# PARKINSON'S PRIORITY THERAPEUTIC CLINICAL PIPELINE REPORT

Q1 2023

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# MARCH 2023

## Index



## Report Objectives

This report provides an overview of therapies currently in clinical development for Parkinson's disease. The program status and result information include updates until March 2023. Brief rationale and progress in several key areas of therapeutic interest are described along with a more detailed listing of specific therapies, current development status and, where appropriate, information about MJFF support (funding or non-funding).

MJFF monitors numerous information sources to assess the therapeutic pipeline for Parkinson's disease. This report is not comprehensive of every approach or intervention being developed today, but represents treatments identified by MJFF research staff as important for monitoring given significance to the Parkinson's community and for understanding MJFF role and impact. The report is mostly focused on pharmacological and biologic therapies, while approaches such as exercise, alternative therapies and behavioral interventions are generally not included. In addition, clinical programs on neuromodulation and technology- enabled therapies represent active MJFF funded programs and are not a full listing of all approaches currently in development.

The report will be updated and distributed on an annual basis. Information in this report is not confidential and is intended only as a guide for communicating pipeline progress with our community stakeholders. Any errors or omissions are not intentional.

If you have any comments or suggestions for this report, please contact:


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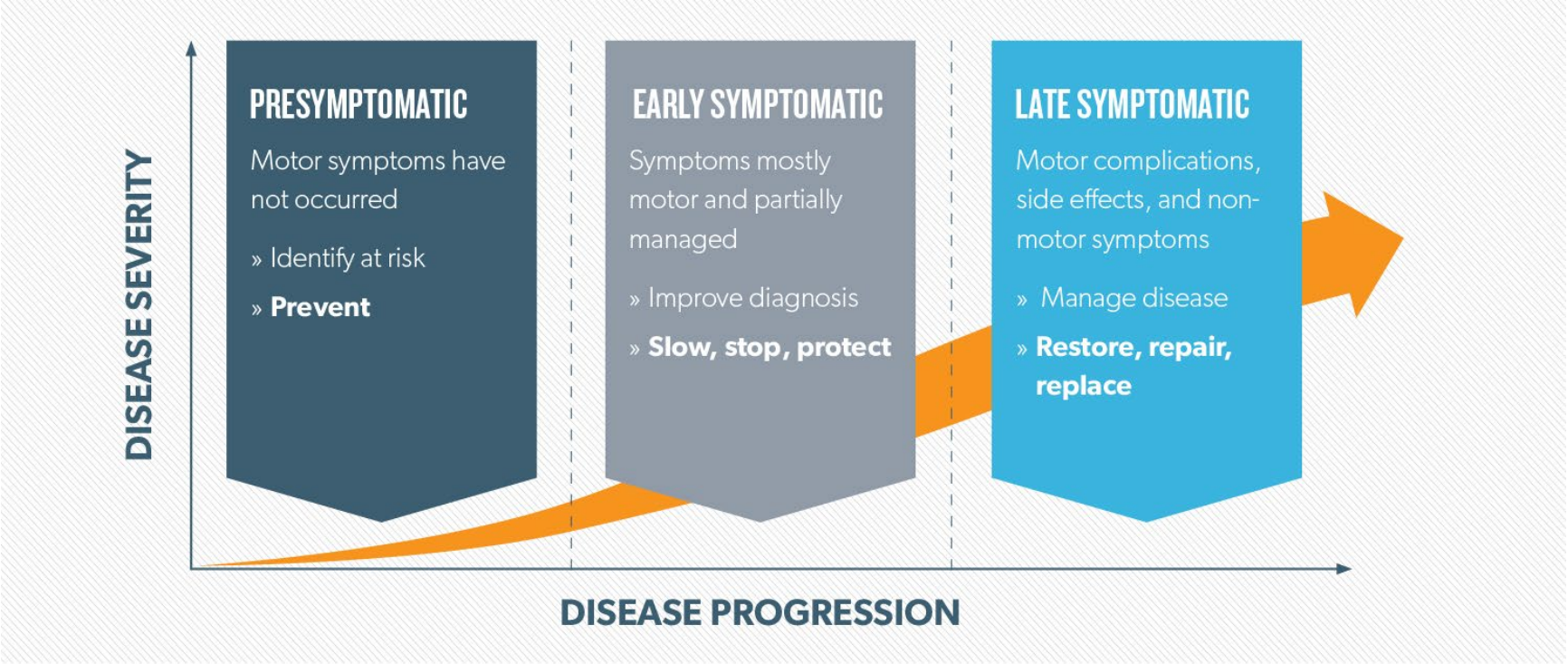
# THE PARKINSON'S CHALLENGE




**Delivering better treatments and cures to people with Parkinson's disease requires developing diverse therapies targeting critical stages and symptoms**

# PARKINSON'S PIPELINES WE MONITOR

Given the many approaches needed for treating the full spectrum of Parkinson's disease challenges, MJFF actively monitors clinical-stage therapeutic programs within the following key areas:

- Therapies targeting underlying Parkinson's disease biology that may over time slow, stop, reverse, or prevent the degenerative process and resulting symptom progression
- Therapies targeting brain chemistry and activity that aim to provide daily relief from disabling Parkinson's symptoms

This report includes program-specific information in some therapeutic areas (e.g., pharmacological and biological), while for other areas (e.g., technology-enabled therapeutics and neuromodulation) it includes higher-level trends and perspectives.

## Parkinson's Disease Biology

Specific Priority Targets:
- Alpha-Synuclein
- LRRK2
- GBA1

Other Targets and Pathways:
- Mitochondrial Impairment
- Oxidative Stress
- Autophagy
- Inflammation
- Microbiome
- Cell Repair
- Cell Replacement
- Other targets

## Brain Chemistry and Activity

- Acetylcholine
- Cannabinoid
- Dopamine
- GABA
- Glutamate
- Epinephrine/Norepinephrine
- Serotonin
- Phosphodiesterase
- Other targets

# 2022 IN REVIEW[1]

**3** **Significant regulatory** events:
- *3 NDAs filed for approval: IPX-203, SPN-830, ABBV-951*
- *2 requiring additional data: SPN-830, ABBV-951*

**9** **Therapies** entered the clinic for PD[2]
- *7 novel treatments[3]*
- *2 repurposed drugs[4]*
- *1 new mechanism/target*

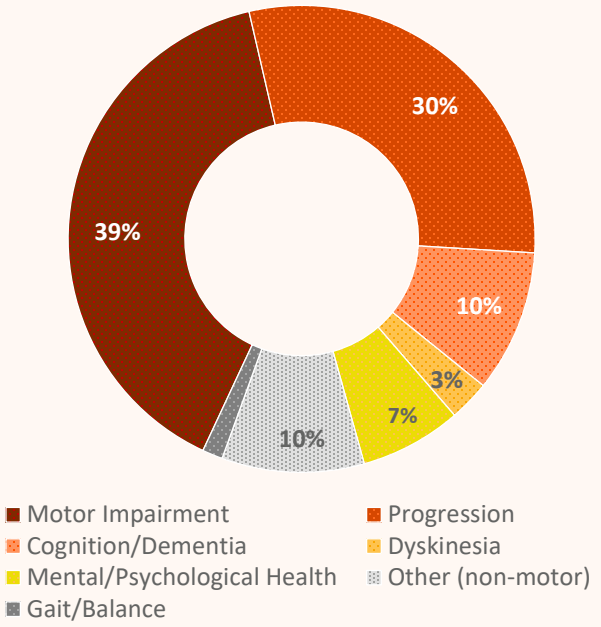
**6** **Programs** advanced in the clinic:
- *Phase 1 → Phase 2*
  - FAScinate Therapeutics | KM-819
  - Inhibikase | ikT148009
  - Vanda Pharma | Fanapt (Iloperidone)
  - CuraSen Therapeutics | CST-2032
- *Phase 2 → Phase 3*
  - Annovis Bio | Buntanetap (ANVS-401)
  - Denali & Biogen | DNL-151/BIIB-122

**2** **Key Agreements & Acquisitions:**
- *Janssen Pharmaceuticals acquired YTX-7739 from Yumanity*
- *ABL Bio entered licensing agreement with Sanofi for development of ABL-301*

[1]Excludes medical devices/neuromodulation, hypoxia therapy, and other non-biomedical therapies
[2]ABL-301; ATH-1017; CX-8998 (entry after prior withdrawn/uninitiated trial); DGX-001; HNC-364; ISN-GSH (Glutathione/Insulin); KW-6002; NEU-723; STEM-PD
[3]Includes non-approved therapies that first entered the clinic prior to 2022 for a different disease indication. Excludes reformulations, repurposed drugs, Phase 4/other, natural medicine/supplement trials, and those that do not have a potential path for development in US/EU
[4]Includes approved drugs being explored as a PD treatment for the first time or for a new symptom

***73 PD drug trials launched in 2022*** *focusing on a variety of indications.* ***Over a quarter of trials*** *(n = 21) targeted disease* ***progression*** *as the primary indication or in addition to a specific symptom (e.g., cognition)*

**Target Therapeutic Indications**
**2022 Initiated Trials**




Phase 1-3 trials (n = 68) **launched** in 2022 exploring pharmacological interventions in PD (currently ongoing or completed). Includes trials that are actively registered on a clinical trial website but are not yet recruiting. Trials targeting more than one indication are counted multiple times (n = 3). Excludes trials for drugs with an unknown intended use (n = 5) or without a specified start date.

