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DISCOVERY SERIES – EMERGING TARGETS IN PARKINSON'S DISEASE

#3 – LRRK2

Leucine–rich repeat kinase 2 (LRRK2)–targeted therapies for the treatment of Parkinson's disease

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Contents

LRRK2 is one of our best validated targets in Parkinson's disease. Pathogenic LRRK2 mutations, particularly G2019S, have firmly established the target's relevance to disease biology, while convergent evidence from kinase activity, Rab phosphorylation, lysosomal dysfunction, mitochondrial stress, and immune signalling has positioned LRRK2 at the centre of multiple Parkinson's–relevant pathways.

However, the field has now moved beyond the question of whether LRRK2 is a credible therapeutic target. The more important question is how LRRK2 biology can be translated into safe, durable, and clinically meaningful therapies across a heterogeneous patient population.

At Atuka, we view LRRK2 not as a narrow genetic subtype marker, but as a mechanistic hub that links several core processes implicated in Parkinson's disease, including vesicular trafficking, lysosomal and autophagic function, mitochondrial homeostasis and neuroimmune regulation. This perspective broadens the relevance of LRRK2 beyond mutation carriers. Increasing evidence that LRRK2 pathway activity is elevated in subsets of idiopathic Parkinson's disease suggests that LRRK2-targeted approaches may have potential in biomarker-defined populations as well as genetically defined disease.

This broader opportunity also creates a more complex translational problem. "LRRK2-PD" should not be treated as a single uniform entity. Clinical and pathological data indicate substantial heterogeneity in penetrance, age of onset, progression, α-synuclein involvement, tau pathology, and biomarker profiles. As a result, the key translational question is not simply whether a model, patient group, or therapeutic approach is "LRRK2-relevant," but which aspect of LRRK2-linked biology it captures.

The therapeutic pipeline reflects this complexity. Small molecule kinase inhibitors, brain-selective inhibitors, targeted protein degraders, and RNA-based approaches are all being advanced, each with distinct implications for tissue exposure, durability of target modulation, reversibility, biomarker response and long-term safety. This diversity should not be interpreted as a lack of confidence in LRRK2. Rather, it indicates that the optimal way to modulate the target remains unresolved.

For this reason, we consider LRRK2 as primarily a translational optimization problem. The next phase of the field will depend on aligning therapeutic modality, patient selection, biomarker strategy, and tissue-specific pharmacology. Success will require more than demonstrating target engagement. It will require understanding how different approaches to LRRK2 modulation translate across central and peripheral compartments, across disease stages and across biologically distinct patient subgroups.

Within this framework, non-human primate studies (NHPs) have a focused and strategic role. Many mechanistic questions can be addressed in rodent models or human cellular systems. NHPs are most valuable when used selectively to resolve translational uncertainties that are difficult to address elsewhere, including CNS versus peripheral exposure, durability of target engagement, modality-dependent effects, and biomarker relationships with relevance to human studies. This supports a hypothesis-driven use of NHPs aligned with both scientific value and 3Rs principles.

Taken together, LRRK2 represents a model case for the broader challenge of translating mechanistically rich targets in neurodegeneration. It is no longer a target-validation story alone. It is a test of how well the field can connect human genetics, pathway biology, therapeutic modality, biomarkers, and translational models to deliver disease-modifying therapies for Parkinson's disease.

INSIGHT

Key Translational Insight: LRRK2 Biology Extends Beyond Mutation Carriers

Increasing evidence indicates that LRRK2 pathway activity is not confined to individuals with pathogenic LRRK2 mutations. Elevated kinase activity and Rab GTPase phosphorylation have been observed in subsets of idiopathic Parkinson's disease, suggesting broader engagement of LRRK2–linked biology across the disease spectrum.

Implications for translation:

- Preclinical models do not need to carry LRRK2 mutations to be informative.
- Model selection should be based on mechanism engagement rather than genotype.
- Patient identification may require biomarker–driven, rather than mutation–driven, strategies.

This perspective shifts the focus from genetic validation toward mechanism–based stratification and highlights the importance of aligning preclinical models with specific biological hypotheses.

Atuka Perspectives on LRRK2 in Parkinson's Disease

The LRRK2 field has moved from genetic discovery into active clinical development. In Atuka's view, this transition reframes LRRK2 from a target-validation question to a translational optimization challenge. The priority is no longer to prove that LRRK2 is relevant to Parkinson's disease, but to determine how best to modulate it safely and effectively across biologically diverse patient populations.

LRRK2 is a mechanistic hub, not a narrow genetic target

LRRK2 has been extensively validated through human genetics, gain-of-function kinase activity, downstream Rab GTPase phosphorylation, and convergent effects on intracellular trafficking pathways. Its significance, however, extends beyond pathogenic mutation carriers.

LRRK2 sits at the intersection of several Parkinson's-relevant processes, including vesicular trafficking, lysosomal and autophagic function, mitochondrial homeostasis, and immune signalling. Evidence of elevated LRRK2 activity and Rab phosphorylation in subsets of idiopathic Parkinson's disease further supports its role as a broader disease-relevant pathway, rather than a target confined to a rare genetic subtype.

This framing expands the therapeutic opportunity but also increases the complexity of translation.

"LRRK2–PD" is not a single disease entity

Clinical and neuropathological data indicate substantial heterogeneity within LRRK2-associated Parkinson's disease (LRRK2-PD). Variability in penetrance, age of onset, progression and pathology, including differences in α-synuclein and tau involvement, suggests that "LRRK2-PD" represents a biological spectrum rather than a single disease entity.

This has important implications for model selection and interpretation. The key question is not whether a model represents LRRK2-PD in general, but which aspects of LRRK2-linked biology it captures. A mechanism-led, rather than label-led, framework is therefore critical for improving translational fidelity.

Pipeline diversity reflects translational complexity

The LRRK2 therapeutic landscape includes small molecule kinase inhibitors, targeted protein degraders, and RNA-based approaches.

This diversity should not be interpreted as uncertainty around target validity. Rather, it reflects unresolved questions about how best to modulate LRRK2 across tissues, disease stages and biological contexts.

The pipeline therefore represents a parallel exploration of the translational design space. Differences between modalities may provide important insight into target biology, pharmacology, therapeutic windows and long-term safety.

