4 2025 - Q1 2026

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PROGRAMS TARGETING OTHER DISEASE BIOLOGY

INFLAMMATION

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
The Scripps Research Institute	PDM608	Granulocyte macrophage colony stimulating factor	Biologic	Progression	**1**	$, Other	Phase 1 results pending H2 2024
Partner Therapeutics	Sargramostim	Granulocyte macrophage colony stimulating factor	Biologic	Progression	**1**	-	Phase 1 interim results Publication
Biohaven	BHV-8000	Janus kinase 1 inhibitor; Tyrosine kinase 2 inhibitor	Small Molecule	Progression	**1**	-	Phase 1 results pending Phase 3 trial pending H2 2024
IntelGenx	INT-0043 (Montelukast)	Leukotriene antagonist	Small Molecule	Progression	**1**	-	Phase 2 trial launch pending H1 2024
Olatec Therapeutics & University of Cambridge	Dapansutrile (OLT-1177)	NLRP3 inhibitor	Small Molecule	Progression	**1**	$	Phase 2 trial launch pending Q2-Q3 2024
Roche	Selnoflast (RO-7486967)	NLRP3 inhibitor	Small molecule	Progression	**1**	Other	Phase 1 results pending H1 2025
Ventus Therapeutics	VENT-02	NLRP3 inhibitor	Small Molecule	Progression	**1**	-	Phase 1 preliminary results pending H1 2024
Ventyx Biosciences	VTX-3232	NLRP3 inhibitor	Small Molecule	Progression	**1**	-	Phase 1 results Press release Phase 2 trial pending H2 2024
Alkahest (Part of Grifols)	GRF-6021	Blood plasma fraction	Peptide	Cognition/ Dementia	**2**	$, Other	Pending update
Alkahest (Part of Grifols)	AKST-4290	Chemokine antagonist	Small Molecule	Progression	**2**	$	Pending update
BioVie	NE-3107	ERK1/2 inhibitor	Small Molecule	Motor Impairment, Progression	**2**	-	Next trial pending
University of Cambridge	Azathioprine	Immuno-suppressant	Small Molecule	Progression	**2**	-	Phase 2 results pending H1 2024
NodThera	NT-0796	Inflammasome inhibitor; NLRP3 inhibitor	Small Molecule	Progression	**2**	-	Phase 2 results Press release
Stockholm Health Care Services	Montelukast	Leukotriene antagonist	Small Molecule	Progression	**2**	-	Phase 2 results Press release

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PROGRAMS TARGETING OTHER DISEASE BIOLOGY

MICROBIOME

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
University of Texas	PRIM-DJ2727	Fecal microbiota (microbiome modulator)	Biologic	Motor Impairment	**1**	-	Phase 1 results Publication
University of California, San Francisco	Rifaximin	Antibiotic	Small Molecule	Motor Impairment	**2**	-	Phase 2 results pending
Medical University of Warsaw	Fecal Transfer	Fecal microbiota (microbiome modulator)	Biologic	Motor Impairment, Progression	**2**	-	Phase 2 results pending H1 2025

OTHER PROGRAMS TARGETING DISEASE BIOLOGY

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
University of Sydney[1]	Albuterol	Adrenoreceptor agonist	Small Molecule	Progression	**2**	-	Phase 2 results pending
	Nilvadipine	Calcium channel antagonist	Small Molecule				
	Alogliptin	DPP-4 inhibitor	Small Molecule				
University of Sydney[2]	Ambroxol	Gcase enhancer	Small Molecule	Progression	**2**	-	Phase 2 trial launch pending
	Doxycycline	Putative asyn inhibitor	Small Molecule				

[1]These treatments are being tested as part of a multi-arm platform trial
[2]These treatments are being tested as independent treatments and as a combined treatment in a single trial

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LEADING PROGRAM DETAILS: OTHER DISEASE BIOLOGY

GLP-1 Receptor Agonists (multiple sponsors)

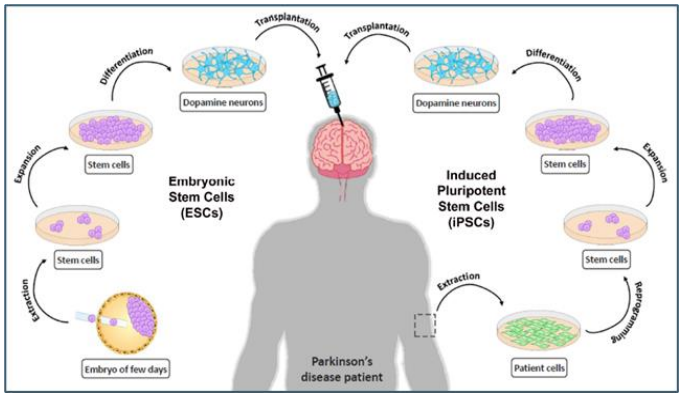
GLP-1 receptor agonists including repurposed exenatide, lixisenatide, liraglutide and semaglutide, among others, are being investigated for their ability to slow PD progression. These drugs mimic the actions of GLP-1, a hormone involved in regulating how cells respond to blood glucose and our feelings of hunger and satiety and several are approved already for diabetes and weight loss. Receptors for GLP-1 are also found within the brain, although their function here is less well understood. Given preclinical data in PD laboratory models suggesting possible protective effects of GLP-1 receptor agonists, there has been strong desire to test these approaches in PD. To date, multiple trials have been performed or are ongoing. While some published findings suggest possible effects on slowing motor decline in some trial participants, findings are not consistent and questions about how these drugs may be acting make interpretation of clinical outcomes challenging. Moreover, many of these drugs come with side effects and complications (such as weight loss) that could be challenging for people with PD.

NLRP3 Inhibitors (multiple sponsors)

Inflammasomes are important cellular protein complexes that form in response to various stimuli to promote an innate immune response and release of pro-inflammatory signals (cytokines). NLRP3 is an important sensing protein leading to inflammasome complex assembly. For neurodegenerative disorders like Parkinson's disease, targeting and inhibiting NLRP3 has become a compelling approach for reducing the potential role of inflammation possibly contributing to neuronal cell loss. As of this report, there are multiple company programs developing and testing so-called NLRP3 inhibitors. These include programs from Olatec (dapansutrile), Roche (selnoflast), Ventus Therapeutics (VENT-02) and Ventyx Biosciences (VTX-3232) with other programs in preclinical stages of development. MJFF has supported a range of efforts to further explore NLRP3, including funding early work that led to the Roche program. In addition, we have supported work to establish possible imaging tracers to detect and assess NLRP3 inflammasomes in the living brain, potentially critical tools for ongoing therapy development.