# CURRENT STATUS OF THE PARKINSON'S PIPELINE[1]

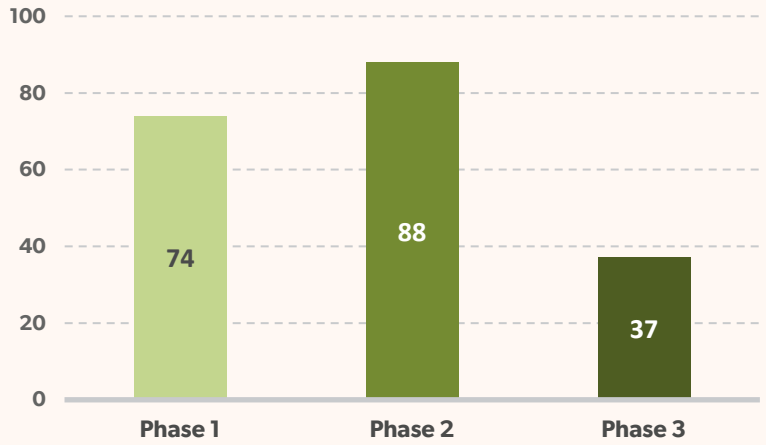
A robust, diverse and rapidly advancing pipeline of therapies being tested in clinical trials is a key metric of progress toward our vision of new treatments and cures for people with Parkinson's disease. Below is a snapshot of the current state of the Parkinson's clinical pipelines we monitor:

**146** unique therapies in clinical testing monitored as potential new Parkinson's disease treatments*

*Number includes treatments with active trials or that have recently completed a phase of clinical testing and remain in active development for PD with commercial potential in US/EU. Reformulations and repurposed drugs are counted as unique therapies. Natural supplements and other dietary approaches are generally excluded unless there is a clear, biologically justified hypothesis being tested. Excludes preclinical programs expected to enter clinic this year, though such preclinical programs are listed under "Parkinson's Priority Program Pipelines".

## Active Trials by Phase

March 2023

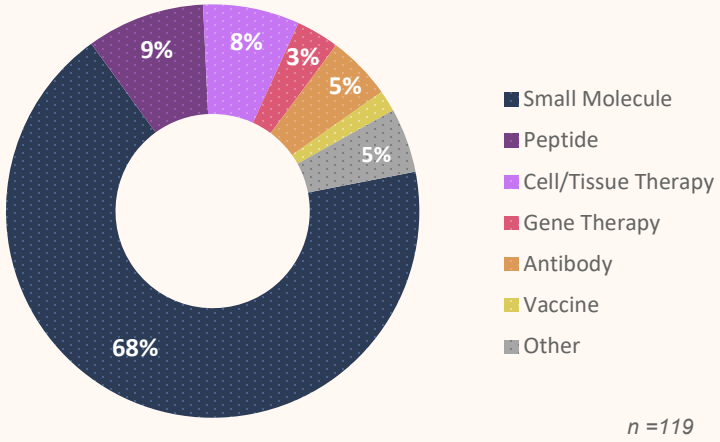



Total estimated number of active interventional drug trials by phase. Programs in "Phase 4" (post-approval) or other undefined stages of clinical development are not included. Total number of active trials is often greater than the number of unique therapies since a drug may be being used in multiple ongoing trials and/or is not considered a new PD therapy (e.g., generic drug development)

*Source: Informa, data accessed March 2023*

## Therapeutic Approach by Program

March 2023

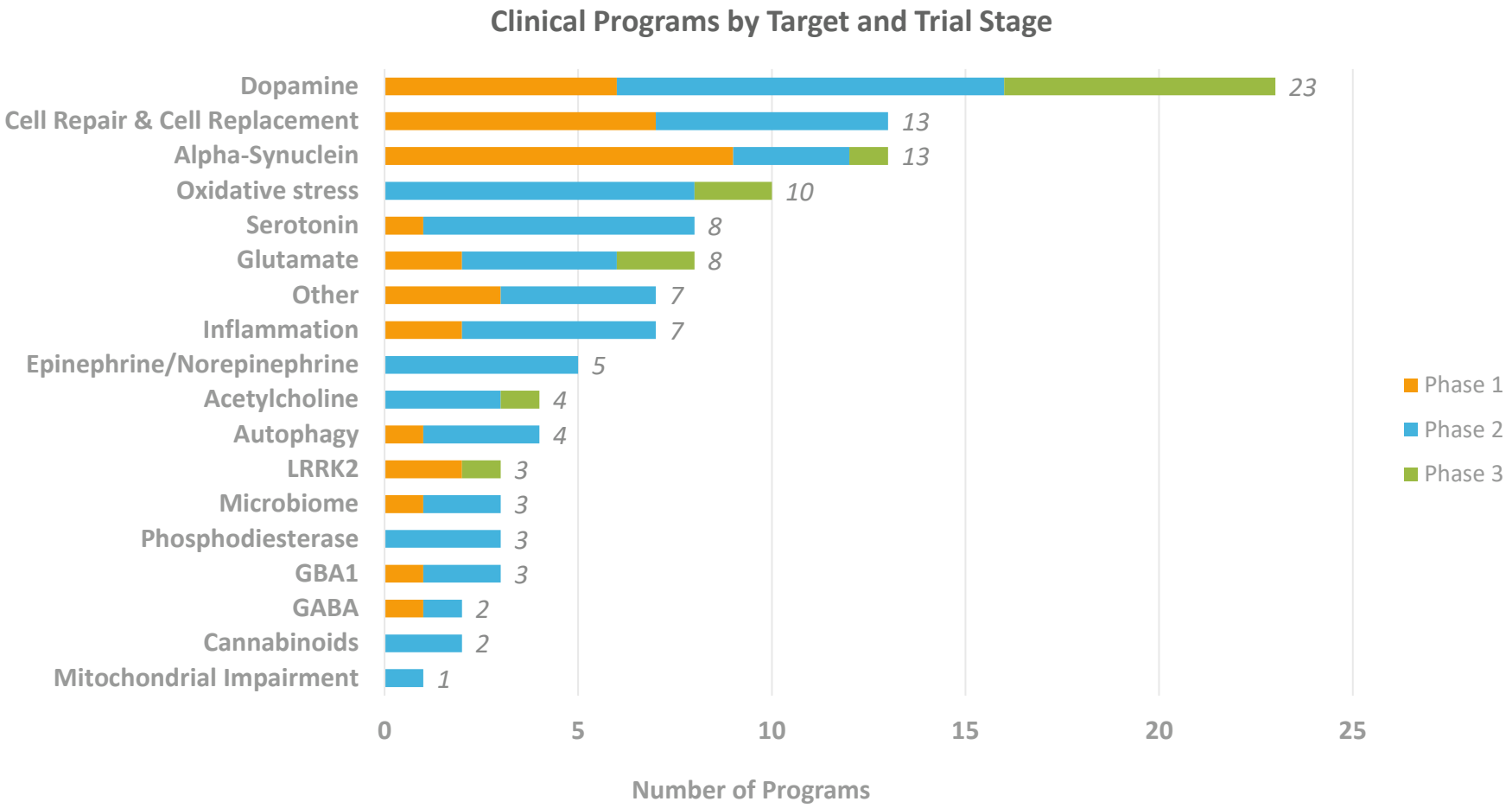



Breakdown of MJFF-monitored clinical programs by therapeutic approach. **Data include programs currently listed in this report and are not comprehensive of all active clinical programs in Parkinson's disease.** Different trials testing the same therapy (e.g., exenatide) are counted once, unless reformulation

[1]Excludes medical devices/neuromodulation, hypoxia therapy, and other non-biomedical therapies