LRRK2 is now an optimization problem

With target validation largely established, the central challenges are now translational. These include selecting the optimal modality, defining robust biomarkers, identifying responsive patient populations, and balancing central nervous system target engagement with peripheral biology and long-term safety.

Additional complexity arises from tissue compartmentalisation, durability of target modulation and the relationship between pharmacodynamic markers and clinical outcomes. Addressing these questions requires integrated approaches that connect mechanism, pharmacology, and clinical context.

NHPs can help resolve specific translational uncertainties

Within this framework, NHP studies have a focused and strategic role. Many mechanistic questions can be addressed in rodent or human cellular systems, but NHPs are particularly valuable when higher translational fidelity is required.

Key applications include assessing tissue compartment exposure, comparing modality-dependent effects, evaluating durability of target engagement and establishing biomarker relationships relevant to human studies. NHPs are therefore best used selectively to resolve specific translational uncertainties, rather than as default efficacy models.

Introduction

LRRK2 mutations (particularly G2019S) are among the most common genetic causes of familial Parkinson's disease (PD) and are associated with increased kinase activity, which may also be observed in some idiopathic cases. Hyperactive LRRK2 impairs lysosomal function and autophagy, promoting α-synuclein aggregation and neuronal stress. Inhibiting or degrading LRRK2 aims to restore cellular homeostasis and slow progression.

Multiple modalities are in development: traditional Type I/II kinase inhibitors, brain-selective designs (to limit lung/kidney risks observed preclinically), PROTAC degraders and antisense oligonucleotides. AI/computational approaches and the MJFF LITE program (launched in 2024) support broader advancement.

While these advances have established LRRK2 as a compelling therapeutic target, they also highlight a shift in the key challenges facing the field. The focus is increasingly moving from target validation toward resolving how best to translate LRRK2 biology into effective therapies. This includes questions of modality, patient selection, biomarker strategy, and tissue-specific effects, which form the central focus of this white paper.

LRRK2 biology and mutations relevant to Parkinson's disease

LRRK2 encodes a large, multifunctional protein belonging to the Roco family, with both GTPase (Roc-COR domains) and kinase activities, plus ankyrin, leucine-rich repeat, and WD40 domains. It regulates critical cellular processes including vesicle trafficking, autophagy-lysosomal pathways, mitochondrial homeostasis, cytoskeletal dynamics, and immune/inflammatory responses (particularly in microglia and peripheral immune cells).

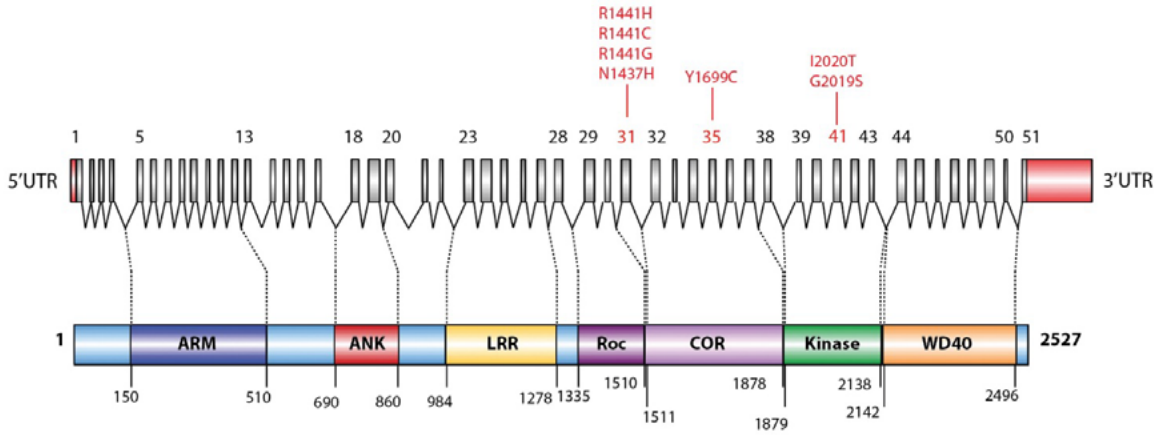

Figure 1. LRRK2 biology and mutations relevant to Parkinson's disease

Pathogenic mutations in LRRK2 cause a gain-of-function effect, primarily through increased kinase activity that leads to hyperphosphorylation of Rab GTPases (e.g., Rab10, Rab29). This disrupts endolysosomal trafficking, impairs autophagy, and promotes neuroinflammation and mitochondrial dysfunction, ultimately contributing to dopaminergic neuron degeneration in the substantia nigra.

Seven missense variants are widely accepted as clearly pathogenic:

- **p.G2019S (kinase domain):** The gene is the most studied, increasing kinase activity by 2-3 times. It contributes to 4-6% of familial Parkinson's disease and 1-2% of sporadic cases worldwide, with higher rates in specific groups like Ashkenazi Jews and North African Berbers, reaching up to 41% in some Moroccan studies. Its age-dependent penetrance varies, with lifetime risk estimates from 17% to 80%, often around 25-50% by age 80.
- **p.R1441C/G/H:** These genetic mutations are located within the Roc GTPase domain of a particular protein. This mutation is characterized by a reduction in GTPase activity, which plays a crucial role in cellular signalling pathways. Interestingly, while GTPase activity decreases, there is an indirect increase in kinase activity, which can influence various downstream processes. The mutation is notably more prevalent among European and Hispanic populations, with a significant concentration in Basque and Spanish cohorts, particularly for the p.R1441G variant. This mutation exhibits a higher penetrance compared to the G2019S mutation, indicating a greater likelihood of manifesting clinical symptoms in carriers. Understanding these genetic variations is essential for assessing disease risk and tailoring personalized treatment strategies.
- **p.N1437H and p.Y1699C (Roc-COR domains), and p.I2020T (kinase domain):** rare pathogenic variants that also increase LRRK2 kinase activity and drive Rab GTPase hyperphosphorylation.

INSIGHT

LRRK2 as a Translational Optimization Problem

With target validation largely established, the central challenge in LRRK2 is now one of optimization across multiple interconnected dimensions.

Key variables include:

> Therapeutic modality: kinase inhibition, targeted degradation, or RNA–based suppression.

> Tissue exposure: central nervous system versus peripheral compartments.

> Durability: sustained versus reversible target modulation.

> Biomarkers: linking pharmacodynamic effects to clinical outcomes.