TREATMENTS SEEKING CELL PROTECTION OR REPLACEMENT

Therapeutic Rationale



Two major approaches to replacing lost dopamine cells in Parkinson's disease using cells derived from different types of stem cells (image from https://bit.ly/2GIngjV)

The isolation of human stem cells in the late 1990s led to an explosion of research to generate replacement cells for neurodegenerative disorders like PD. Identification of growth factors (natural chemical 'fertilizer' important for growing brain cells) and other cellular factors have also pointed to possible ways to protect or restore function of existing brain cells impacted by PD. These approaches are generally agnostic to disease cause making them potentially beneficial to all people with Parkinson's.

Current Landscape

Prior attempts to transplant dopamine-producing cells and tissues or to deliver growth factors into the brains of people with PD have not been generally successful. Newer approaches using improved methods and advanced technologies are underway.

Pipeline progress highlights include:

- Further results from pipeline leader BlueRock Therapeutics showing that people who received transplants of bemdaneprocel (BRT-DA01), the company's stem cell-derived dopamine replacement therapy, exhibited improvements in motor function 18 months after transplantation which the company says supports launching a Phase 2 trial potentially later this year.
- Emergence of newer company players in the cell replacement pipeline including Aspen Neuroscience and Kenai Therapeutics, both of which are developing cell replacement strategies leveraging induced pluripotent stem cells.
- Progress reported from Bayer subsidiary Asklepios BioPharmaceutical in its Phase 1 trial of growth factor gene therapy AB-1005 (AAV-GDNF) showing safety and tolerability as well as possible benefits over 18 months in motor function that justify launching a Phase 2 trial potentially later this year.

MJFF Perspective and Role

While treatments targeting disease pathology offer potential for slowing progression, they may not necessarily restore function in people who have advanced disease. Therefore, efforts to repair or even replace damaged neurons remain an important focus of the therapeutic pipeline. MJFF was an early supporter of much foundational work in the use of stem cell-derived dopamine cell replacement as well as supporting several programs to deliver growth factors. With newer programs entering the clinic, MJFF is now closely monitoring progress and opportunistically supporting studies that may inform this promising pipeline. One note of caution: some clinics around the world offer unregulated cell therapies directly to patients with limited information on what is being delivered or long-term safety and benefits. As of today, no cell-based therapy has been approved for PD and people seeking out such treatments should speak with their doctors and carefully weigh the potential risks.

PROGRAMS SEEKING CELL PROTECTION

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Axoltis Pharma	NX-210c	Beta 1 integrin agonist	Peptide	Progression	**1**	-	Phase 1 trial ongoing
Herantis	HER-096 (xCDNF)	CDNF agonist	Peptide	Progression	**1**	-	Phase 1 results Press release
Asklepios Bio (Bayer)	AAV2-GDNF	GDNF agonist	Gene Therapy	Progression	**1**	-	Phase 1 interim results Press release
University of Arizona	Allopregnanolone	GABA receptor allosteric modulator	Other	Progression	**1**	-	Phase 1 results pending H1 2025
Shanghai iCELL Biotechnology	Stem Cell Therapy	Human amniotic epithelial stem cells	Cell/Tissue Therapy	Progression	**1**	-	Phase 1 results pending 2026
InnoMedica	Talineuren (GM1)	Neural regeneration	Other	Progression	**1**	-	Phase 1 results pending Q3 2024
Daewoong Pharmaceutical, HanAll Biopharma & NurrOn Pharmaceuticals	ATH-399A	Nurr1 agonist	Small Molecule	Progression	**1**	$, Other	Phase 1 results pending H2 2024
University at Buffalo	Lithium	Nurr1 agonist	Small Molecule	Progression	**1**	-	Phase 1 results Publication
Neuronascent	NNI-362	p70S6 kinase phosphorylation stimulator	Small Molecule	Progression	**1**	-	Phase 2 trial launch pending H1 2024
Io Therapeutics	IRX-4204	RXR agonist	Small Molecule	Progression	**1**	$	Phase 2 trial pending
IMAC Holdings, Inc	MSCTC-0010	Umbilical cord-derived mesenchymal stem cells	Cell/Tissue Therapy	Bradykinesia	**1**	-	Phase 1 results pending
Hope Biosciences	HB-adMSC	Adipose-derived mesenchymal stem cells	Cell/Tissue Therapy	Progression	**2**	-	Phase 2 results pending
University of Texas	Allogeneic MSCs	Bone marrow-derived mesenchymal stem cell	Cell/Tissue Therapy	Progression	**2**	$	Phase 2 results pending

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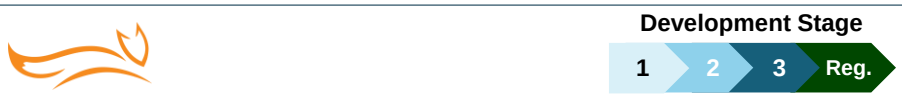

PROGRAMS SEEKING CELL PROTECTION

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Athira Pharma	Fosgonimeton (ATH-1017)	HGF agonist	Small Molecule	Cognition/ Dementia	2	$, Other	Phase 2 results Press release
Algorae Pharmaceuticals[1]	NTCell	Pig choroid plexus cells	Cell/Tissue Therapy	Progression	2	-	Next trial pending
Technical University of Munich	Fasudil	ROCK inhibitor	Small Molecule	Progression	2	-	Phase 2 results pending Q4 2024