# THE CLINICAL PIPELINE IS BEST BAROMETER OF PROGRESS[1]

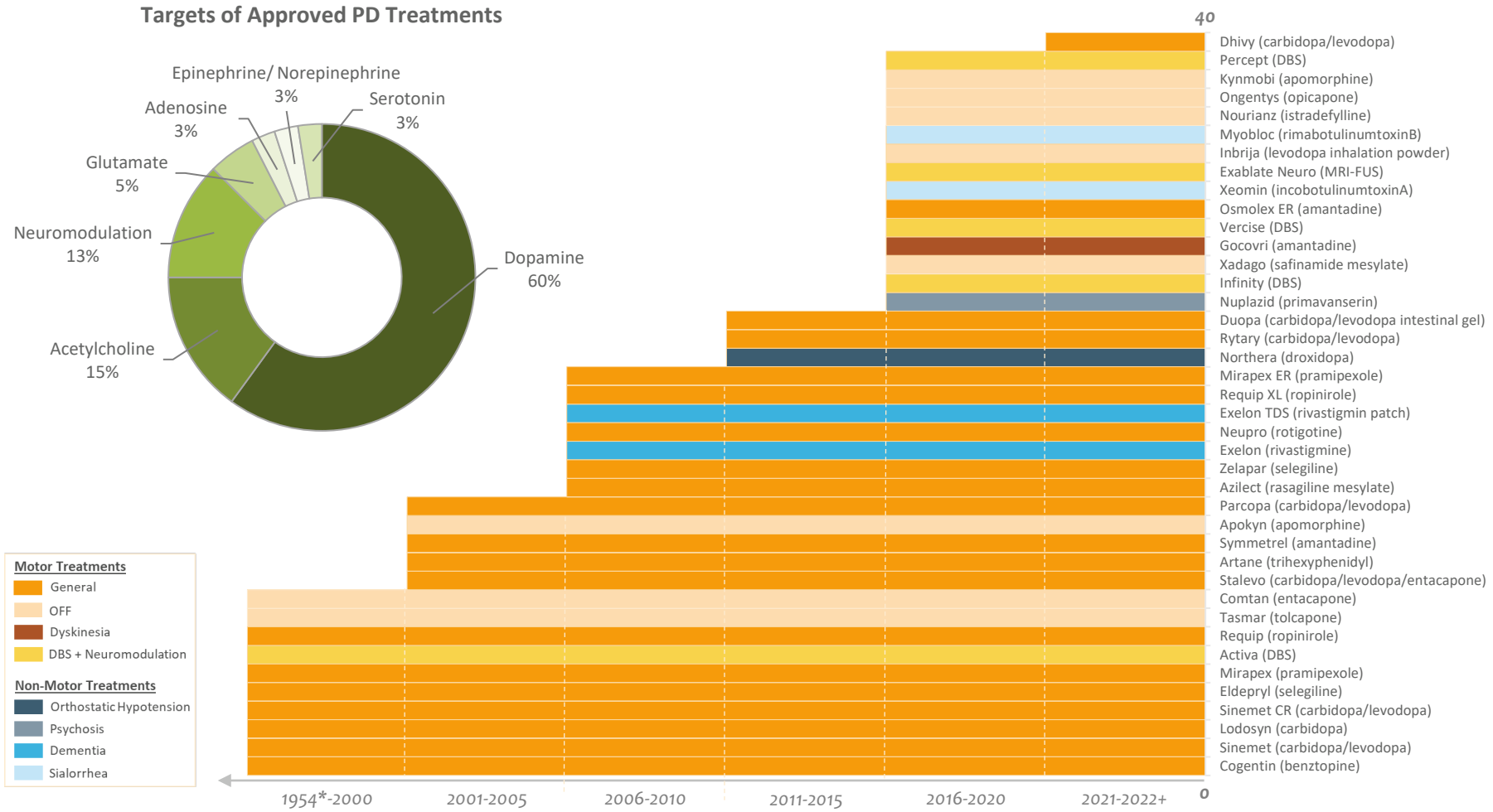
Several clinical-stage programs are targeting novel pathways addressing the underlying disease biology or brain chemistry targets addressing motor and non-motor symptoms. Below is an overview of programs included within this report by target and clinical trial stage.




[1]Excludes medical devices/neuromodulation, hypoxia therapy, and other non-biomedical therapies

# APPROVED THERAPIES

As the clinical pipeline grows, we hope to see new and diverse therapies reach market and move into the hands of the patient. Below is a visual overview of Parkinson's drug approvals in the United States and an overview of those approved treatments by target




Total cumulative number of approved Parkinson's therapies over time with more than 30 drugs indicated for Parkinson's disease or related symptoms as of this report. Note that some treatments such as Xeomin and Myobloc are approved for general symptoms but were tested in a Parkinson's population and shown to have benefit. Several older drugs such as Eldepryl (Selegiline) and Symmetrel (Amantadine) have been discontinued, although there are generic and/or reformulation versions available on market.

**first therapy approved for Parkinson's*

# Parkinson's Priority Therapeutic Areas

## TREATMENTS TARGETING ALPHA-SYNUCLEIN

### Therapeutic Rationale

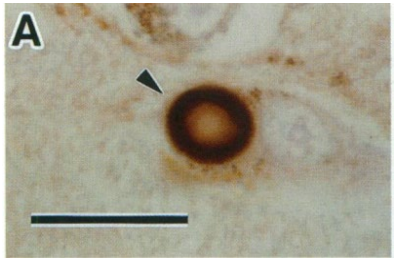
Genetic and pathological evidence strongly supports a critical role of the alpha-synuclein (aSyn) protein in PD. Presence of aSyn-containing aggregates called “Lewy bodies” (see image below) within certain brain cells of almost all people with PD—and evidence that this pathology may spread from cell to cell—provides strong rationale for seeking treatments that can target the production, spread and/or clearance of this abnormal toxic form of the protein.

### Current Landscape & Looking Ahead

Treatments seek to target aSyn pathology in multiple ways. Some leverage the immune system and antibodies to specifically remove abnormal aSyn. Others target cellular mechanisms involved in handling or clearing aSyn or seek to reduce spread of aSyn pathology from cell to cell. Several leading programs are moving through mid (Phase 2) and advanced (Phase 3) testing.

### MJFF Perspective and Role

Given its potentially central role in PD pathogenesis, MJFF’s efforts are multi-layered and seek to translate a diverse range of aSyn therapeutics into the clinic. Moreover, the Foundation has robust efforts in developing biomarkers and imaging methods for measuring aSyn that could support improved diagnosis, disease subtyping and measures of therapeutic target engagement. One particularly promising measurement is seen with advances in so-called aSyn seeding amplification assays (see right).




*One of the first images published from the brain of a Parkinson’s patient of a Lewy body chemically stained to visualize the alpha-synuclein protein (Baba et al., American Journal of Pathology 1998)*

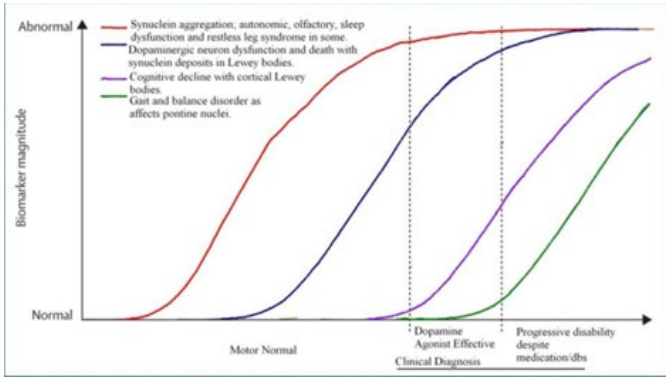
### α-Synuclein seed amplification assay (SAA)

Accurate aSyn biomarker are critically needed to identify individuals in early stages of α-synucleinopathy, for accurate diagnosis, and for target engagement of asyn-targeted therapies.

α-Synuclein SAA is a novel biomarker that distinguishes PD from controls and reflects underlying pathology. This is a robust diagnostic tool that can reduce the time needed to diagnose Parkinson's disease, help ensure biologic homogeneity in PD clinical trials and act as enrichment tool for trials.

Results from a Parkinson’s Progression Markers Initiative (PPMI) study evaluating aSyn SAA performance in CSF samples from a large cohort of patients with PD, individuals at-risk for PD and healthy controls (n=1145) confirm that a-syn SAA accurately differentiates PD patients from healthy controls (see *Andrew Siderowf, et al. 2022. Zenodo. https://doi.org/10.5281/zenodo.7004865*).

Almost all prodromal PPMI participant with either hyposmia or RBD, plus DAT deficit were SAA positive, suggesting this is an early biomarker of disease pathology that precedes onsets of PD motor symptoms. Together, these results have important implications for how we think about the earliest stages of PD as well as how we may improve clinical trial design.

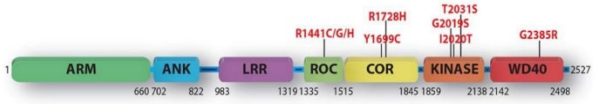



*The ability to measure aSyn seeding offers the potential to capture some of the earliest progression stages of PD, possibly before the onset of dopamine cell loss and prior to the onset of the symptoms of PD*

## TREATMENTS TARGETING LRRK2

### Therapeutic Rationale

Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene explain 1-40% of cases of PD depending on the population studied. LRRK2 is a 'kinase': a protein that chemically modifies other proteins in the cell 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 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 & Looking Ahead

Programs in clinical testing seek to reduce LRRK2's pathological function either by inhibiting its kinase activity or reducing production of the LRRK2 protein. 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. The LRRK2 pipeline continues to grow as companies bring additional programs into clinical testing.

### MJFF perspective

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.

## TREATMENTS TARGETING GBA1

### Therapeutic Rationale

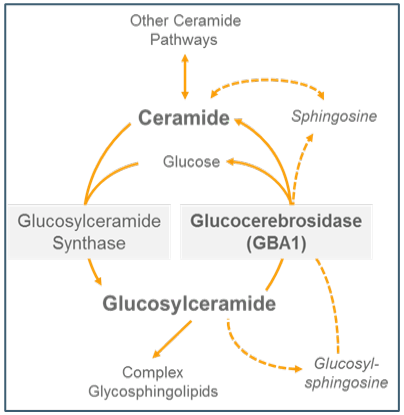
Genetic variation in the GBA1 gene are common risk factors for PD. The protein encoded by the gene (known as glucocerebrosidase or "GCase") regulates metabolism of important lipid molecules in cells, but when dysfunctional may lead to toxic accumulation of these lipids. Mutations in GBA1 are also linked to Gaucher disease and people with this disorder are at higher risk for PD. PD patients with GBA1-associated gene changes often have an earlier age of disease onset, more frequent cognitive issues and may progress more rapidly. Whether altered GCase activity explains PD cases without GBA1 mutations is an area of active study.

