DISCOVERY SERIES – EMERGING TARGETS IN PARKINSON'S DISEASE

#2 — BDNF/TrkB

The Potential of BDNF/TrkB Pathway Modulation in Parkinson's Disease

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Brain–derived neurotrophic factor (BDNF), and its receptor TrkB, have long been recognized as central to neuronal survival, growth, and plasticity. In Parkinson's disease, where dopaminergic neurons progressively degenerate, the BDNF/TrkB pathway represents one of the most compelling targets for disease–modifying therapy.

Despite decades of research and early setbacks with protein infusion, recent advances in gene therapy, novel small-molecule agonists, and a clearer understanding of the interaction between TrkB signaling and α-synuclein pathology have re-energized this field.

Parkinson's disease (PD) is characterized by a progressive dysfunction and loss of dopaminergic neurons in the substantia nigra. Approaches that harness the brain's own restorative mechanisms to slow the neurodegeneration that occurs in PD have been researched for decades and, despite early promise, have been beset with technical hurdles. Targeting Brain-Derived Neurotrophic Factor (BDNF) and its high-affinity receptor, Tropomyosin receptor kinase B (TrkB), is one such approach that showed early promise that could not be translated in clinical efficacy. However, recent advances in gene therapy and a more in-depth understanding of BDNF/ TrkB biology that has revealed additional ways to modulate this system, suggest we are on the brink of being able to manipulate the BDNF/ TrkB system and produce disease-modifying therapies for PD.

Summary of the neuroprotective pathways activated by BDNF/ TrkB

Activation of the TrkB receptor by BDNF triggers an intracellular signalling cascade that promotes neuronal survival, differentiation, and synaptic plasticity (Figure 1).

There are three major pathways involved in this process. Together, activation of these pathways enhances dopaminergic survival, improves neuronal function, and protects dopaminergic neurons from toxic insults.

PI3K/Akt Pathway

This pathway is a central player in promoting cell survival. Once activated by the BDNF-TrkB complex, it inhibits apoptotic (cell death) signals and promotes the expression of pro-survival genes. This pathway is critical for protecting dopaminergic neurons from various toxins and cellular stressors.

PLCγ Pathway

This pathway, leading to the mobilization of intracellular calcium and the activation of protein kinase C (PKC), is also involved in promoting neuronal survival and plasticity, further contributing to the overall health and function of dopaminergic neurons.

MAPK/ERK Pathway

The activation of this pathway is essential for neuronal differentiation, growth, and synaptic plasticity. For dopaminergic neurons, this translates to the maintenance of their complex structure, the promotion of new connections, and the enhancement of dopamine neurotransmission.

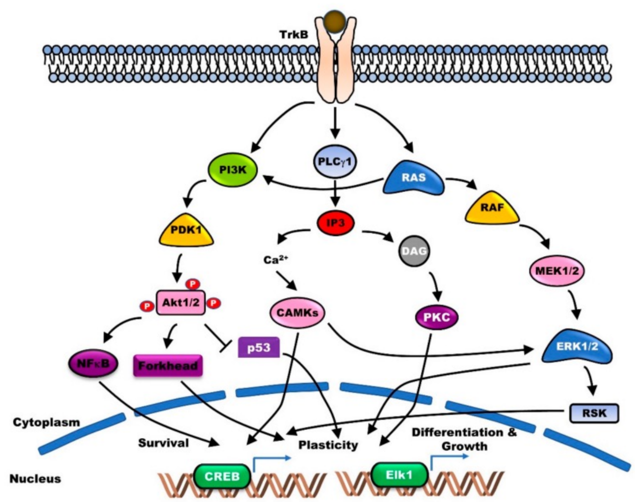

Figure 1. BDNF/ TrkB signalling activates several intracellular signalling cascades that support neuronal survival, plasticity, and differentiation and growth. From Jin, 2020.

HISTORICAL PERSPECTIVE

1. Discovery

The discovery of BDNF In the 1950s by Rita Levi-Montalcini and Stanley Cohen revolutionized our understanding of neuronal survival and growth, introducing the concept of neurotrophic factors – proteins essential for the development, maintenance, and survival of neurons. This groundbreaking work laid the conceptual groundwork for future neuroprotective strategies, and earned them the Nobel Prize in Physiology or Medicine in 1986.