[1]Previously Living Cell Technologies

PROGRAMS SEEKING CELL REPLACEMENT

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
BlueRock Therapeutics	Bemdaneprocel (MSK-DA01/ BRT-DA01)	Dopamine cell replacement (derived from hESCs)	Cell/Tissue Therapy	Motor Impairment	1	$	Phase 1 results Press release
International Stem Cell Corporation	ISC-hpNSC	Dopamine cell replacement (derived from hPSCs)	Cell/Tissue Therapy	Motor Impairment	1	-	Pending update
Region Skåne, Lund University, Novo Nordisk & University of Cambridge	STEM-PD	Dopamine cell replacement (derived from hESCs)	Cell/Tissue Therapy	Motor Impairment	1	-	Phase 1 results pending 2027
Kyoto University & Sumitomo Dainippon	iPSC-DA Transplants	Dopamine cell replacement (derived from iPSCs)	Cell/Tissue Therapy	Motor Impairment	2	$	Phase 2 results pending U.S. phase 2 trial launched

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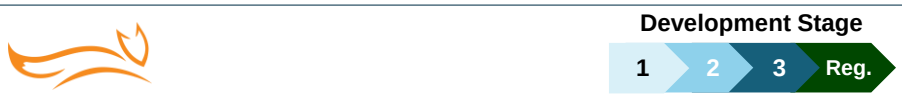


LEADING PROGRAM DETAILS: CELL PROTECTION OR REPLACEMENT

Bemdaneprocel/BRT-DA01 (BlueRock Therapeutics)

Investigational stem cell therapy in development for PD. Bemdaneprocel uses embryonic pluripotent stem cells differentiated into dopamine neurons that are then surgically transplanted into the brains of people with PD to offer a renewed source of dopamine production. As such, the approach seeks to restore and retain motor function but like other cell replacement efforts is not expected to fundamentally stop disease progression. A Phase 1 trial in its final stages has already reported safety and early efficacy data and a Phase 2 trial is planned to launch by end of 2024. Bemdaneprocel represents one of several emerging cell replacement programs in the Parkinson's disease pipeline with other approaches in testing or preparing to enter clinical trials.

Fosgonimeton/ATH-1017 (Athira Pharma)

Investigational small molecule delivered via subcutaneous injection in development for Alzheimer's disease, Parkinson's disease dementia and dementia with Lewy bodies. Fosgonimeton is a positive modulator of the HGF/MET neurotrophic signaling pathway where it may have multiple effects on neuronal health and function. Initial testing in healthy individuals and those with Alzheimer's disease suggests the drug is safe and tolerable and that it can alter electrophysiological measures that may associate with cognitive function. A Phase 2 trial in Parkinson disease dementia and dementia with Lewy bodies did not meet its primary goal of showing benefit measured by a combination of electrophysiological and cognitive measures, although analyses suggest possible pro-cognitive trends on a subset of these measures. A Phase 2/3 trial is ongoing in Alzheimer's disease with data readouts expected later in 2024.

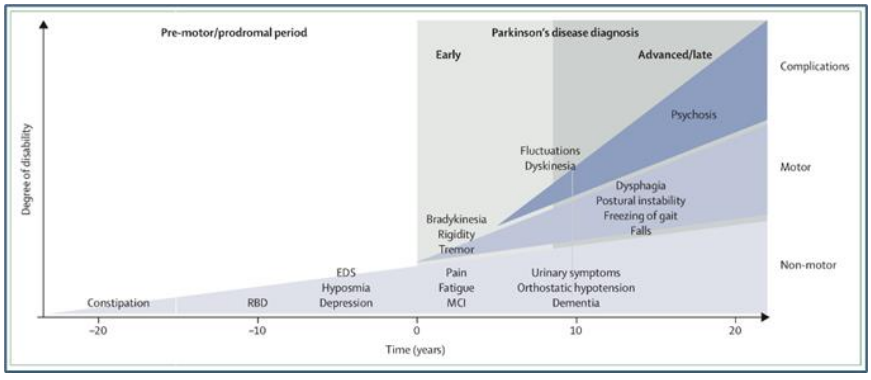
Protective Cell Therapy

While some sponsors are developing stem cell-based approaches to replace lost cells, other groups are using stem cells for their potential to deliver possible protective factors that may support or modulate neuronal health. Mesenchymal stem cells are a common source, are obtained from a variety of body tissues (e.g., bone marrow, adipose tissue, umbilical cord and amniotic fluid) and may provide such protective factors. Multiple sponsors are testing approaches with mesenchymal stem cells (MJFF is funding one such approach), delivered usually through intravenous infusion, to assess safety and potential impact on Parkinson's disease progression and/or symptoms. While potentially promising, regulators have expressed concern about stem cell and other "regenerative" therapies being made directly available to patients. It is important to understand that despite what may be found online, no such therapy has yet to be approved for use in Parkinson's disease.

TARGETING BRAIN NEUROCHEMISTRY

Therapeutic Rationale

People with PD experience a range of symptoms, including hallmark motor symptoms like slow movement, limb rigidity and rest tremor, as well as other are movement problems (e.g., gait and balance) and so-called 'non-motor' features (e.g., cognitive impairment, dementia, psychiatric challenges, mood disorders, sleep issues and constipation). Loss of neurons in the substantia nigra region of the brain that produce the neurochemical dopamine are a primary cause of many of the movement-related symptoms and support dopamine replacement—in particular levodopa—as core therapy for people with PD. Understanding of the pathology driving many non-motor symptoms is less advanced and may reflect loss or dysfunction of other populations of neurons (and their associated neurochemical messengers) in the brain.



Timing and diversity of motor and non-motor symptoms represent an important aspect impacting quality of life for people with PD (Image from Kalia et al., Lancet 2015)

Current Landscape

A long-standing focus of the pipeline has been to optimize dopamine-directed treatments to address complications that arise as PD advances (e.g., sudden OFF periods and dyskinesias). Non-motor symptoms have historically been treated with existing symptom-specific medicines, but increasingly drug makers are exploring PD-specific medications. Other brain chemicals involved in regulating movement or non-motor functioning are also increasingly being explored.

Program progress highlights include:

- Advancement of multiple late-stage, dopamine delivery optimization programs into regulatory and FDA approval consideration, including ABBV-951 from AbbVie, SPN-830 from Supernus, IPX203 from Amneal and ND0612 from Neuroderm. While initial FDA responses have required some sponsors (AbbVie and Supernus) to provide additional data, it is expected that one or more of these approaches could get FDA regulatory approval by end of the year.
- Positive progress of several programs seeking to develop improved dopamine receptor agonists, including mesdopetam from IRLAB, tavapadon from Cerevel Therapeutics and a combination dopamine receptor agonist and MAO-B inhibitor P2B001 from Pharma Two B.