### Current Landscape & Looking Ahead

Drug makers are primarily seeking 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.

### MJFF perspective

MJFF efforts have focused on identifying factors that may influence GCase and its impact on the lysosomal pathway. Through this work, the Foundation hopes to nominate additional targets with therapeutic potential and refine patient enrichment strategies for identifying people at-risk for this form of PD.

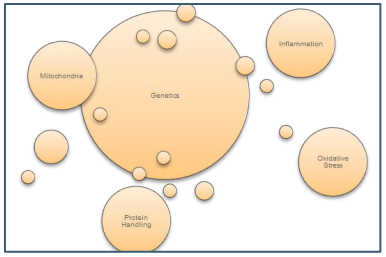



*Schematic of the complex lipid pathway in which GBA1 functions. Impaired GBA1 can lead to accumulation of glucosylceramide which may underlie toxicity in Parkinson's disease in people with this impairment.*

## OTHER TREATMENTS TARGETING 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, inflammation 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 & Looking Ahead

A robust pipeline of drugs are targeting various hypothesized mechanisms contributing to PD. Quite often, investigators test so-called 'repurposed' therapies: therapies approved for other indications which are then tried in a new disease such as PD. As these treatments already have safety and other data, they can often be moved quickly into clinical testing. However, these approaches can also be challenging to interpret as drugs may have variety of effects. As biological understanding of PD improves, companies can develop more targeted and optimized therapies.

### MJFF perspective

MJFF supports work to expand biological understanding of PD (including implementation of ASAP initiatives like the Collaborative Research Network and the Global Parkinson's Genetics Program). With this insight, we then seek to validate emerging targets and novel therapeutic approaches. A major challenge in advancing drugs against these mechanisms is lack of pathway-specific biomarkers that can help inform patient stratification and therapeutic's target engagement, making interpretation of trial results challenging. This also drives major effort from MJFF to discover and validate better measurement of disease biology.

## CELL REPAIR AND REPLACEMENT

### Therapeutic Rationale

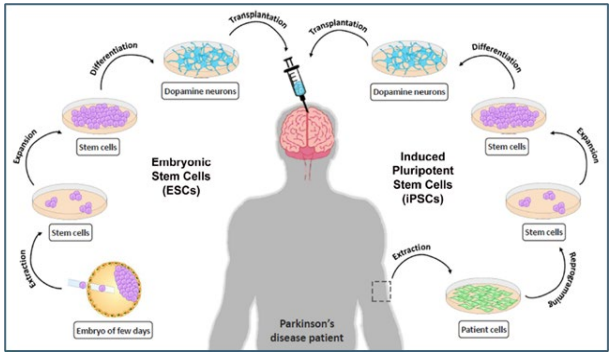
The isolation of human stem cells in the late 1990s led to an explosion of research to generate replacement cells for disorders like Parkinson's disease. Moreover, identification of growth factors (natural chemical 'fertilizer' important for growing brain cells) have also pointed to ways to possibly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

### Current Landscape & Looking Ahead

Early trials with fetal tissue transplantation or delivery of growth factors were not successful, but newer approaches using improved methods and advanced technologies are underway to either protect and repair existing cells or replace damaged dopamine cells which may improve motor function. A major challenge is that some clinics are offering unregulated 'stem cell therapies' directly to patients with limited information on what is being delivered or long-term safety and benefits. (For this report, MJFF monitors programs reporting clinical trials but are unable to monitor these unregulated clinics.)

### MJFF perspective

With newer programs entering the clinic, MJFF is closely monitoring progress and opportunistically supporting studies that may inform this promising pipeline.




*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)*

## TREATMENTS TO ADDRESS MOTOR SYMPTOMS

### Therapeutic Rationale

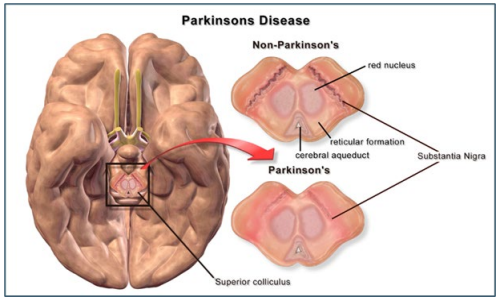
Slow movement, limb rigidity and rest tremor represent early diagnostic symptom hallmarks of PD. Additional challenges with posture, gait and balance may also exist. Loss of dopamine-producing neurons in the substantia nigra region of the brain are a primary (although not entire) cause of many of these movement-related symptoms. This discovery led to the use of dopamine replacement—in particular levodopa—as first-line therapy for people with Parkinson's.

### Current Landscape & Looking Ahead

A major focus of the pipeline is to optimize delivery of dopamine medications to address issues that arise as the disease advances (e.g., sudden OFF periods and dyskinesias). Other brain chemicals involved in regulating aspects of movement are also increasingly being explored (glutamate, serotonin, etc.). Surgical interventions such as deep brain stimulation (DBS) or Focused Ultrasound remain an option for some at later stages of disease and continue to be optimized. (See separate summary in this report.) Some late-stage (Phase 3) dopamine-targeting programs with positive, clinically meaningful results, are in discussion with FDA for approval.

### MJFF perspective

Motor impairment remains a key driver of PD symptom management. Addressing more complicated motor symptoms such as gait disturbances (e.g., balance issues linked to falls, freezing) is still a challenging unmet need and focus of MJFF. Advances in use of technology (including DBS) offers new ways to address these symptoms.

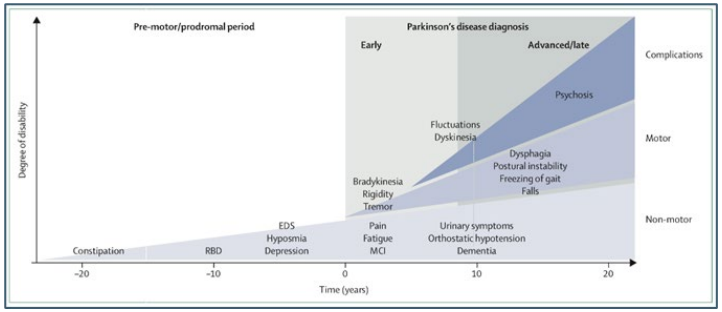



*Loss of dopamine cells in the substantia nigra underlie Parkinson's motor symptoms (image https://bit.ly/2BV03XH)*

## TREATMENTS TO ADDRESS NON-MOTOR SYMPTOMS

### Therapeutic Rationale

While motor symptoms are a primary feature of PD, non-motor symptoms are often the most burdensome. These symptoms include cognitive impairment and dementia, psychiatric challenges, mood disorders, sleep issues and constipation, to name a few. Not everyone exhibits all symptoms or suffers them at the same time during the disease course which points to the complex nature of PD. Moreover, the underlying pathology leading to these non-motor symptoms is often less understood, hindering new treatment development.




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

### Current Landscape & Looking Ahead

Treating non-motor symptoms has historically been through use of existing medicines that target these symptoms non-specifically. In recent years, approvals for drugs to treat PD-specific non-motor features such as psychosis (Nuplazid) and orthostatic hypotension (Northera) reveal a growing interest among companies to develop drugs for these critical needs. Therapies targeting cognitive issues are a common focus in the pipline, but potential treatments for a variety of mood disorders and psychological/mental health symptoms are also being explored. Many of these treatments focus on non-dopamine brain chemical signaling pathways (e.g., acetylcholine, serotonin, etc).

### MJFF perspective

Understanding and treating non-motor features such as cognitive changes is an important focus for MJFF. Support seeks to advance trial designs as well as clinical outcome assessments and measures.

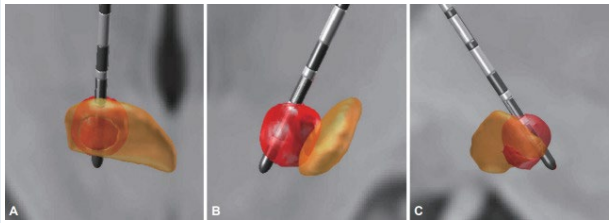
## NEUROMODULATION

### Therapeutic Rationale

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

### Current Landscape & Looking Ahead

Deep brain stimulation (DBS) is a leading approved treatment option for some patients and can reduce medication requirements. By surgically implanting electrodes to stimulate specific brain regions and adjusting this stimulation, a trained clinician can help people improve motor function. In addition, focused ultrasound (FUS) ablation therapy may also improve function by lesioning (with focused sound waves) a small part of the brain circuitry impacted by PD. Both DBS and FUS 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.




*Some researchers are exploring better ways to direct DBS stimulation in the brain to improve ability to impact symptoms (Paff M, et. al. J Mov Disord. 2020 Sep;13(3):185-198.*

### MJFF perspective

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.