> Patient selection: genetic versus biomarker–defined populations.

These variables are interdependent and cannot be optimized in isolation. Together, they define a multidimensional translational problem that extends beyond traditional preclinical efficacy models and requires integrated, mechanism–aware approaches.

Additional variants (e.g., p.G2385R and p.R1628P, particularly in Asian populations) are generally considered risk alleles with reduced penetrance, rather than fully penetrant pathogenic mutations. In contrast, loss-of-function (truncating) LRRK2 variants do not appear to increase PD risk and, in some contexts, have been reported as neutral or potentially protective.

Mutation	Domain	Effect	Prevalence	Penetrance
p.G2019S	Kinase	Increases kinase activity	Common globally	Incomplete, age-dependent
p.R1441C/G/H	Roc GTPase	Reduces GTPase activity	European/Hispanic populations	Generally higher
p.N1437H, p.Y1699C, p.I2020T	Roc-COR, Kinase	Elevated kinase activity	Rarer	Not specified
p.G2385R, p.R1628P	Not specified	Risk factors	Asian populations	Lower

Figure 2. Key Pathogenic Mutations in LRRK2

Prevalence and clinical features

Mutations in the LRRK2 gene represent one of the most common genetic contributors to Parkinson's disease, accounting for approximately 5–6% of familial cases and 1–2% of sporadic cases worldwide. However, the prevalence of LRRK2 variants exhibits significant geographic and ethnic variability, largely driven by founder effects. For example, the G2019S mutation is particularly enriched in specific populations, including Ashkenazi Jewish and North African Berber groups, where carrier frequencies are substantially higher than the global average. This variability underscores the importance of population-specific screening strategies and has implications for clinical trial design and therapeutic targeting.

The clinical phenotype associated with LRRK2-related PD (LRRK2-PD) closely resembles that of idiopathic Parkinson's disease, both in presentation and progression. Reported median ages at onset cluster around 56–60 years, varying by cohort and method, aligning with sporadic PD. Notably, approximately one-third of individuals with LRRK2 mutations experience earlier onset, before the age of 50, indicating a broader age distribution than traditionally appreciated. Tremor is frequently a prominent early symptom, often presenting as the initial clinical manifestation.

Analysis of longitudinal UPDRS Part III Data from the Parkinson's Precision Medicine Initiative (PPMI; formerly Parkinson's Progression Markers Initiative) suggests both similarities and potential differences in disease trajectory between LRRK2-associated and sporadic Parkinson's disease.

At diagnosis, LRRK2-associated PD exhibits lower motor impairment compared to sporadic PD, albeit with a slightly younger age at diagnosis (59.8 vs 62.5 years). While this could reflect earlier detection or differences in clinical ascertainment, the modest age difference suggests that additional factors, such as phenotype or underlying disease biology, may also contribute. Over approximately the first 5–7 years following diagnosis, both cohorts demonstrate broadly similar rates of motor progression.

Beyond this period, the data suggest a possible divergence, with LRRK2-associated PD showing a comparatively slower rate of worsening. However, this apparent separation should be interpreted with caution. Increased variability and reduced sample sizes at later timepoints may influence the observed trajectories, and alternative explanations, including scale characteristics at higher disease severity or cohort composition effects, cannot be excluded. These findings support the view that LRRK2-associated PD may differ not only in genetic aetiology but also in disease trajectory, reinforcing the importance of mechanism-aware longitudinal analysis, biomarker development, and patient stratification in clinical studies.

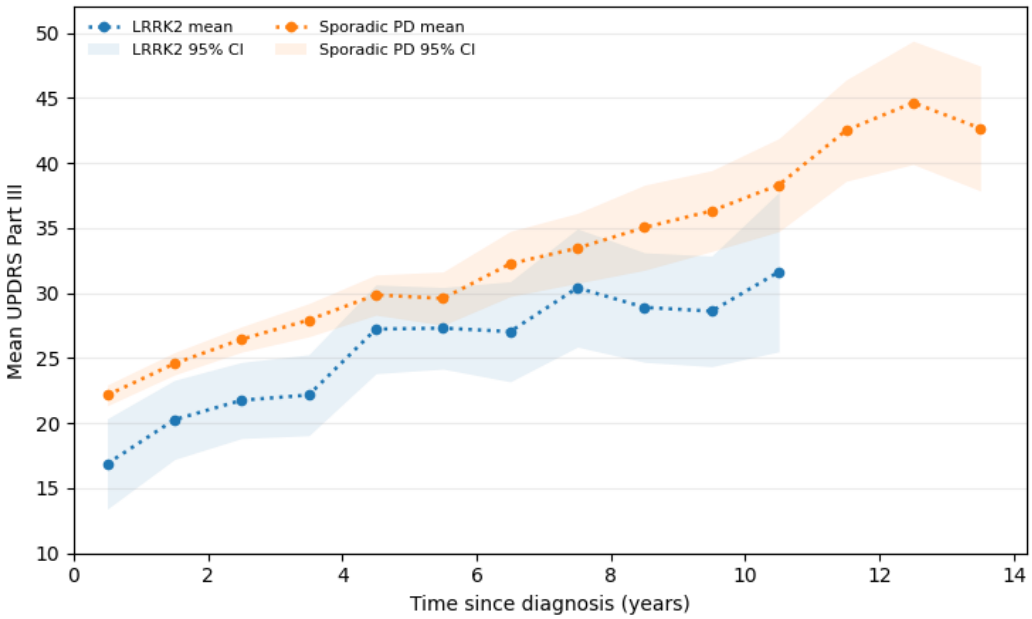

Figure 3. UPDRS Part III: Binned mean vs time since diagnosis

Non-motor symptoms are also prevalent and may include sleep disturbances, depression, anxiety, autonomic dysfunction, and cognitive impairment. While the overall non-motor burden is comparable to idiopathic PD, some studies suggest subtle differences in the frequency or severity of specific features, though findings remain inconsistent.

Neuropathologically, LRRK2-associated Parkinson's disease shows considerable heterogeneity. Approximately 50–60% of cases display classical Lewy body pathology, characterized by α-synuclein aggregation or detectable signals in blood-based α-synuclein Seed Amplification Assays (SAA). In contrast, tau pathology appears to be more consistently observed, with some series reporting near-universal presence. This divergence suggests that LRRK2-PD may not represent a single pathological entity but rather a spectrum of overlapping proteinopathies. Additionally, a subset of mutation carriers displays atypical or milder neurodegenerative changes, as well as distinct anatomical patterns of brain involvement, further highlighting the biological complexity of LRRK2-driven disease.