A seminal 1991 study published in Nature by Hyman and colleagues demonstrated BDNF as a potent survival factor for cultured dopaminergic neurons from the substantia nigra. This finding galvanised research activity, positioning BDNF as a prime candidate for a neuroprotective therapy for PD. The subsequent discovery of its high-affinity receptor, Tropomyosin receptor kinase B (TrkB), in the early 1990s further solidified this hypothesis. The TrkB receptor, a member of the receptor tyrosine kinase family, was shown to be activated upon BDNF binding, triggering a cascade of intracellular signaling pathways that collectively promote neuronal survival, differentiation, and synaptic plasticity.

The BDNF–TrkB pathway in Parkinson's disease

In people with PD, there are several changes to both BDNF and TrkB that occur as part of the disease process or in response to intervention (Table 1). Thus, dysfunction in the BDNF/TrkB system may be responsible for some of the pathological and behavioural changes that occur in the disease and that modulation of this system may be of therapeutic benefit.

The Biology of BDNF and TrkB

When secreted, BDNF is in an inactive form (pre-pro-BDNF) which, in a two-step process, is cleaved firstly to proBDNF and then to BDNF (also called mature BDNF). These two peptides have different functions, with proBDNF binding to the p75 neurotrophin receptor (p75NTR) which induces apoptosis. Conversely, BDNF binds to the TrkB receptor promoting neuronal survival. Thus, to promote neuronal survival, it is important to ensure that TrkB activation occurs without excessive p75NTR activation, and an inability to cleave proBDNF has been linked to Alzheimer's disease. Compounds that can continuously elevate the conversion of proBDNF to BDNF can enhance cognition and potentially offer a novel therapeutic approach to harnessing the protective mechanisms engaged by activating the BDNF/ TrkB system.

Table 1. Potential role of BDNF and TrkB in people with PD

POTENTIAL ROLES OF BDNF IN PARKINSON'S DISEASE	POTENTIAL ROLES OF IN TRKB IN PARKINSON'S DISEASE
Decreased Expression: People with Parkinson's disease show significantly reduced BDNF mRNA in the substantia nigra and reduced BDNF protein in the substantia nigra and striatum. Decreased BDNF levels may be implicated in the pathogenesis of Parkinson's disease.	Expression: TrkB mRNA is not consistently altered in the substantia nigra of people with Parkinson's disease. In the striatum, TrkB mRNA and protein levels are often increased after dopamine depletion. In general, the TrkB signalling pathway remains intact in people with Parkinson's disease.
Axonal Transport: Defects in BDNF anterograde transport from nigrostriatal and corticostriatal projections are implicated, potentially linked to α–Synuclein accumulation. Impaired transport of BDNF may contribute to neuronal dysfunction	TrkB Depletion: Heterozygous TrkB depletion leads to progressive loss of SNc neurons in aged rats and mice, increasing vulnerability to MPTP treatment. Impaired TrkB signaling may exacerbate neuronal loss in PD.