## TECHNOLOGY-ENABLED THERAPIES

### 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 & Looking Ahead

A growing number of groups are testing technologies to improve motor (e.g., cueing devices improving freezing of gait) and non-motor symptoms (e.g., adapting healthy sleep patterns with light therapy), 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 those therapies, regulatory requirement and clinical development paths can vary. Importantly, clinical adoption and utility of these technologies remains an open question, requiring more real-world data to be collected.


*Digital Closed Loop Gait Training Therapeutic (Ellis TD, Earhart GM, 2021;11(s1):S95-S101. doi: 10.3233/JPD-202407. PMID: 33646177; PMCID: PMC8292155.*

### MJFF perspective

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.

# Parkinson’s Priority Program Pipelines

# ALPHA-SYNUCLEIN

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Alterity Therapeutics** | ATH-434[1] | aSyn disaggregator | | Progression | 1 | $ | Phase 1 trial pending |
| **BioArctic** | BAN-0805[2] | aSyn disaggregator | | Progression | 1 | - | Phase 2 trial pending |
| **AstraZeneca & Takeda** | MEDI-1341/ TAK-341 | aSyn disaggregator | | Progression | 1 | - | Phase 1 results pending |
| **UCB** | UCB-7853 | aSyn disaggregator | | Progression | 1 | - | Phase 1 results pending Q3 2023 |
| **Vaxxinity** | UB-312 | aSyn disaggregator | | Progression | 1 | $ | Phase 1 results pending H1 2023 |
| **ABL Bio & Sanofi** | ABL-301 | aSyn inhibitor | | Progression | 1 | - | Phase 1 results pending H2 2023 |
| **Janssen Pharmaceutical** | YTX-7739[3] | Stearoyl-CoA desaturase + aSyn toxicity inhibitor | | Progression | 1 | $ | Pending update following acquisition |
| **AC Immune** | ACI-7104 | aSyn disaggregator | | Progression | 1b | $ | Update on planned phase 2 trial in H2 2023 |
| **MODAG & Teva** | Anle-138b | aSyn disaggregator | | Progression | 1b | $ | Phase 1b results pending H1 2023 |
| **Novartis & UCB** | UCB-0599 | aSyn inhibitor | | Progression | 2a | $, Other | Phase 2a results pending H2 2024 |

[1]MSA prioritized for initial development. Future plans include proof-of-concept study in PD.
[2]AbbVie terminated collaboration with BioArctic on aSyn portfolio despite Phase 1 results supporting continued development of ABBV-0805. BioArctic is currently seeking partners.
[3]YTX-7739, previously a Yumanity program, was acquired by Janssen Pharmaceutical in 2022.

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

Development Stage: 1 2 3 Reg.

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# ALPHA-SYNUCLEIN CONT'D

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Enterin** | Kenterin[1] (ENT-01) | aSyn inhibitor | | Cognition/Dementia | 1 | - | Phase 2a trial pending 2023 |
| | | | | Psychosis | 1 | - | Phase 2a trial pending 2023 |
| | | | | Constipation | 2b | - | Pending update |
| **Prothena & Roche** | Prasinezumab | aSyn disaggregator | | Progression | 2b | Other | Phase 2b topline results pending 2024 |
| **University of Tübingen** | Prasinezumab[2] | aSyn disaggregator | | Cognition/Dementia | 2b | $ | Phase 2b trial launch pending Q4 2023 |
| **Annovis Bio** | Buntanetap[3] (ANVS-401) | Amyloid + tau + aSyn inhibitor[3] | | Progression | 3 | $ | Phase 3 interim analysis pending Q2 2023 |

[1]Development for specific PD symptoms, potential effect on overall disease progression
[2]Investigator initiated study is testing Prasinezumab (Roche's aSyn disaggregator mAb) in patients with GBA mutations to evaluate effectiveness in cognition. Study is planned to start recruitment in Q4 2023.
[3]Annovis ANVS-401 currently has potential to target multiple proteins, including aSyn, to improve axonal transport.

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

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# LRRK2

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Biogen** | BIIB-094 | LRRK2 gene expression inhibitor (Antisense oligonucleotides) | Other | Progression | 1 | $, Other | Phase 1 results pending Q4 2023-Q1 2024 |
| **Neuron23** | NEU-723 | LRRK2 kinase inhibitor | | Progression | 1 | - | Phase 1 results pending Q3 2023 |
| **Denali & Biogen** | DNL-151/ BIIB-122 | LRRK2 kinase inhibitor | | Progression | 3 | Other | Phase 3 results pending 2031 |

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

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## GBA1

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Bial Biotech** | BIA 28-6156/ LTI-291 | Glucocerebrosidase enhancer | | Progression | 1 | $, Other | Pending update |
| **Prevail Therapeutics (Eli Lilly) & Regenxbio** | PR-001 | GCase restoration | | Progression | 1 2 | Other | Phase 1/2 results pending 2028 |
| **IRCCS National Neurological Institute** | Ambroxol | Glucocerebrosidase enhancer | | Progression | 2 | - | Phase 2 results pending Q2-Q3 2024 |
| **Lawson Health Research Institute** | Ambroxol | Glucocerebrosidase enhancer | | Progression | 2 | - | Phase 2 results pending Q4 2023 - Q1 2024 |
| **University College, London** | Ambroxol | Glucocerebrosidase enhancer | | Progression | 2 | - | Phase 3 trial launch pending H2 2023 |

## MITOCHONDRIAL IMPAIRMENT

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Sheffield Teaching Hospital** | Ursodiol (UDCA) | Mitochondrial enhancer | | Progression | 2 | $ | Phase 2 results - primary endpoint not met. Publication pending |

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

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# OXIDATIVE STRESS

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **University of Florida & NINDS** | Exenatide | GLP-1 agonist | | Progression | 1 | - | Phase 1 results pending |
| **Radbound University** | Hypoxia Therapy | Hypoxic preconditioning | Other | Progression | 1 2 | $ | Phase 1 results pending Q2 2023<br>Phase 2a trial launch pending Q3 2023 |
| **FAScinate Therapeutics (Kainos Medicine)** | KM-819 | FAF1 antagonist | | Progression | 2 | - | Phase 2 results pending Q4 2025 - Q1 2026 |
| **Stockholm Health Care Services** | Exenatide | GLP-1 agonist | | Progression | 2 | - | Phase 2 results pending Q4 2023 |
| **Cedars-Sinai Medical Center & Novo Nordisk** | Liraglutide | GLP-1 agonist | | Progression | 2 | - | Phase 2 positive results.<br>Press release |
| **University Hospital, Toulouse & Sanofi** | Lixisenatide | GLP-1 agonist | | Progression | 2 | - | Phase 2 results pending 2023 |
| **Neuraly** | NLY-01 (pegylated exenatide) | GLP-1 agonist | | Progression | 2 | - | Phase 2 topline results - primary endpoint not met. Further analysis pending.<br>Press release |
| **Invex & Peptron** | PT-320 (exenatide SR) | GLP-1 agonist | | Progression | 2 | - | Phase 2 trial ongoing |
| **Oslo University & Novo Nordisk** | Semaglutide | GLP-1 agonist | | Progression | 2 | - | Phase 2 results pending Q4 2024 - Q1 2025 |
| **Gateway Institute** | ISN-GSH (insulin-glutathione) | Insulin receptor agonist + reducing agent | | Cognition/Dementia | 2 | - | Phase 2 results pending H2 2024 |

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

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

# OXIDATIVE STRESS CONT'D

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **HealthPartners Institute** | Novolin R (intranasal insulin) | Insulin receptor agonist | | Multiple Symptoms | 2 | - | Phase 2 results pending Q3 2023 |
| **Zhejiang University School of Medicine** | Idebenone | Reducing agent | | Progression | 2 3 | - | Phase 2/3 results pending H1 2023 |
| **University College London** | Exenatide | GLP-1 agonist | | Progression | 3 | $ | Phase 3 results pending Q2-Q3 2024 |

# AUTOPHAGY

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **1st Biotherapeutics** | 1st-102 (FB-101) | c-Abl kinase inhibitor | | Progression | 1 | - | Phase 1 results pending |
| **Inhibikase** | ikT-148009 | c-Abl kinase inhibitor | | Progression | 2 | $ | Phase 1 positive results Press release Phase 2 results pending Q4 2023 |
| **Il-Yang Pharmaceutical** | Radotinib | c-Abl kinase inhibitor | | Progression | 2 | - | Phase 2 results pending Q2-Q3 2025 |
| **SPARC** | Vodobatinib (K-0706) | c-Abl kinase inhibitor | | Progression | 2 | Other | Phase 2 results pending H1 2023 |