INSIGHT

Pipeline Diversity as a Signal of Translational Complexity

The breadth of the LRRK2 therapeutic pipeline—spanning small molecule inhibitors, protein degraders and RNA–based approaches—is unusual for a target at this stage of development.

Rather than reflecting redundancy, this diversity should be interpreted as an informative feature of the field. It indicates that while LRRK2 is strongly validated, key questions remain unresolved regarding how best to modulate its activity across different tissues, disease stages and patient populations.

From this perspective, the pipeline represents a parallel exploration of the translational design space, where different modalities may provide complementary insights into target biology, pharmacology, and therapeutic windows.

Collectively, these findings indicate that while LRRK2-PD is clinically similar to idiopathic PD, it is underpinned by diverse molecular and pathological mechanisms. This heterogeneity has important implications for biomarker development, patient stratification, and the design of targeted therapeutic interventions.

FEATURE	LRRK2–ASSOCIATED PD	IDIOPATHIC PD
Prevalence	~5–6% familial, ~1–2% sporadic	Majority of PD cases
Genetic Basis	LRRK2 mutations (e.g., G2019S)	Typically none identified
Age at Onset	Median 56–60 years; ~30% <50	Typically 60+ years
Initial Symptom	Often tremor–dominant	Variable (tremor or bradyki–nesia)
Motor Presentation	Asymmetric, similar to idiopathic PD	Asymmetric onset
Levodopa Response	Strong and sustained	Strong (may fluctuate over time)
Disease Progression	Sometimes slower (esp. G2019S)	Variable
Non–Motor Symptoms	Common; similar spectrum	Common
Lewy Body Pathology	~50–60%	~80–90%
Tau Pathology	Frequent; sometimes predomi–nant	Less prominent
Pathological Heterogeneity	High	Moderate
Clinical Distinguishability	Indistinguishable without ge–netics	N/A

LRRK2 biology: a mechanistic hub in Parkinson's disease

LRRK2 is now best understood as a central regulatory node within multiple Parkinson's disease-relevant pathways, including vesicular trafficking, lysosomal-autophagic function, mitochondrial homeostasis, and immune signalling. Pathogenic mutations were critical in revealing this role, but the underlying biology extends beyond mutation carriers and is increasingly observed across subsets of idiopathic PD.

All pathogenic LRRK2 mutations converge on a gain-of-function increase in kinase activity (typically 2- to 4-fold elevation), regardless of whether the mutation is in the kinase domain (e.g., G2019S, I2020T) or the Roc-COR GTPase domain (e.g., R1441C/G/H, Y1699C). A key functional output of LRRK2 activity is the phosphorylation of a subset of Rab GTPases, master regulators of intracellular membrane trafficking, including Rab8A, Rab10, Rab12, and Rab29. Dysregulated Rab phosphorylation alters their localisation and effector interactions, disrupting intracellular trafficking and initiating downstream cellular dysfunctions relevant to neuronal health.

These effects propagate across several interconnected pathways:

- **Impaired autophagy-lysosomal pathway:** LRRK2-dependent Rab phosphorylation disrupts endosomal sorting, autophagosome transport, and lysosomal maturation, leading to reduced clearance of damaged proteins and organelles. This results in accumulation of autophagic substrates and lysosomal stress, reflected by biomarkers such as elevated urinary BMP. This pathway is increasingly viewed as a central node linking LRRK2 activity to broader PD pathology and represents a key axis for therapeutic intervention.
- **Disrupted vesicle trafficking and synaptic homeostasis:** Altered Rab function impairs trafficking between the trans-Golgi network, endosomes, lysosomes, and synaptic terminals. This compromises synaptic vesicle recycling and neurotransmitter release, potentially contributing to early functional deficits prior to overt neurodegeneration.
- **Mitochondrial dysfunction and oxidative stress:** LRRK2 influences mitochondrial dynamics, including fission/fusion balance, mitophagy, and electron transport chain activity. Dysregulation leads to mitochondrial fragmentation, reduced ATP production, increased reactive oxygen species and impaired clearance of damaged mitochondria, collectively increasing neuronal vulnerability.
- **Neuroinflammation via microglial activation:** LRRK2 is highly expressed in microglia and peripheral immune cells, where it regulates inflammatory signalling pathways. Pathogenic activation enhances pro-inflammatory cytokine release and alters cellular metabolism. Recent evidence indicates that LRRK2 mutations can reprogram microglial metabolism toward a glycolytic, pro-inflammatory state, further amplifying neurodegenerative processes.
- **Additional downstream effects:** LRRK2 activity has also been linked to primary ciliogenesis, cytoskeletal dynamics, Wnt signalling and protein translation, reflecting its broad regulatory role across cellular systems.

These mechanisms are not restricted to mutation carriers. Elevated LRRK2 kinase activity and Rab phosphorylation have been detected in subsets of idiopathic PD, supporting a broader role for LRRK2-linked biology across the disease spectrum. From a translational perspective, this shifts the key question from whether a model contains an LRRK2 mutation to whether it captures relevant aspects of LRRK2-regulated biology. This distinction is critical for aligning preclinical models with specific therapeutic hypotheses and patient populations.

Importantly, elevated LRRK2 kinase activity and Rab hyperphosphorylation have been detected in postmortem brain tissue and peripheral blood from a subset of idiopathic (non-mutation carrier) PD patients, supporting the hypothesis that LRRK2 hyperactivity contributes to disease pathogenesis beyond purely monogenic cases. Companion diagnostics (e.g., Neuron23's approach) aim to identify "LRRK2-driven" PD, including those with activating SNPs, potentially expanding the treatable population to 20-30% of idiopathic cases.