MJFF Perspective and Role

Addressing and acutely reducing the impact of PD symptoms is a major ongoing need and critical to making PD more manageable and increasing quality of life. MJFF has supported a range of efforts, including therapeutic development and testing of potential symptom-directed therapies as well as establishing clarity on ideal, patient-meaningful functional measurements. More recently, MJFF is putting ever greater focus on addressing gait disturbances (i.e., balance and freezing issues linked to falls) as well as cognitive impairment and dementia.

PROGRAMS TARGETING BRAIN NEUROCHEMISTRY

DOPAMINE

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Dizlin Medical Design	Infudopa (LD/CD)	Dopamine precursor	Small Molecule	Motor Impairment	1	-	Next trial pending H2 2024
Lundbeck	Lu-AF28996	Dopamine receptor agonist	Small Molecule	Motor Impairment, OFF	1	-	Phase 1 results pending H2 2025
Serina Therapeutics	SER-214 (rotigotine)	Dopamine receptor agonist	Small Molecule	Motor Impairment	1	-	Phase 1 results pending
Adhera Therapeutics	MLR-1019 (Armesocarb)	Dopamine reuptake inhibitor	Small Molecule	Dyskinesia	1	-	Pending update
Guangzhou Henovcom Bioscience	HNC-364	MAO-B inhibitor	Small Molecule	Motor Impairment	1	-	Phase 1 results pending
S. Biomedics	TED-A9	A9 dopaminergic neuron precursor cell therapy	Cell/Tissue Therapy	Motor Impairment	2	-	Phase 2 results pending H1 2026
Intrance Medical Systems	Lecigon (LD/CD/ entacapone pump)[1]	COMT inhibitor, Dopamine precursor	Small Molecule	Motor Impairment	2	-	Phase 3 trial pending
SynAgile	DopaFuse (LD/CD)	Dopamine precursor	Small Molecule	Motor Impairment	2	-	Phase 2 results Press release
PureIMS	PIMS-703 (inhaled levodopa)	Dopamine precursor	Small Molecule	OFF	2	-	Pending next trial
University Hospital, Lille & InBrain Pharma	A-Dopamine	Dopamine receptor agonist	Small Molecule	Motor Impairment	2	-	Phase 2 results pending
Alexza Pharmaceuticals	AZ-009 (apomorphine)	Dopamine receptor agonist	Small Molecule	OFF	2	Other	Pending next trial
Kissei Pharma & Affamed	KDT-3594	Dopamine receptor agonist	Small Molecule	Motor Impairment	2	-	Ongoing phase 2 trial
Chase Therapeutics	CTC-413 (pramipexole ER)	Dopamine receptor agonist, NK-1 receptor antagonist	Small Molecule	Motor Impairment, Progression	2	-	Phase 2 results pending H1 2025
UCB	UCB-0022	Dopamine receptor positive allosteric modulator	Small Molecule	Motor Impairment	2	Other	Phase 2 topline results pending H1 2025

[1]Lecigon is available across Europe and is awaiting FDA approval to initiate a pivotal Phase 3 trial in the US

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[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.

PROGRAMS TARGETING BRAIN NEUROCHEMISTRY

DOPAMINE

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
IRLAB Therapeutics	Mesdopetam (IRL-790)	Dopamine receptor antagonist	Small Molecule	Dyskinesia	2	-	Phase 2 results Press release
Cerevance	CVN-424	Dopamine signaling modulator	Small Molecule	Motor Impairment, OFF	2	Other	Phase 3 trial pending
Pharma Two B	P2B-001 (pramipexole/ rasagiline)	Dopamine agonist, MAO-B inhibitor	Small Molecule	Motor Impairment	3	-	Pending NDA submission Press release
Luye Pharma Group	LY-03003 (rotigotine ER)	Dopamine receptor agonist	Small Molecule	Motor Impairment	3	-	Phase 3 results Press release
Cerevel Therapeutics[1]	Tavapadon (PF-06649751)	Dopamine receptor agonist	Small Molecule	Motor Impairment	3	Other	Phase 3 results pending H1 2024
AbbVie	ABBV-951 (LDP/LCD infusion)[2]	Dopamine precursor	Small Molecule	Motor Impairment	Reg	-	NDA decision pending 2024
Amneal	IPX-203 (LD/CD)	Dopamine precursor	Small Molecule	Motor Impairment	Reg	-	NDA decision pending 2024
Neuroderm (part of MT Pharma)	ND-0612 (LD/CD pump)	Dopamine precursor	Small Molecule	Motor Impairment	Reg	$, Other	NDA decision pending Q2 2024
Supernus Pharmaceuticals	SPN-830 (apomorphine infusion)	Dopamine receptor agonist	Small Molecule	OFF	Reg	-	Negative NDA decision, resubmission pending Press release

[1]AbbVie has agreed to acquire Cerevel in mid-2024
[2]ABBV-951 is already approved in several EU countries, Canada, the UK and Japan

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PROGRAMS TARGETING BRAIN NEUROCHEMISTRY

ACETYLCHOLINE

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Takeda	TAK-071	Muscarinic M1 receptor agonist	Small Molecule	Cognition/ Dementia, Gait/Balance	2	$, Other	Pending Update
Anavex Life Sciences	Blarcamesine (ANAVEX-2-73)	Acetylcholine receptor antagonist, Sigma-1 receptor agonist	Small Molecule	Cognition/ Dementia, Progression	2	$, Other	Phase 3 trial pending
NHS & University of Bristol	Rivastigmine	Acetylcholinesterase inhibitor	Small Molecule	Gait/Balance	3	-	Phase 3 results pending Q2 2024

CANNABINOIDS

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Parkinson's UK & King's College London	Cannabidiol (CBD)	Cannabinoid receptor agonist	Small Molecule	Psychosis	2	-	Phase 2 results pending
University of Colorado	Cannabidiol (CBD)	Cannabinoid receptor agonist	Small Molecule	Motor Impairment	2	-	Phase 2 results Publication
University Health Network, Toronto	Cannabis Oil	Cannabinoid receptor agonist	Small Molecule	Pain	2	-	Phase 2 results pending

GABA

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
MeiraGTx	AAV-GAD	Glutamate decarboxylase stimulant	Gene Therapy	Motor Impairment	2	$, Other	Phase 2 results pending Q2-Q3 2024

[a]MJFF roles include direct funding at any stage of development ($) or additional support (Other) such as recruitment or protocol advice. MJFF continuously engages with companies to understand challenges and opportunities and this may not be fully reflected in this report.
[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.