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

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# INFLAMMATION

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Neuramedy Co. Ltd.** | NM-101[1] | Toll-like receptor 2 antagonist | | Progression | 1 | - | Phase 1 trial launch pending Q2 2023 |
| **Longevity Biotech** | LBT-3627[1] | Vasoactive intestinal polypeptide agonist | | Progression | 1 | $ | Phase 1 trial pending Q3 2023 |
| **The Scripps Research Institute** | PDM608[1] | Granulocyte macrophage colony stimulating factor | Biologic | Progression | 1 | $ | Phase 1 trial launch pending Q2 2023 |
| **Partner Therapeutics** | Sargramostim | Granulocyte macrophage colony stimulating factor | Biologic | Progression | 1b | - | Phase 1 results pending Q4 2024 - Q1 2025 |
| **Roche** | RO-7486967 | NLRP3 inhibitor | | Progression | 1b | Other | Phase 1b results pending Q4 2023 |
| **BioVie** | NE-3107 | ERK1/2 inhibitor | | Motor Impairment, Progression | 1 2 | - | Phase 1/2 positive results Press release |
| **Alkahest** | GRF-6021[2] | Blood plasma fraction | | Cognition/Dementia | 2 | $, Other | Pending update |
| **Alkahest** | AKST-4290[2] | Chemokine antagonist | | Progression | 2 | $ | Pending update |
| **University of Cambridge** | Azathioprine | Immunosuppressant | | Progression | 2 | - | Phase 2 results pending H1 2024 |
| **Stockholm Health Care Services** | Montelukast | Leukotriene antagonist | | Progression | 2 | - | Phase 2 results pending |

[1]In preclinical stage, expected to enter Phase 1 in 2023
[2]No recent updates on development plans following Alkahest acquisition by Grifols in 2021

Vaccine | Antibody | Gene Therapy | Small Molecule | Cell/Tissue Therapy | Peptide

Development Stage: 1 2 3 Reg.

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# MICROBIOME

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **University of Texas** | PRIM-DJ2727 | Fecal microbiota (microbiome modulator) | Other | Motor Impairment | 1 | - | Phase 1 results pending H1 2023 |
| **4D Pharma** | MRx-0005[1] MRx-0029[2] | Inflammation inhibitor (microbiome modulator) | Other | Progression | 1 2 | Other | Phase 1/2 trial pending |
| **University of California San Francisco** | Rifaximin | Antibiotic |  | Motor Impairment | 1 2 | - | Phase 1/2 results pending Q4 2023-Q1 2024 |
| **Medical University of Warsaw** | Fecal transfer | Fecal microbiota (microbiome modulator) | Other | Motor Impairment, Progression | 1 2 | - | Phase 1/2 results pending Q4 2024-Q1 2025 |

[1-2]In preclinical stage, expected to enter Phase 1 in 2023

Vaccine  Antibody  Gene Therapy  Small Molecule  Cell/Tissue Therapy  Peptide 


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# CELL REPAIR

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Taiwan Mitochondrial Applied Technology Co.** | MitoCell[1] | Adipose-Derived Mesenchymal Stem Cells | Cell/Tissue Therapy | Progression | 1 | - | Phase 1 trial launch pending H1 2023 |
| **Herantis** | HER-096[1] (xCDNF) | CDNF agonist | Peptide | Progression | 1 | - | Phase 1 trial launch pending H1 2023 |
| **InnoMedica** | Talineuren (GM1) | Neural regeneration | Other | Progression | 1 | - | Phase 1 pending update |
| **Hebei Newtherapy Bio-Pharma** | Allogeneic MSCs | Umbilical cord-derived mesenchymal stem cells | Cell/Tissue Therapy | Progression | 1 | - | Phase 1 results pending |
| **IMAC Holdings** | MSCTC-0010 | Umbilical cord-derived mesenchymal stem cells | Cell/Tissue Therapy | Bradykinesia | 1 | - | Phase 1 results pending |
| **Asklepios Bio (Bayer)** | AAV2-GDNF | GDNF agonist | Gene Therapy | Progression | 1b | - | Phase 1b results pending Q2-Q3 2027 |
| **Herantis** | HER-902 (rhCDNF) | CDNF agonist | Peptide | Progression | 1 2 | Other | Pending update |
| **University of Texas** | Allogeneic MSCs | Bone marrow-derived mesenchymal stem cell | Cell/Tissue Therapy | Progression | 2a | $ | Phase 2a results pending H2 2023 |
| **Hope Biosciences** | HB-adMSC | Adipose-derived mesenchymal stem cells | Cell/Tissue Therapy | Progression | 2 | - | Phase 2 results pending Q2-Q3 2023 |
| **Athira Pharma** | ATH-1017 | HGF agonist | Small Molecule | Cognition/Dementia | 2 | $, Other | Phase 2 results pending Q2 2023 |
| **Living Cell Technologies** | NTCell | Pig choroid plexus cells | Cell/Tissue Therapy | Progression | 2b | - | Phase 3 trial pending H1 2024 |

[1]In preclinical stage, expected to enter Phase 1 in 2023

Vaccine | Antibody | Gene Therapy | Small Molecule | Cell/Tissue Therapy | Peptide

Development Stage: 1 2 3 Reg.

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# CELL REPLACEMENT

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **BlueRock Therapeutics** | MSK-DA01 | Dopamine cell replacement (derived from hESCs) | ◉ | Motor Impairment | 1 | $ | Phase 1 interim results pending Q3-Q4 2023 |
| **Region Skåne, Lund University & University of Cambridge** | STEM-PD | Dopamine cell replacement (derived from hESCs) | ◉ | Motor Impairment | 1 | - | Phase 1 results pending 2027 |
| **International Stem Cell Corporation** | ISC-hpNSC | Dopamine cell replacement (derived from hPSCs) | ◉ | Motor Impairment | 1 | - | Pending update |
| **ASU-Banner Neuro Research Center** | Allogeneic DA progenitor cells[1] | Dopamine cell replacement (derived from iPSCs) | ◉ | Progression | 1b | $ | Phase 1b trial launch pending Q2 2023 |
| **Aspen Neuro** | ANPD-001[1] | Dopamine cell replacement (derived from iPSCs) | ◉ | Progression | 1 2 | - | Phase 1/2 trial pending |
| **Kyoto University & Sumitomo Dainippon** | iPSC-DA Transplants | Dopamine cell replacement (derived from iPSCs) | ◉ | Motor Impairment | 1 2 | $ | Phase 1/2 results pending Q4 2023 - Q1 2024 U.S. trial pending 2024 |

[1]In preclinical stage, expected to enter Phase 1 in 2023

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

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# DOPAMINE

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Dizlin Pharmaceuticals** | Infudopa (LD/CD) | Dopamine receptor agonist | | Motor Impairment | 1 | - | Pending update |
| **Lundbeck** | Lu-AF28996 | Dopamine receptor agonist | | Motor Impairment, OFF | 1 | - | Phase 1 results pending Q3-Q4 2023 |
| **Serina Therapeutics** | SER-214 (rotigotine) | Dopamine receptor agonist | | Motor Impairment | 1 | - | Phase 1 results pending |
| **Luye Pharma Group** | LY-03009 | Dopamine stimulation | | Motor Impairment | 1 | - | Pending next trial |
| **UCB** | UCB-0022 | D1 positive allosteric modulators D1 PAM | | Motor Impairment | 1 | - | Phase 1 results pending H1 2023 |
| **Guangzhou Henovcom Bioscience** | HNC-364 | MAO-B | | Motor Impairment | 1 | - | Phase 1 results pending Q2 2023 |
| **Sinopia Biosciences** | SB-0110[1] | Dopamine receptor pathway modulator | | Dyskinesia, Motor Impairment | 1b | $ | Phase 1b trial launch pending Q2 2023 |
| **University Hospital, Lille & InBrain Pharma** | A-dopamine | Dopamine receptor agonist | | Motor Impairment | 1 2 | - | Phase 1/2 results pending Q3-Q4 2023 |
| **Oxford BioMedica** | AXO-Lenti-PD[2] | Dopamine synthesis | | Motor Impairment | 1 2 | Other | Pending update |

[1]SB-0110 is in preclinical stage, expected to enter Phase 1 in 2023
[2]Sio Gene Therapies discontinued development in 2022 after several manufacturing and development challenges. Rights were returned to Oxford BioMedica, who plans to out-license the program to a suitable partner

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# DOPAMINE CONT'D

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Chase Therapeutics** | CTC-413 (pramipexole ER) | Dopamine receptor agonist, NK-1 receptor antagonist | | Motor Impairment, Progression | 2 | - | Phase 2 results pending Q4 2023 - Q1 2024 |
| **SynAgile** | DopaFuse (CD/LD) | Dopamine receptor agonist | | Motor Impairment | 2 | - | Phase 2 positive topline results Press release |
| **Intrance Medical Systems** | Lecigon[1] (CD/LD/entacapone pump) | Dopamine agonist, COMT inhibitor | | Motor Impairment | 2 | - | Phase 3 trial pending |
| **Eli Lilly** | Mevidalen[2] (LY-3154207) | Dopamine receptor agonist | | Cognition/Dementia | 2 | Other | Pending next trial |
| **PureIMS** | PIMS-703 (inhaled levodopa) | Dopamine receptor agonist | | OFF | 2 | - | Pending update |
| **Cerevance** | CVN-424 | Dopamine signaling modulator | | Motor Impairment, OFF | 2 | - | Phase 2/3 trial launch pending Q2 2023 |
| **Kissei Pharma & Affamed** | KDT-3594 | Dopamine receptor agonist | | Motor Impairment | 2b | - | Ongoing phase 2b trial |
| **IRLAB Therapeutics & Ipsen** | Mesdopetam (IRL-790) | Dopamine receptor antagonist | | Dyskinesia | 2b | - | Phase 2b topline results - primary endpoint not met; Further analysis pending Press release |
| **Luye Pharma Group** | LY-03003 (rotigotine ER) | Dopamine receptor agonist | | Motor Impairment | 3 | - | Pending update |
| **Neuroderm (MT Pharma)** | ND-0612 (CD/LD pump) | Dopamine receptor agonist | | Motor Impairment | 3 | $, Other | Phase 3 positive results Press release |

[1]Lecigon is available across Europe. Currently awaiting FDA approval to initiate pivotal Phase 3 trial in the US
[2]Development is indicated for Symptomatic LBD. Previous trials have included LBD associated with idiopathic PD

Vaccine | Antibody | Gene Therapy | Small Molecule | Cell/Tissue Therapy | Peptide

Development Stage: 1 2 3 Reg.