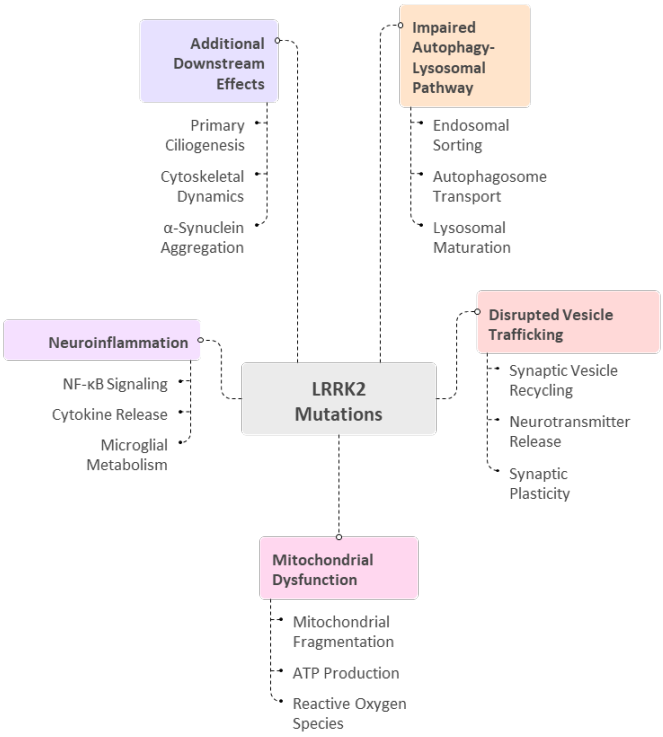

Figure 4. Mechanism Linking LRRK2 Mutations to Parkinson's Disease

Together, these convergent mechanisms position LRRK2 as a therapeutically relevant node across both genetic and non-genetic Parkinson's disease. Consistent with this, Atuka and others have demonstrated positive effects of LRRK2 inhibition in preclinical models of Parkinson's disease that do not carry LRRK2 mutations, reinforcing the broader relevance of LRRK2-driven biology. However, this same biology is distributed across multiple pathways, cell types, and tissues, introducing complexity in how therapeutic modulation translates across systems. As a result, effective drug development requires mechanism-aware, translationally aligned approaches that explicitly account for this heterogeneity.

From a translational perspective, LRRK2 safety should therefore be viewed not solely as a toxicology challenge, but as a design constraint that intersects with modality selection, tissue exposure, durability of target engagement and biomarker strategy. Understanding and resolving these relationships will be critical for defining the therapeutic window and optimizing long-term clinical outcomes.

In this context, translationally relevant models, including NHPs, play an important role in linking target engagement to tissue-specific biology and safety signals across modalities.

Clinical and preclinical pipeline: LRRK2–targeted therapeutics

The therapeutic landscape targeting LRRK2 has rapidly evolved, with multiple modalities advancing across clinical and preclinical stages. These programs reflect diverse strategies, including kinase inhibition, targeted protein degradation, and RNA-based approaches, aimed at achieving effective and sustained modulation of LRRK2 activity. Below is an overview of key programs shaping the field.

Clinical programs

Denali Therapeutics / Biogen – BIIB122 (DNL151)

BIIB122 is a second-generation, once-daily, central nervous system (CNS)-penetrant Type I LRRK2 kinase inhibitor and represents one of the most advanced programs in the field.

Early-phase clinical data (Phase 1/1b) demonstrated robust target engagement, including:

- ~90% peripheral inhibition of phosphorylated LRRK2 (pS935) and Rab10
- ~50% reduction of LRRK2 levels in cerebrospinal fluid (CSF)
- Favorable tolerability profile

The LUMA trial (Phase 2b; NCT05348785) is a large, global study enrolling approximately 600–650 patients with early-stage Parkinson's disease, including both idiopathic cases and LRRK2 mutation carriers. The study is designed to assess long-term treatment effects over an extended follow-up period consistent with a disease-modification approach. Study completion is expected in 2026, with top-line results anticipated subsequently.

The Phase 2b LUMA trial evaluated BIIB122 (DNL151) in ~650 patients with early-stage Parkinson's disease. Despite strong biomarker evidence of target engagement, including >90% peripheral LRRK2 inhibition and measurable CNS activity (similar to the Phase 1/1b trial), the study failed to meet both its primary and secondary clinical endpoints, showing no significant slowing of disease progression versus placebo. Following the readout, Biogen and Denali have discontinued development of BIIB122 in idiopathic

PD, although Denali will continue the genetically stratified BEACON study in carriers of pathogenic LRRK2 variants.

Neuron23 — NEU–411

Neuron23 is advancing a precision medicine strategy centered on identifying patients with genetically or functionally activated LRRK2.

Its lead program, NEU-411, is being evaluated in the NEULARK trial (Phase 2; NCT06680830), a global, placebo-controlled study in early-stage PD patients with LRRK2-driven disease, defined by either mutations or activating single nucleotide polymorphisms (SNPs). Enrollment is ongoing, with primary completion expected in September 2026.

A key differentiator of Neuron23's approach is the integration of a companion diagnostic, which may enable more targeted patient selection and improve the probability of demonstrating clinical efficacy.

Brenig Therapeutics — BT–267

BT-267 is a next-generation, brain-optimized LRRK2 kinase inhibitor designed to achieve high central nervous system exposure while minimizing peripheral toxicity, an important consideration given LRRK2 expression in organs such as the lung and kidney.

Interim Phase 1 data presented at AD/PD 2026 demonstrated favorable safety and tolerability, robust CNS penetration, and pharmacokinetics supportive of once-daily dosing. Evidence of target engagement was observed through dose-dependent reductions in LRRK2 pathway biomarkers, including urinary BMP. The company intends to initiate Phase 1b and Phase 2 proof-of-concept studies in Parkinson's disease in early 2026.

Arvinas — ARV–102

ARV-102 represents a novel modality: an oral proteolysis-targeting chimera (PROTAC) designed to catalytically degrade LRRK2 protein rather than inhibit its activity.

Phase 1 data presented at AD/PD 2026 (March 18, 2026) demonstrated:

≥50% reduction of LRRK2 protein in CSF by Day 14

Sustained suppression through Day 28 across multiple dose levels (20–80 mg daily)

Reduction in disease-relevant biomarkers

Favorable safety profile, with only mild to moderate adverse events reported

This program provides early clinical validation for targeted protein degradation in neurodegenerative disease and may offer advantages in achieving deeper and more sustained target suppression.

Arvinas plans to expand development into related neurodegenerative indications, including a Phase 1b study in progressive supranuclear palsy (PSP) in Q2 2026.