PROGRAMS TARGETING BRAIN NEUROCHEMISTRY

GLUTAMATE

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
VistaGen	AV-101	AMPA receptor agonist, NMDA antagonist	Small Molecule	Dyskinesia	**1**	-	Phase 1 results pending
Allyx Therapeutics	ALX-001 (BMS-984923)[1]	mGluR5 silent allosteric modulator	Small Molecule	Progression	**1**	$	Phase 1 results pending H2 2025
BrainX Corporation	Ceftriaxone	Cell wall synthesis inhibitor	Small Molecule	Cognition/ Dementia	**2**	-	Phase 2 results pending Q2-Q3 2025
Sage Therapeutics	SAGE-718	NMDA receptor agonist	Small Molecule	Cognition/ Dementia	**2**	Other	Phase 2 topline results pending H1 2024
VA Office of Research and Development	Ketamine	NMDA receptor antagonist	Small Molecule	Depression	**2**	-	Phase 2 trial launch pending Q3 2024
Yale University	Ketamine	NMDA receptor antagonist	Small Molecule	Depression	**2**	$	Phase 2 results pending H1 2025
Pharmather	PT-001 (Ketamine)	NMDA receptor antagonist	Small Molecule	Dyskinesia	**2**	-	Phase 3 trial launch pending Q3 2024
Wayne State University	Memantine[1]	NMDA receptor antagonist	Small Molecule	Progression	**3**	-	Phase 3 results pending

[1]Sponsor hypothesizes treatment may target alpha-synuclein transmission or pathology

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[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.

PROGRAMS TARGETING BRAIN NEUROCHEMISTRY

EPINEPHRINE/NOREPINEPHRINE

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
CuraSen Therapeutics	Clenbuterol (CST-103)	Adrenoreceptor agonist	Small Molecule	Multiple Symptoms, Progression	2	-	Next trial pending
CuraSen Therapeutics	CST-2032	Adrenoreceptor agonist	Small Molecule	Cognition/ Dementia	2	-	Phase 2 results Press release
Cedars-Sinai Medical Center	Terazosin	Adrenoreceptor antagonist	Small Molecule	Progression	2	-	Phase 2 results pending H1 2026
University of Iowa	Terazosin	Adrenoreceptor antagonist	Small Molecule	Progression	2	$	Phase 1 results Publication
Cedars-Sinai Medical Center	Carvedilol	Adrenoreceptor antagonist (putative antioxidant actions)	Small Molecule	Progression	2	-	Phase 2 results pending Q3 2024
IRLAB Therapeutics	Pirepemat (IRL-752)	Adrenoreceptor antagonist, Serotonin antagonist	Small Molecule	Cognition/ Dementia, Gait/Balance	2	-	Phase 2 topline results pending H1 2025
Ralph H. Johnson VA Medical Center	Methylphenidate	Norepinephrine/ dopamine dual reuptake inhibitor	Small Molecule	Apathy	2	-	Phase 2 trial launch pending H1 2024

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PROGRAMS TARGETING BRAIN NEUROCHEMISTRY

SEROTONIN

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Vanda Pharmaceuticals	Fanapt (Iloperidone)	Dopamine antagonist, Serotonin antagonist	Small Molecule	Psychosis	2	-	Phase 2 results pending
Silo Pharma & Maastricht University	Ketamine & Psilocybin	NMDA receptor antagonist, Serotonin receptor agonist	Small Molecule	Cognition/ Dementia, Mood	2	-	Phase 2 results pending
Neurolixis	Befiradol (NLX-112)	Serotonin receptor agonist	Small Molecule	Dyskinesia	2	$, Other	Next trial pending
Bukwang Pharmaceutical	JM-010	Serotonin receptor agonist	Small Molecule	Dyskinesia	2	Other	Phase 2 topline results pending H2 2024
University College, London	Ondansetron	Serotonin receptor agonist	Small Molecule	Hallucinations	2	-	Phase 2 results pending H1 2025
Silo Pharma & UCSF	Psilocybin	Serotonin receptor agonist	Small Molecule	Anxiety, Depression	2	-	Phase 2 results pending H1 2025
University Hospital of Strasbourg	Pimavanserin (Nuplazid)	Serotonin receptor antagonist	Small Molecule	Impulse Control Disorder	2	-	Phase 2 results pending H1 2025
University of Michigan & NIA	Citalopram	Serotonin reuptake inhibitor	Small Molecule	Cognition/ Dementia	2	-	Phase 2 results pending Q2-Q3 2026

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[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.

PROGRAMS TARGETING BRAIN NEUROCHEMISTRY

OTHER NEUROCHEMICAL TARGETS

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Viage Therapeutics (formerly Digestome Therapeutics)	DGX-001	Vagal nerve stimulator	Peptide	Cognition/ Dementia	**1**	-	Phase 1 results Press release
Kyowa Kirin	Istradefylline (KW-6002)	Adenosine receptor antagonist	Small Molecule	Cognition/ Dementia	**2**	-	Phase 2 results pending H2 2025
Intra-Cellular Therapies	Lenrispodun (ITI-214)	Phosphodiesterase 1 inhibitor	Small Molecule	Motor Impairment	**2**	$, Other	Phase 2 results pending H1 2025
Eisai	Irsenontrine (E-2027)	Phosphodiesterase 9A inhibitor	Small Molecule	Cognition/ Dementia	**2**	-	Pending update
Celon Pharma	CPL-36	Phosphodiesterase 10A inhibitor	Small Molecule	Dyskinesia	**2**	-	Phase 2 results pending Q3 2024
University of Queensland	Levetiracetam	SV2A modulator	Small Molecule	Cognition/ Dementia	**2**	-	Phase 2 results pending Q4 2024
Jazz Pharma	JZP-385[1]	T-type calcium channel antagonist	Small Molecule	Motor Impairment	**2**	Other	Phase 2 results pending Q2 2024