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# DOPAMINE CONT'D

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Cerevel Therapeutics** | Tavapadon (PF-06649751) | Dopamine receptor agonist | | Motor Impairment | 3 | Other | Phase 3 results pending Q2-Q3 2024 |
| **Pharma Two B** | P2B-001 (pramipexole /rasagiline) | Dopamine agonist, MAO-B inhibitor | | Motor Impairment | 3 | - | Phase 3 positive results Press release |
| **AbbVie** | ABBV-951 (LCD/LDP infusion) | Dopamine receptor agonist | | Motor Impairment | 3 | - | Negative NDA decision, resubmission pending Press release |
| **Amneal** | IPX-203 (CD/LD) | Dopamine receptor agonist | | Motor Impairment | 3 | - | NDA decision pending Q3 2023 |
| **Supernus Pharmaceuticals** | SPN-830 (apomorphine infusion) | Dopamine receptor agonist | | OFF | 3 | - | Negative NDA decision, resubmission pending Press release |

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

## ACETYLCHOLINE

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **University of Queensland** | Levetiracetam | Acetylcholine receptor agonist | | Cognition/Dementia | 2 | - | Phase 2 results pending Q4 2023 - Q1 2024 |
| **Takeda** | TAK-071 | Muscarinic M1 receptor agonist | | Cognition/Dementia, Gait/Balance | 2 | $, Other | Phase 2 results pending H1 2023 |
| **Anavex Life Sciences** | Blarcamesine (ANAVEX-2-73) | Sigma-1 receptor agonist, Acetylcholine receptor antagonist | | Cognition/Dementia, Progression | 2 | $, Other | Phase 2 positive results Press release |
| **NHS & University of Bristol** | Rivastigmine | Acetylcholinesterase inhibitor | | Gait/Balance | 3 | - | Phase 3 results pending Q4 2023 |

## CANNABINOIDS

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Parkinson's UK & King's College London** | Cannabidiol (CBD) | Cannabinoid receptor agonist | | Psychosis | 2 | - | Phase 2 results pending Q1 2024 |
| **University of Colorado** | Cannabidiol (CBD) | Cannabinoid receptor agonist | | Motor Impairment | 2 | - | Phase 2 results pending |
| **University Health Network, Toronto** | Cannabis Oil | Cannabinoid receptor agonist | | Pain | 2 | - | Phase 2 results pending H1 2023 |

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

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## GABA

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Sage Therapeutics & Biogen** | SAGE-324[1] | GABAA receptor agonist | Small Molecule | Motor Impairment | 1 | - | Pending next trial |
| **MeiraGTx** | AAV-GAD | Glutamate decarboxylase stimulant | Gene Therapy | Motor Impairment | 1 2 | $, Other | Phase 1/2 results pending H1 2024 |

[1]Ongoing Phase 2 in essential tremor, next steps for further clinical development in PD pending

## GLUTAMATE

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Appello Pharma** | AP-472 | Glutamate receptor agonist | Small Molecule | Dyskinesia, Motor Impairment | 1a | $ | Pending update |
| **VistaGen** | AV-101 | AMPA receptor agonist, NMDA antagonist | Small Molecule | Dyskinesia | 1b | - | Phase 1b results pending H1 2023 |
| **Sage Therapeutics** | SAGE-718 | NMDA receptor agonist | Small Molecule | Cognition/Dementia | 2 | Other | Phase 2 results pending Q3-Q4 2023 |
| **BrainX Corporation** | Ceftriaxone | Cell wall synthesis inhibitor | Small Molecule | Cognition/Dementia | 2 | - | Phase 2 results pending Q4 2023 - Q1 2024 |
| **Yale University** | Ketamine | NMDA receptor antagonist | Small Molecule | Depression | 2 | $ | Phase 2 results pending H2 2024 |
| **Pharmather** | PT-001 (Ketamine) | NMDA receptor antagonist | Small Molecule | Dyskinesia | 2 | - | Phase 3 trial pending |
| **Addex Therapeutics** | Dipraglurant (ADX-48621) | Glutamate receptor antagonist | Small Molecule | Dyskinesia | 2 3 | $ | Pending update |
| **Wayne State University** | Memantine[1] | NMDA receptor antagonist | Small Molecule | Progression | 3 | - | Phase 3 results pending Q3 2023 |

[1]Possible aSyn transmission inhibition

Vaccine | Antibody | Gene Therapy | Small Molecule | Cell/Tissue Therapy | Peptide

Development Stage: 1 2 3 Reg.

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

# EPINEPHRINE/NOREPINEPHRINE

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **University of Iowa** | Terazosin | Alpha-1 adrenergic antagonist | | Progression | 1 | $ | Phase 1 results pending H1 2023 |
| **Cedars-Sinai Medical Center** | Terazosin | Alpha-1 adrenergic antagonist | | Progression | 2 | - | Phase 2 results pending Q4 2025-Q1 2026 |
| **CuraSen Therapeutics** | CST-2032 | Adrenoreceptor agonist | | Cognition/Dementia | 2a | - | Phase 2a results pending Q4 2023 - Q1 2024 |
| **Cedars-Sinai Medical Center** | Carvedilol | Adrenoreceptor antagonist (putative antioxidant actions) | | Progression | 2 | - | Phase 2 results pending Q2 2023 |
| **CuraSen Therapeutics** | Clenbuterol (CST-103) | Adrenoreceptor agonist | | Multiple Symptoms, Progression | 2 | - | Phase 2 positive topline results Press release |
| **IRLAB Therapeutics** | Pirepemat (IRL-752) | Adrenoreceptor antagonist, Serotonin antagonist | | Cognition/Dementia, Gait/Balance | 2b | - | Phase 2b topline results pending H1 2024 |

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

Development Stage: 1 2 3 Reg.

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# SEROTONIN

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Sumitomo Dainippon (DS Pharma)** | DSP-9632P | Serotonin receptor agonist | | Dyskinesia | 1 | - | Phase 1 results pending H2 2023 |
| **Neurolixis** | Befiradol (NLX-112) | Serotonin receptor agonist | | Dyskinesia | 2a | $, Other | Phase 2a positive results Press release |
| **Vanda Pharma** | Fanapt (Iloperidone) | Dopamine antagonist; Serotonin antagonist | | Psychosis | 2 | - | Phase 2 results pending Q4 2023 |
| **Silo Pharma & UCSF** | Psilocybin | Serotonin receptor agonist | | Anxiety, Depression | 2 | - | Phase 2 results pending Q2-Q3 2023 |
| **University College, London** | Ondansetron | Serotonin receptor antagonist | | Hallucinations | 2 | - | Phase 2 results pending H1 2025 |
| **University Hospital of Strasbourg** | Pimavanserin (Nuplazid) | Serotonin receptor antagonist | | Impulse | 2 | - | Phase 2 results pending Q3 2023 |
| **University of Michigan & NIA** | Citalopram | Serotonin reuptake inhibitor | | Cognition/Dementia, Progression | 2 | - | Phase 2 results pending H2 2025 |
| **Silo Pharma & Maastricht University** | Ketamine & Psilocybin | NMDA receptor antagonist; Serotonin receptor agonist | | Cognition/Dementia, Mood | 2b | - | Phase 2b trial ongoing |
| **Bukwang Pharmaceutical** | JM-010 | Serotonin receptor agonist | | Dyskinesia | 2b | Other | Phase 2b results pending Q4 2023-Q1 2024 |

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

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# PHOSPHODIESTERASE

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Celon Pharma** | CPL-36 | Phosphodiesterase 10A inhibitor | | Dyskinesia | 2 | - | Phase 2 results pending H1 2023 |
| **Eisai** | Irsenontrine (E-2027) | Phosphodiesterase 9A inhibitor | | Cognition/Dementia | 2 | - | Phase 2 results - primary endpoint not met. Results report |
| **Intra-Cellular Therapies** | Lenrispodun (ITI-214) | Phosphodiesterase 1 inhibitor | | Motor Impairment | 2 | $, Other | Phase 2 results pending Q4 2024-Q1 2025 |