Oncodesign Precision Medicine / Servier — OPM–201 / S221237

OPM-201 / S221237 is a small-molecule LRRK2 kinase inhibitor that has completed Phase 1 evaluation in healthy volunteers. The Phase I trial showed an overall favorable safety and tolerability profile, with no serious adverse events reported. The studies confirmed systemic exposure and demonstrated target engagement at higher dose levels, supporting proof of mechanism. In March 2026, the program received a $6.92 million grant from The Michael J. Fox Foundation (MJFF) to support advancement into Phase 1b studies in early Parkinson's disease patients, with a projected start in 2027. The program is part of the LRRK2 Investigative Therapeutics Exchange (LITE) initiative, which aims to accelerate the development of LRRK2-targeted therapies.

Biogen — BIIB094

BIIB094 (Biogen): an antisense oligonucleotide (ASO) targeting LRRK2, representing an RNA-based approach to reducing protein expression. Phase 1 data demonstrated reduction of LRRK2 levels in cerebrospinal fluid with a favorable safety and tolerability profile, providing early clinical validation of RNA-mediated target suppression.

Additional Programs

Other companies, including 1st Bio Therapeutics Inc. and Guizhou Inochini Technology Co. Ltd., have also advanced small-molecule LRRK2 kinase inhibitors into Phase 1. Notably, 1ST-104 is a dual LRRK2/c-Abl inhibitor; c-Abl is another well-established therapeutic target in Parkinson's disease.

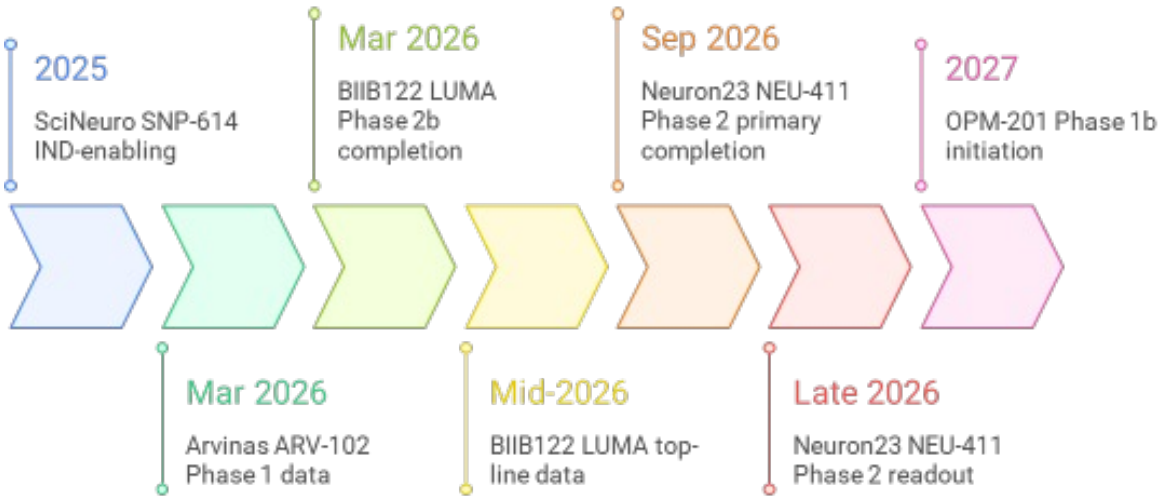

Figure 5. Key Milestones

Preclinical programs

Alongside clinical-stage progress, a new wave of preclinical innovation is driving the next generation of LRRK2-targeted therapies. These efforts aim to overcome limitations of earlier approaches, especially constraints in CNS selectivity, peripheral safety, and sustained target modulation.

Brain–Selective and Next–Generation Small Molecules

Montara Therapeutics is advancing LRRK2 inhibitors using its proprietary BrainOnly platform, which is designed to achieve selective drug exposure within the central nervous system while minimizing systemic distribution. This approach directly addresses safety concerns associated with peripheral LRRK2 inhibition, particularly in organs such as the lung and kidney. If successful, brain-restricted inhibitors could enable higher effective dosing and improved therapeutic windows.

Similarly, Seal Rock Therapeutics is developing novel LRRK2-targeting small molecules as part of The Michael J. Fox Foundation's LRRK2 Investigative Therapeutics Exchange (LITE) program. These efforts are focused on optimizing potency, selectivity and pharmacokinetic properties to support future clinical translation.

RNA–Based Therapeutics

SciNeuro is developing SNP-614, an antisense oligonucleotide (ASO) designed to reduce LRRK2 expression at the mRNA level. This modality offers a highly specific mechanism for lowering LRRK2 protein levels and may provide sustained target suppression with infrequent dosing. The program received a $5 million grant from The Michael J. Fox Foundation in November 2025 to support IND-enabling studies, reflecting growing confidence in RNA-based approaches for neurodegenerative diseases. This approach is mechanistically distinct from kinase inhibition or protein degradation and may offer advantages in achieving sustained target reduction, while introducing different considerations around delivery, durability and reversibility.

Additional Small–Molecule Programs

Other companies, including Novorex (NRX02067), KeifeRx LLC, Seloterra, Starg (Wuhan) Pharmaceutical Tech Co Ltd and Hangzhou Highlightll Pharmaceutical Co Ltd, are advancing preclinical small-molecule LRRK2 inhibitors. While details remain limited, these programs contribute to a diversified pipeline aimed at improving selectivity, brain penetration, and long-term safety.

INSIGHT

Role of Non–Human Primates in LRRK2 Translation

Non–human primate (NHP) models play a focused and strategic role in LRRK2 research. While many mechanistic questions can be addressed in rodent or human cellular systems, NHP studies are particularly valuable for resolving translational uncertainties.

Key applications include:

- Evaluating tissue compartment exposure (CNS versus peripheral).
- Comparing modality–dependent effects across therapeutic strategies.
- Assessing durability of target engagement.
- Establishing biomarker relationships with relevance to human studies.

In this context, NHPs are best deployed selectively to address specific translational questions, rather than as default efficacy models. This supports a hypothesis–driven approach aligned with both scientific rigor and 3Rs principles.