[1]Previously under development as CX-8998 by Cavion (acquired by Jazz Pharma)

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LEADING PROGRAM DETAILS: BRAIN NEUROCHEMISTRY

ABBV-951 (AbbVie)

Investigational drug and subcutaneous delivery system combination of the medications foscarbidopa and foslevodopa for the treatment of motor symptoms in PD. The liquid drug formulation is a solution of carbidopa and levodopa that has been modified to become active once inside the body. Initial Phase 1 testing confirmed safety and tolerability profile of the approach as well as its pharmacokinetic characteristics. Phase 3 trial results showed significant 2-3-hour increases in patient 'ON' time without dyskinesias compared with standard oral levodopa/carbidopa. Unfortunately, an initial attempt in 2023 to seek FDA approval was rejected and additional information about the subcutaneous pump device delivering the drug combination was requested. While the treatment has now been approved in several EU countries, Canada, the UK and Japan, AbbVie has resubmitted an application to the FDA with anticipated regulatory approval in 2024.

IPX203 (Amneal)

Investigational oral small molecule extended-release formulation of carbidopa/levodopa to treat motor symptoms of PD. Phase 3 trial results reported the new formulation significantly increased ON time (and reduced OFF time) compared to immediate-release formulations, even when dosed less frequently. In 2023, the FDA rejected Amneal's initial application for IPX-203, requesting additional data on the carbidopa used in the drug. In early 2024, Amneal provided a complete response in a resubmission to the FDA.

Mesdopetam (IRLAB)

Investigational oral small molecule dopamine D3 receptor antagonist in development as a treatment for levodopa-induced dyskinesias. Initially tested to address core motor symptoms, results from its Phase 2 trial did not show a meaningful in improving ON time, but did demonstrate significant anti-dyskinetic effects. In March 2024, IRLAB announced it would based on positive FDA feedback move into a Phase 3 study.

LEADING PROGRAM DETAILS: BRAIN NEUROCHEMISTRY

ND0612 (NeuroDerm)

Investigational drug and subcutaneous delivery system combination of the medications levodopa and carbidopa for the treatment of motor symptoms in PD. Early trial data confirmed the long-term safety and positive tolerability profile of the approach while more recently announced positive results from a Phase 3 trial showed superior efficacy to oral levodopa/carbidopa. MJFF funded earlier studies of this therapy, helping to de-risk the concept and support its advance into late-stage development. The FDA is currently reviewing an application for possible approval in 2024.

P2B001 (Pharma Two B)

Investigational oral small molecule combination of extended-release dopamine receptor agonist pramipexole and the monoamine oxidase inhibitor rasagiline for the treatment of motor symptoms in PD. Early trial data confirmed safety and tolerability of P2B001 while Phase 3 data showed it to be efficacious when given once a day compared with either pramipexole or rasagiline alone in patients with early untreated PD. Compared to available extended-release pramipexole, P2B001 was reported to have significantly fewer side effects, such as daytime sleepiness, orthostatic hypotension and hallucinations. An NDA submission is being prepared for submission to the FDA.

SPN-830 (Supernus Pharmaceuticals)

Investigational drug and subcutaneous delivery system combination of apomorphine, a dopamine receptor agonist, for the treatment of OFF episodes in PD. Phase 3 trial results found that apomorphine infusion significantly decreased OFF time by more than two hours compared to placebo. The company has made two attempts to gain FDA approval, filing applications in 2022 and 2023. In both cases, FDA declined the application (most recently in April 2024), requesting additional information about the delivery approach and other aspects. The company has indicated it will resubmit an application. Apomorphine is already available in other formulations, such as via injection (Apokyn) and as an under-the-tongue dissolvable strip (Kynmobi), both of which can be used on demand for sudden, unexpected OFF times. If approved, SPN-830 would offer a continuous subcutaneous delivery option.

LEADING PROGRAM DETAILS: BRAIN NEUROCHEMISTRY

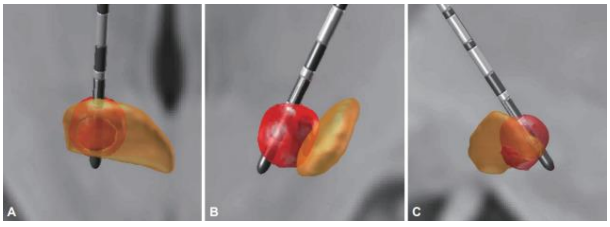
Tavapadon (Cerevel Therapeutics)

Investigational oral small molecule partial dopamine D1/D5 receptor agonist for the treatment of motor symptoms in PD. Prior Phase 2 studies confirmed tavapadon safety and tolerability. The TEMPO trials, a combination of three Phase 3 studies (TEMPO-1, TEMPO-2 and TEMPO-3) and an open-label extension (TEMPO-4) are exploring effects of tavapadon as monotherapy in early-stage PD or as adjunctive therapy in late-stage PD. Recent data reported from TEMPO-3 suggest that tavapadon can increase ON time when used as adjunctive therapy. Data from the other TEMPO trials is expected later in 2024.

Neuromodulation

Therapeutic Rationale

Over the course of PD, standard medications may become less effective at controlling symptoms or associate with increasingly disabling complications, such as dyskinesia. Approaches to directly target and modulate abnormal brain activity can offer alternative options for people with PD.



Advances in Deep Brain Stimulation may improve symptom control (Paff M, et. al. J Mov Disord. 2020 Sep;13(3):185-198.

Current Landscape

Approved surgical interventions include deep brain stimulation (DBS) and focused ultrasound (FUS) ablation therapy, which seek to modulate abnormal brain activity associated with PD. These approaches may be an option for some patients and can reduce medication requirements. With DBS, surgically implanting electrodes to stimulate specific brain regions and adjusting this stimulation, a trained clinician can help people improve motor function. FUS ablation therapy may also improve function by lesioning (with focused sound waves) a small part of the brain circuitry impacted by PD. Both approaches continue to be optimized in ways to improve possible benefits to people with PD, including exploring their use in earlier stages of the disease, creating ‘smarter’ DBS that can dynamically respond to someone’s clinical state, or assessing impact on non-motor features. In addition, a variety of other neuromodulatory approaches (e.g., various electrical or magnetic stimulation strategies) are being explored that may offer less-invasive ways to target brain activity.