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

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# OTHER TARGETS

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| ***Adenosine*** | | | | | | | |
| **Kyowa Kirin** | Istradefylline (KW-6002) | Adenosine receptor antagonist | | Cognition/Dementia | 2 | - | Phase 2 results pending H2 2025 |
| ***Nurr1*** | | | | | | | |
| **NurrOn Pharmaceuticals** | ATH-399A[1] | Synthetic ligand of Nurr1 agonists | | Progression | 1 | $ | Phase 1 trial launch pending Q3 2023 |
| ***Progranulin (PGRN)*** | | | | | | | |
| **Alector & GSK** | AL-101 | Sortilin inhibitor | | Progression | 1a | - | Phase 1a positive results Press release |
| ***Other/Multiple*** | | | | | | | |
| **Digestome Therapeutics** | DGX-001 | Vagal nerve stimulator | | Non-motor Symptoms | 1 | - | Phase 1 results pending H1 2023 |
| **Praxis Precision Medicines** | PRAX-944[2] | Calcium channel antagonist | | Motor Impairment | 1 | Other | Phase 2 trial launch pending H1 2023 |
| **University of Sydney[3]** | Alogliptin, Albuterol, Nilvadipine | DPP-4 inhibitor, Calcium channel antagonist, Adrenoreceptor agonist | | Motor Impairment, Progression | 2 | - | Phase 2 results pending |
| **Clene Nanomedicine** | CNM-Au8 | Gold nanocrystals, bioenergetics | Other | Progression | 2 | $ | Phase 2 trial pending H1 2023 |
| **Jazz Pharma** | CX-8998[4] | T-type calcium channel antagonist | | Motor Impairment | 2 | - | Phase 2 results pending Q2-Q3 2024 |

[1]ATH-399A is in preclinical stage, expected to enter Phase 1 in 2023
[2]PRAX-944 is in clinic for essential tremor (ET). Expected to enter Phase 2 for PD in 2023
[3]Treatments are being studied in parallel as part of a single trial platform effort
[4]Prior Phase 2 trial was withdrawn prior to initiation. New Phase 2 trial initiated in Dec. 2022. For purposes of this report, classifying as moving into clinic and Phase 2 for the first time

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

Development Stage: 1 2 3 Reg.

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

*Programs included on this slide represent active MJFF-funded programs supporting technology-enabled therapeutics and neuromodulation and are not a full listing of all approaches currently in development.*

## DEVICES AND TECHNOLOGIES

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Newel Health** | Soturi app | Digital therapeutic for medication optimization | Other | Motor Impairment, Treatment Plan Optimization | 2 | $ | Phase 2 trial launch pending Q2 2023 |
| **Shirley Ryan AbilityLab** | Wearable Airbag Technology | Fall detection and mitigation | Other | Motor Impairment | 2 | $ | Phase 2 results pending Q1 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 |
| **Long Island University** | Understand Me for Life App | Speech intelligibility app | Other | Speech | 2 | $ | Phase 2 results pending H1 2026 |
| **Sibel Health** | ADAM+ platform | Swallowing and drooling digital therapeutic | Other | Dysphagia, Sialorrhea | 3 | $ | Phase 3 results pending H1 2025 |

## NEUROMODULATION

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **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 H1 2024 |
| **Cleveland Clinic** | V-GAIT platform | STN-DBS neural signatures, DBS programming | Other | Motor Impairment | 2 | $ | Phase 2 results pending H1 2025 |

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

Development Stage: 1 2 3 Reg.

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# OTHER NON-PHARMACOLOGICAL

| Sponsor | Therapeutic | Mechanism | Approach | Indication | Stage[a] | MJFF Role[b] | Status or Results Expected[c] |
|---|---|---|---|---|---|---|---|
| **Leiden University Medical Center** | Head-up tilt during sleep (HUTS) | Autonomic dysfunction | Other | Orthostatic Hypotension, Supine Hypertension | 2 | $ | Phase 2 results pending H1 2024 |

Vaccine Antibody Gene Therapy Small Molecule Cell/Tissue Therapy Peptide

Development Stage: 1 2 3 Reg.

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# Appendix

# PENDING AND DISCONTINUED PROGRAMS

*Programs included on the following slides have been removed from active monitoring due to lack of progress, uncertainty in current development status or announced discontinuation. Trials will be removed from this section after 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[a] | MJFF Role[b] | Status |
|---|---|---|---|---|---|
| ***Industry*** | | | | | |
| Cortexyme | Atuzaginstat (COR-388) | Progression | 1 | - | Development discontinued. FDA placed a clinical hold on COR-388 and company announced any future development will be in other indications |
| Alexza Pharmaceuticals | AZ-009 (apomorphine) | OFF | 1 | - | No updates on development or next steps since completion of phase 1 trial in 3/2020 |
| Biogen | BIIB-118 | Sleep | 1 | - | Development discontinued based on strategic review |
| Collaborative Medicinal | Cu(II)ATSM | Progression | 1 | $ | Active development for ALS but no significant progress in PD since 2019. Further activity in PD possible, but assume development has been deprioritized |
| Sunovion | DSP-6745 | Psychosis | 1 | Other | Development discontinued |
| E-Scape Bio | ESB-1609 | Progression | 1 | - | Development discontinued (*company ceasing operations)* |
| Lundbeck | Lu-AF82422 | Progression | 1 | - | MSA has been prioritized with no immediate plans for continued development in PD |
| Adhera Therapeutics | MLR-1019 (armesocarb) | Dyskinesia | 1 | - | No update since press release regarding planned 2021 phase 2 trial |
| Nobilis Therapeutics | NBTX-001 (Xenon gas) | Anxiety, Energy, Pain | 1 | - | Phase 1 trial was expected to end in 12/2021 and is likely completed. No update since 2021 |
| Neuropore | NPT-520-34 | Progression | 1 | - | Phase 1 trial completed in 2019. No update since press release stating intent for exploring another study in 1/2020. |
| PTC Therapeutics | PTC-857 | Progression | 1 | - | Completed Phase 1 trial, prioritizing PTC-857 as a treatment for ALS, no further development plans for PD GBA |
| Atlantic Healthcare | Renzapride (ATL-1251) | Gastroparesis | 1 | - | No update since listed as Phase 1 on company pipeline in 2020 |

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# PENDING AND DISCONTINUED PROGRAMS

| Sponsor | Therapeutic | Indication | Stage[a] | MJFF Role[b] | Status |
|---|---|---|---|---|---|
| ***Industry*** | | | | | |
| RaQualia Pharma | RQ-10 | Constipation | 1 | $ | No further clinical development in multiple years; interest in out-licensing compound for additional studies |
| King's College London & AstraZeneca | Saracatinib | Psychosis | 1 | - | No recent updates – assume development has been deprioritized |
| XW Pharma | Valiloxybate (XW-10172) | Sleep | 1 | - | No update since announcing plans for Phase 2 trial in 2021 press release |
| Xoc Pharmaceuticals | XC-130 | Motor Impairment | 1 | - | Phase 1 trial was expected to close in 4/2022 but no update since 9/2021 |
| AstraZeneca & King's College London | AZD-0328 | Cognition/Dementia | 2a | $ | Phase 2 trial was terminated prior to recruitment start. No further development planned |
| Impel NeuroPharma | INP-107 (CD/LD) | Motor Impairment, OFF | 2a | - | No recent updates. Planned study in 3/2022 did not start. Completion of Phase 1 trial in 2019 |
| Theranexus | THN-102 (flecainide/modafinil) | Sleep | 2a | - | Development discontinued after failure to find potential partner for development |
| Seelos Therapeutics | Aplindore (SLS-006) | Motor Impairment | 2 | | Not in active development. Company continuing to evaluate next steps |
| B&A Therapeutics | Bumetanide | Gait/Balance, Motor Impairment | 2 | - | Development discontinued (*company ceasing operations*) |
| DS Pharma | EPI-589 | Progression | 2 | - | No update since completion of phase 2 trial in 2019 |
| Vivifi Biotech | GDNF | Progression | 2 | $ | Vivifi is seeking out partners to move towards another trial as of October 2022 |
| Aptinyx | NYX-458 | Cognition/Dementia | 2 | Other | Negative read-out of phase 2 in February 2023 - program discontinued |
| Sunovion | Ulotaront (SEP-363856) | Psychosis | 2 | Other | Phase 2 study completed in 2020. No updates on next steps for PD psychosis - schizophrenia appears to be prioritized |

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# PENDING AND DISCONTINUED PROGRAMS

| Sponsor | Therapeutic | Indication | Stage[a] | MJFF Role[b] | Status |
|---|---|---|---|---|---|
| ***Industry*** | | | | | |
| Kyowa | KW-6356 | Motor Impairment | 2b | - | Development discontinued |
| ***Academic & Research Institutions*** | | | | | |
| 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 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 |
| University of Jordan | Allogeneic MSCs | Multiple Symptoms | 1 2 | - | Phase 1/2 trial was supposed to end in 2021 and is likely complete. No update since 2021 |
| NINDS | Flumazenil | Motor Impairment | 1 2 | - | No updates on next steps. Phase 1/2 trials ended in 2021 Phase 1/2 results reported Study Results |
| Hospices Civils de Lyon | Clonidine | Impulse | 2 | - | Last phase 2 trial was completed in 2021, but no results or next steps shared |

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