Strategic Significance of the Preclinical Pipeline

The current LRRK2 therapeutic landscape is notable not only for its maturity, but for the breadth of approaches being actively pursued. While most advanced programs utilize Type I kinase inhibitors targeting the active conformation, alternative approaches, including Type II inhibitors, remain relatively underexplored, reflecting both structural challenges and unresolved questions around optimal target modulation. Despite this theoretical advantage, no late-stage Type II LRRK2 inhibitors have emerged, suggesting significant structural and drug design challenges. Increasingly, innovation is occurring at the level of modality rather than binding mode, with emerging strategies such as brain-selective inhibitors, targeted protein degradation and RNA-based suppression aiming to address limitations observed with first-generation compounds. Importantly, the diversity of the pipeline should be interpreted as an informative feature of the field rather than redundancy. Unlike many therapeutic areas where early convergence occurs around a single modality, LRRK2 remains actively explored across multiple intervention strategies. This reflects a target that is both highly validated and biologically complex, where the optimal approach to modulation remains unresolved.

INSIGHT

Safety as a Translational Design Constraint

Preclinical safety findings associated with LRRK2 inhibition are largely driven by on–target effects in peripheral tissues, including lung, kidney and immune system.

These observations highlight that safety in LRRK2 is not solely a toxicology issue, but a function of how the target is modulated.

Key considerations include:

- Balancing central efficacy with peripheral biology.
- Managing tissue–specific target engagement.
- Selecting modalities with appropriate exposure and durability profiles.

This framing positions safety as an integral component of translational strategy, directly influencing modality selection, dosing approaches and long–term therapeutic potential.

The diversity of emerging approaches highlights several key translational themes:

- CNS versus peripheral balance: Brain-restricted designs aim to decouple central efficacy from peripheral biology and potential on-target toxicity
- Modality-dependent biology: Inhibition, degradation and RNA-based suppression may differentially impact pathway dynamics, durability and compensatory responses
- Durability and exposure: Distinct pharmacokinetic and pharmacodynamic profiles raise important questions around sustained target engagement versus reversibility
- Ecosystem acceleration: Collaborative initiatives such as MJFF's LITE program are actively de-risking early-stage development and enabling cross-modality comparison

Collectively, these efforts define a multidimensional translational landscape in which modality selection, tissue exposure, durability of effect, and biomarker response must be considered in an integrated manner. From this perspective, the central challenge is no longer whether LRRK2 can be modulated, but how to modulate it most effectively across different biological contexts and patient populations. This framing also has implications for preclinical strategy. The diversity of modalities increases the importance of models that can resolve translational questions—such as CNS versus peripheral effects, biomarker linkage and durability—rather than simply demonstrating target engagement or efficacy in isolation. In this context, comparative and mechanism-aware preclinical approaches become critical for informing clinical decision-making.

Key Takeaways

- Clinical momentum is accelerating, with multiple Phase 2 trials expected to report results between 2026–2027.
- Modality diversification (inhibitors, degraders, ASOs) increases the likelihood of identifying an optimal therapeutic approach.
- Precision medicine strategies, including genetic and biomarker-driven patient selection, are becoming central to clinical development.
- Safety and CNS selectivity remain critical differentiators across programs.

Pipeline Comparison

COMPOUND / MODALITY	DEVELOPER	STAGE (MAY 2026)	KEY FEATURES / NOTES
BIIB122 (kinase inhibitor)	Denali/Biogen	Phase 2b (LUMA; did not meet primary or secondary clinical endpoints	QD dosing, strong CNS penetration, largest targeted PD trial
NEU–411 (kinase inhibitor)	Neuron23	Phase 2 (NEULARK; enrolling)	Companion diagnostic for LRRK2–driven PD
BT–267 (kinase inhibitor)	Brenig	Phase 1 (data at AD/PD 2026); Phase 1b/2 planning	Brain–optimized, minimized peripheral exposure
ARV–102 (PROTAC)	Arvinas	Phase 1 (positive PD data Mar 2026 at AD/PD)	≥50% CSF LRRK2 reduction sustained 28 days; PSP plans
OPM–201 (kinase inhibitor)	Oncodesign	Phase 1 complete; Phase 1b prep (2027)	$6.92M MJFF grant, March 2026
1ST–104 (kinase inhibitor)	Bio Therapeutics Inc	Phase 1	Also inhibits cAbl
WXWH–0226 (kinase inhibitor)	Guizhou Inochini Technology Co Ltd	Phase 1	unknown
BrainOnly (kinase inhibitor)	Montara	Preclinical	Brain–selective combination therapy approach
SRT–055 (kinase inhibitor)	Seal Rock	Preclinical	LITE program support
SNP–614 (ASO)	SciNeuro	Preclinical (IND–enabling)	$5M MJFF grant, Nov 2025
NRX02067 (kinase inhibitor	Novorex	Preclinical	non–ATP competitive; positive data in PFF–mouse reported at SFN 2025.
	Innovstone	Preclinical	
KFRX–06 (kinase inhibitor)	KeifeRx LLC	Preclinical	Also inhibits cAbl and c–KIT
Unknown (kinase inhibitor)	Seloterra	Preclinical	Also targets α–synuclein
CC–004 (kinase in–hibitor)	Starg (Wuhan) Phar–maceutical Tech Co Ltd	Preclinical	unknown
HL–500 (kinase in–hibitor)	Hangzhou Highlightll Pharmaceutical Co Ltd	Preclinical	unknown

Safety and Challenges

Preclinical safety signals associated with LRRK2 inhibition have, to date, not translated into significant adverse findings in early clinical studies. In Phase 1 and Phase 2 trials, LRRK2 inhibitors have generally demonstrated favorable tolerability profiles, with adverse events predominantly mild and transient in nature. The most commonly reported events include headache and gastrointestinal disturbance, consistent with the class profile observed across early CNS trials.

Peripheral on-target effects.

The predominant preclinical safety concern reflects LRRK2's physiological role in peripheral tissues. In non-human primates, LRRK2 kinase inhibition has been associated with morphological changes in type II pneumocytes, most notably accumulation of lamellar bodies. These findings are reversible upon cessation of dosing and have not been accompanied by impaired pulmonary function. In the kidney, LRRK2 is enriched in proximal tubule cells, where it regulates lysosomal and vesicular trafficking; chronic inhibition may perturb these pathways, though renal effects in clinical studies remain to be fully characterised. Given LRRK2's role in immune cell signalling, potential immunomodulatory effects during prolonged treatment also warrant continued monitoring.

Modality-dependent safety profiles.