MJFF Perspective and Role

MJFF has supported research to advance novel DBS systems and programming as well as supporting earlier clinical exploration of FUS. For this report, we have included examples of studies MJFF has funded but have not tracked all studies exploring neuromodulation given the breadth and complexity of this pipeline.

MJFF-SUPPORTED PROGRAMS LEVERAGING NEUROMODULATION

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
The Regents of the University of California, San Francisco	Bidirectional neurostimulator	Adaptive DBS	Other	Motor Impairment	**1**	$	Phase 1 results pending H1 2024
Wake Forest School of Medicine	Brainstem Neuromodulation Device	Non-invasive vestibular stimulation (tvCVS)	Other	Motor Impairment	**2**	$	Phase 2 results pending H2 2024
Cleveland Clinic	V-GAIT platform	STN-DBS neural signatures, DBS programming	Other	Motor Impairment	**2**	$	Phase 2 results pending H1 2025

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[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.

Other Technology-Enabled Approaches

Therapeutic Rationale

The use of digital health technologies is emerging as an important part of medical care and research. These technologies refer to a wide range of applications, such as wearable devices, smartphone applications and other technology-enabled solutions to improve existing care and rehabilitative therapy or to assist people in minimizing the impact of symptoms.

Current Landscape

A growing number of groups are testing technologies to improve motor (e.g., cueing devices to improve freezing of gait) and non-motor symptoms (e.g., adapting healthy sleep patterns with light therapy). Approaches may also support the delivery of care for a more personalized, on-demand intervention (e.g., speech training applications) or optimize clinical and/or self-care management (e.g., medication adherence smartphone applications). Based on the intended use and associated risk of these therapies, regulatory requirements and clinical development paths can vary. Importantly, clinical adoption and utility of these technologies remains an open question, requiring more real-world data.

MJFF Perspective and Role

MJFF supports better use of technology for treatment and measurement of PD and monitors this sector to better understand the utility of these technologies, regulatory and policy challenges, and infrastructures needed to utilize these new types of therapies. While we do not formally track all technologies in clinical testing, we include a few MJFF-funded programs in this report.

MJFF-SUPPORTED PROGRAMS LEVERAGING OTHER TECHNOLOGY-ENABLED THERAPIES

Sponsor	Therapeutic	Mechanism	Approach	Indication	Stage	MJFF Role[a]	Status[b]
Leiden University Medical Center	Head-up tilt during sleep (HUTS)	Autonomic dysfunction	Other	Orthostatic Hypotension, Supine Hypertension	2	$	Phase 2 results pending H1 2024
Newel Health	Soturi app	Digital therapeutic for medication optimization	Other	Motor Impairment, Treatment Plan Optimization	2	$, Other	Phase 2 results pending H2 2024
Shirley Ryan AbilityLab	Wearable Airbag Technology	Fall detection and mitigation	Other	Motor Impairment	2	$	Phase 2 results pending H1 2024
Skip Innovations, Inc	Powered Wearable Devices for Walking Assistance	Mechanistic gait device	Other	Motor Impairment	2	$	Phase 2 trial launch pending H1 2024
Queensland University of Technology	Photoreceptor Enhanced Light Therapy (PELT)	Melanopsin dysfunction	Other	Motor Impairment, Quality of Life, Sleep	2	$	Phase 2 results pending H1 2024
Teachers College, Columbia University	Understand Me for Life App	Speech intelligibility app	Other	Speech	2	$, Other	Phase 2 results pending H1 2026
Ecole Polytechnique Fédérale de Lausanne (EPFL)	ARC IM	Spinal cord stimulation therapy	Other	Motor impairment	2	$, Other	Phase 2 results pending 2029
Sibel Health	ADAM+ platform	Swallowing and drooling digital therapeutic	Other	Dysphagia, Sialorrhea	3	$, Other	Phase 3 results pending H1 2025

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APPENDIX 1

PROGRAMS PLANNING TO ENTER THE CLINIC SOON

ENTERING CLINIC SOON

Sponsor	Therapeutic	Mechanism	Approach	Indication	Pathway	MJFF Role[a]	Status[b]
Tridem Bioscience	Tridem Bioscience Vaccine	aSyn pathology inhibitor	Vaccine	Progression	Alpha-Synuclein	-	Phase 1 trial pending Q2 2024
Taiwan Mitochondrial Applied Technology Co.	MitoCell	Adipose-derived mesenchymal stem cells	Cell/Tissue Therapy	Progression	Cell Protection	-	Phase 1 trial launch pending H1 2024
Aspen Neuro	ANPD-001	Dopamine cell replacement (derived from iPSCs)	Cell/Tissue Therapy	Motor Impairment	Cell Replace-ment	-	Phase 2 trial pending
Kenai Therapeutics (Previously Ryne Biotechnology)	RNDP-001 (Allogeneic DA progenitor cells)	Dopamine cell replacement (derived from iPSCs)	Cell/Tissue Therapy	Motor Impairment	Cell Replace-ment	$	Phase 1 trial pending
Sinopia Biosciences	SB-0110	Dopamine receptor pathway modulator	Small Molecule	Dyskinesia, Motor Impairment	Dopamine	$	Phase 1 trial pending
IRLAB Therapeutics	IRL-757	Cortical enhancer	Small Molecule	Apathy	Epinephri-ne/Norep-inephrine	$, Other	Phase 1 trial launch pending H1 2024
Forest Hills Lab	FHL-301 (Gemfibrozil)	PPAR alpha antagonist	Small Molecule	Progression	Inflamma-tion	-	Phase 2 trial launch pending Q4 2024 - Q1 2025
Neuramedy Co. Ltd.	NM-101	Toll-like receptor 2 antagonist	Antibody	Progression	Inflamma-tion	-	Phase 1 trial launch pending
Longevity Biotech	LBT-3627	Vasoactive intestinal polypeptide agonist	Peptide	Progression	Inflamma-tion	$, Other	Phase 1 trial pending H1 2024
1st Biotherapeutics	FB-418	c-Abl kinase inhibitor, LRRK2 kinase inhibitor	Small Molecule	Progression	LRRK2	-	Phase 1 trial launch pending