Brain-selective inhibitors (e.g., BT-267, Montara's BrainOnly platform) are specifically designed to minimize systemic exposure, potentially reducing peripheral on-target effects while preserving central efficacy. PROTAC degraders such as ARV-102 achieve deeper target suppression through catalytic protein degradation, which may confer advantages in durability but introduces distinct questions around reversibility. ASO-based approaches (BIIB094, SNP-614) reduce LRRK2 at the mRNA level with infrequent dosing but require careful consideration of CNS delivery and long-term consequences of sustained protein reduction.

Open questions.

Critical unanswered questions include the long-term consequences of sustained LRRK2 inhibition in chronically treated patients, the optimal degree of target engagement required for clinical benefit without unacceptable peripheral effects, and whether biomarkers such as urinary BMP can serve as reliable sentinels of on-target peripheral activity in clinical monitoring. The MJFF LITE programme and associated workshops (e.g., June 2025) are actively working to standardize biomarker and toxicology testing frameworks across the field, which will be important for cross-programme comparisons as Phase 2 data mature.

Patient selection and timing.

Optimal patient selection remains an active area of development. Genetic stratification (mutation carriers) provides the most tractable starting point, but biomarker-based identification of LRRK2-driven disease in non-carriers may substantially expand the treatable population. Timing of intervention is also likely to be critical: pre-symptomatic or early-stage treatment is theoretically advantageous but requires robust predictive biomarkers and long-term safety data to support a favourable benefit–risk profile in individuals who may not yet have significant disability.

Conclusion

The LRRK2 pipeline is advancing rapidly, and the future of LRRK2-targeted therapies will depend less on further target validation than on how effectively LRRK2 biology can be translated across heterogeneous patient populations and complex systemic environments. LRRK2 is now firmly established as one of the most genetically and mechanistically validated targets in Parkinson's disease, but the next phase of the field will be defined by questions of modality, patient selection, biomarker strategy, tissue exposure, durability of target engagement, and long-term safety.

The recent failure of BIIB122's Phase 2b LUMA study represents an important inflection point for the Parkinson's disease field, raising critical questions around patient selection, timing of intervention, and the optimal strategy for modulating LRRK2 biology. Despite the disappointing outcome, multiple next-generation approaches continue to advance, including precision inhibitors such as Neuron23's NEU-411, brain-optimized compounds from Montara and Brenig, protein degraders from Arvinas, and RNA-based approaches from Biogen and SciNeuro. Collaborative initiatives such as MJFF's LITE programme are also helping accelerate cross-modality learning and a deeper understanding of how best to target the LRRK2 pathway in Parkinson's disease.

If clinical efficacy is confirmed, LRRK2-targeted therapies could become among the first mechanism-based treatments to address a core driver of Parkinson's disease pathology, marking a shift from symptomatic management toward true disease modification. Success would not only establish LRRK2 as a cornerstone therapeutic target but also provide a broader paradigm for targeting upstream molecular drivers in neurodegeneration.

Important challenges remain. These include achieving sufficient and sustained target engagement in the brain while minimizing peripheral toxicity, addressing the biological heterogeneity of LRRK2-associated pathology, and demonstrating clear clinical benefit in a disease characterized by slow progression and variable trajectories. Precise patient stratification and robust biomarkers will be essential to unlock the full therapeutic potential of LRRK2-directed approaches.

Despite these hurdles, the convergence of human genetics, advancing drug modalities, biomarker development and increasing clinical momentum provides cautious optimism. In this sense, LRRK2 represents not only a compelling opportunity for disease modification in Parkinson's disease, but also a model case for the broader challenge of translating mechanistically rich targets into effective therapies for neurodegenerative disease.

Good science depends on good welfare.

Read about Atuka's approach to the research use of animals at atuka.com/animal-welfare-at-atuka.

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About the Author

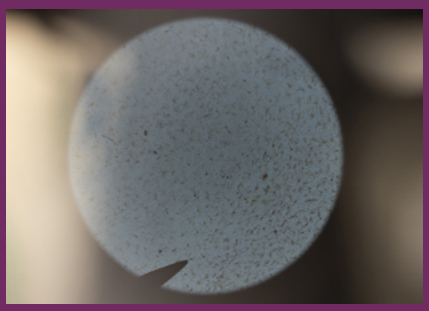
Dr. Michael Hill's research interest is in the neuropharmacology of Parkinson's disease, with a particular focus on understanding the complex interactions among the various neurotransmitter systems affected by the condition. With over 25 years of experience in the preclinical CRO sector, Michael has dedicated his career to advancing Parkinson's disease research and driving the development of innovative and more effective treatments. He has played a pivotal role in the development of numerous therapeutics, collaborating extensively with both large pharmaceutical companies and biotech firms to strategically guide their preclinical programs toward successful clinical trials. Since joining Atuka in 2011, Michael has continued to make significant contributions to the field and currently serves as the company's Chief Revenue Officer.











A cure for Parkinson's, faster, through the world's best preclinical neuroscience.

Atuka's lead scientists have dedicated their careers to furthering our understanding of Parkinson's disease, advancing novel therapeutics, and alleviating the burden of those suffering from neurological disorders.

For more than 20 years, we have collaborated with our partners to provide preclinical services that expand the frontiers of Parkinson's disease research, and help make new, life-changing therapeutics a reality. Our neuroscientists have extensive preclinical experience developing therapies for numerous indications—including Parkinson's, cognitive disorders, Alzheimer's, ALS and other movement disorders such as dystonia and dyskinesia—across multiple modalities, including small molecules and biologics.

Founded by Dr. Jonathan Brotchie in 2003, Atuka has been involved in the preclinical evaluation of more than 300 potential therapeutics, predominantly in Parkinson's disease, of which more than 30 have progressed to clinical trials—a level of experience without equal in our field globally.

Our lead scientists have collectively published more than 300 peer-reviewed, highly-cited papers, and individually possess h-indices ranging from 25 to 70.

Atuka has collaborated with over 90 organizations, including large pharmaceutical and biotech companies, charitable foundations, universities, and government agencies. Over the course of more than 400 preclinical projects, targeting more than 60 mechanisms of action, we have built an extremely rich understanding of Parkinson's disease, its causes, and potential treatments.

With offices and facilities in Toronto and Suzhou, our team is diverse both in background and expertise, bringing to every one of our partner engagements a spirit of close collaboration, along with a commitment to the highest ethical standards in scientific research.

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