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ENTERING CLINIC SOON

Sponsor	Therapeutic	Mechanism	Approach	Indication	Pathway	MJFF Role[a]	Status[b]
Brenig Therapeutics	BT-0267	LRRK2 inhibitor	Small Molecule	Progression	LRRK2	-	Phase 1 trial pending 2024
Mission Therapeutics	MTX-325	USP30 inhibitor	Small Molecule	Progression	Mitochon-drial Impairm-ent	$	Phase 1 trial launch pending H1 2024
Kariya Pharmaceuticals	KP-405	GLP-1/GIP agonist	Peptide	Progression	Oxidative and Metabolic Stress	-	Phase 1 trial launch pending Q3 2024

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APPENDIX 2

DISCONTINUED PROGRAMS AND PROGRAMS WITH UNCERTAIN STATUS

DISCONTINUED AND UNCERTAIN PROGRAMS

Programs included in this section have been removed from active monitoring due to lack of progress, uncertainty in current development status or publicly announced discontinuation. Programs are removed from this section after approximately one year if there are no additional updates (press release, website update, etc.). If further development can be confirmed, a program will be moved back to the main section of this report.

Sponsor	Therapeutic	Indication	Stage	MJFF Role[a]	Status[b]
Alector & GSK	AL-101	Progression	**1**	-	Alzheimer's appears to have been prioritized with no immediate plans for continued development in PD.
Hebei Newtherapy Bio-Pharma	Allogeneic MSCs	Motor Impairment, Progression	**1**	-	Phase 1 trial was expected to end in 2022, but there has been no update on the trial status since 2021.
Appello Pharma	AP-472	Dyskinesia, Motor Impairment	**1**	$	No updates since early 2022
Sumitomo Dainippon Pharma (DS Pharma)	DSP-9632P	Dyskinesia	**1**	-	Program discontinued
Luye Pharma Group	LY-03009	Motor Impairment	**1**	-	No update on development or next steps since 2021
Praxis Precision Medicines	PRAX-944	Motor Impairment	**1**	Other	As of 2022, a phase 2 trial in PD was planned to start in H1 2023, but no update has been shared about the trial starting. Essential Tremor appears to be prioritized.
Sage Therapeutics & Biogen	SAGE-324	Motor Impairment	**1**	-	Essential Tremor appears to be prioritized. No recent updates regarding development for PD
Seelos Therapeutics	Aplindore (SLS-006)	Motor Impairment	**2**	-	Development status unclear
Sio Gene Therapies & Oxford BioMedica	AXO-Lenti-PD	Motor Impairment	**2**	Other	Sio Gene Therapies discontinued development in 2022 after several manufacturing and development challenges. Rights were returned to Oxford BioMedica, who planned to out-license the program to a suitable partner. In 2023, Oxford BioMedica discontinued development of its therapeutic products.

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[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.

DISCONTINUED AND UNCERTAIN PROGRAMS

Sponsor	Therapeutic	Indication	Stage	MJFF Role[a]	Status or Results Expected[b]
Herantis	HER-902 (rhCDNF)	Progression	**2**	Other	Development discontinued due to strategic review
4D Pharma	MRx-0005	Progression	**2**	Other	4D Pharma entered administration in 2022. No updates regarding continued development have been shared since.
4D Pharma	MRx-0029	Progression	**2**	Other	4D Pharma entered administration in 2022. No updates regarding continued development have been shared since.
DS Pharma	EPI-589	Progression	**2**	-	Phase 2 trial completed in 2019. No updates on next steps for PD - ALS appears to be prioritized.
Vivifi Biotech	GDNF	Progression	**2**	$	Vivifi is seeking out partners to move towards another trial as of November 2023.
Enterin	Kenterin (ENT-01)	Psychosis	**1**	Other	Status is unclear and program may be in similar status as other Kenterin programs.
		Cognition/ Dementia	**1**	-	Enterin withdrew a planned phase 1 trial and stated the withdrawal reason was that the compound will not be studied for the indication.
		Constipation	**2**	Other	Most recent phase 2 was terminated in 2/2022. No updates on development or next steps since then
Eli Lilly	Mevidalen (LY-3154207)	Cognition/ Dementia	**2**	Other	No update on development or next steps since early 2022
DS Pharma	Ulotaront (SEP-363856)	Psychosis	**2**	Other	No updates on next steps for PD psychosis - other indications appear to be prioritized. Phase 2 trial completed in 2020
Addex Therapeutics	Dipraglurant (ADX-48621)	Dyskinesia	**3**	$	Active development for post-stroke recovery but no updates on development plans since phase 3 trial was terminated in 2022. Assume PD development has been deprioritized

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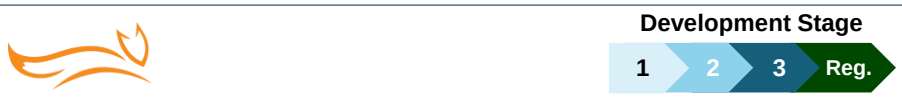
[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.



DISCONTINUED AND UNCERTAIN PROGRAMS

Sponsor	Therapeutic	Indication	Stage	MJFF Role[a]	Status[b]
NIH/NINDS	AAV2-GDNF	Progression	**1**	-	Phase 1 trial completed in 2/2022, but no updates on results or next steps are currently available
University of Florida & NINDS	Exenatide	Progression	**1**	-	Phase 1 trial completed in 8/2021. No updates on results or next steps since then.
University of Minnesota	Ursodiol (UDCA)	Progression	**1**	-	Found to be reasonably safe and well tolerated, but small cohort (n=5) and variable pharmacokinetic results. Suggested larger studies needed to gather additional clinical data but did not indicate plans to do so. Study completed in early 2022.
Hospices Civils de Lyon	Clonidine	Impulse Control Disorder	**2**	-	Phase 2 trial completed in 2021. No updates on next steps Publication

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[b]Dates of expected results are estimates derived from publicly available press releases or estimated study completion dates.