POTENTIAL ROLES OF BDNF IN PARKINSON'S DISEASE	POTENTIAL ROLES OF IN TRKB IN PARKINSON'S DISEASE
Release: While direct evidence for impaired BDNF release in Parkinson's disease is lacking, beneficial effects of exogenous BDNF hint at reduced BDNF/ TrkB signaling. Boosting BDNF/ TrkB signaling may be a useful therapeutic approach.	Interaction with α-Synuclein: α-Synuclein binds directly to TrkB, blocking BDNF/TrkB signaling and contributing to dopaminergic cell death in PD models. This is a potential mechanism by which α-synuclein could reduce BDNF/ TrkB signalling, removing an endogenous protective pathway.
Deep Brain Stimulation (DBS): DBS, a common treatment for Parkinson's disease motor symptoms, has been shown to increase BDNF protein levels in the striatum, substantia nigra, and motor cortex, and may partially rescue BDNF transport impairments. Recent data suggest that DBS may modify disease progression as well as treating motor symptoms. Restoration of BDNF signaling may underpin this disease-modifying effect.	Subcellular Distribution: In Parkinson's disease, TrkB receptors accumulate as intracellular clusters. This accumulation is linked to impaired cell-surface transport and potential issues with lysosomal degradation pathways. Dopamine D1 receptor (DRD1) activation promotes TrkB surface translocation, while D2 receptor activation decreases it. The interplay between DRD1 and BDNF signaling is important in maintaining healthy neuronal circuits, especially in the striatum.
Therapeutic Potential: BDNF acts as a neurotrophic factor for substantia nigra dopaminergic neurons, promoting dopamine uptake and protecting against toxicity in Parkinson's disease models. Direct BDNF delivery to the brain is challenging due to delivery difficulties and potential side effects. Gene therapy, either delivering BDNF or TrkB, is a promising approach, as are small molecule and antibody approaches to directly activate TrkB. In addition, approaches that modulate BDNF/ TrkB signaling are being developed and may provide another way of harnessing the therapeutic potential of the BDNF/ TrkB signaling pathway. Physical activity also boosts BDNF levels and may ameliorate Parkinson's disease symptoms, potentially through BDNF upregulation in corticostriatal projections. This may be one of the reasons why exercise has repeatedly been shown to be beneficial for people with Parkinson's disease.	

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2. Preclinical promise

Initial in vitro findings, demonstrating that BDNF was neuroprotective, were expanded upon in various animal models of Parkinson's disease and provided a wealth of evidence supporting the therapeutic potential of BDNF.

Early studies involving the direct infusion of recombinant BDNF protein into the brains of parkinsonian rodents and non-human primates yielded encouraging results. These studies demonstrated that BDNF could protect dopaminergic neurons from neurotoxin-induced cell death, leading to a preservation of striatal dopamine levels and an improvement in motor function. However, these early successes also highlighted a major hurdle that would come to define the field: the challenge of delivery. BDNF is a large protein that does not readily cross the blood-brain barrier (BBB), the highly selective border that protects the brain from harmful substances in the blood. This meant that direct, invasive delivery to the brain was necessary, a prospect fraught with technical difficulties and potential complications for human patients.

Modulation of BDNF/ TrkB signalling

BDNF signalling is adaptive to environmental cellular conditions and receptor trafficking is a key mechanism to achieving this. One example of this is the Shp2 negative feedback loop, where activation of TrkB phosphorylates Shp2, a key step in the activation of the PI3K/Akt and MAPK/ERK survival pathways. However, phosphorylated Shp2 can also bind to and dephosphorylate TrkB, reducing its activity via a caveolin-1 dependent mechanism (Figure 1). Approaches that manipulate this regulatory process, and produce enhanced TrkB activation, are being explored as novel targets in neurodegenerative disorders.

It is possible that the efficacy of some BDNF/ TrkB based therapies, such as direct infusion of BDNF, may be limited by this negative feedback loop.

Physiological role of BDNF/ TrkB signalling

Although outside the scope of this paper, which focusses on the potential of targeting the BDNF/ TrkB system as a disease-modifying approach in PD, it is worth noting that the BDNF/ TrkB system is an important mediator in activity-dependent synaptic plasticity and dysfunction and disruption of this system can cause neurodevelopmental disorders. Moreover, in the adult brain, BDNF regulated activity-dependent synaptic plasticity is thought to be important in enhancing cognitive flexibility and memory consolidation, as well as facilitating repair following injury or neurodegeneration.

Given the important role that BDNF and TrkB have in dynamic modulation of synaptic plasticity and maintenance of the CNS, it is unsurprising that they are widely expressed throughout the CNS, especially in the cerebral cortex, hippocampus, and cerebellum. BDNF and TrkB are also expressed by dopaminergic neurons in the substantia nigra and activation of TrkB by BDNF has been shown to be neuroprotective in a range of animal models of PD. In the striatum, TrkB receptors are expressed on medium spiny neurons and are essential for their survival. BDNF is not synthesised in the striatum but rather it is synthesised in the midbrain and cerebral cortex and transported to the striatum from these areas.

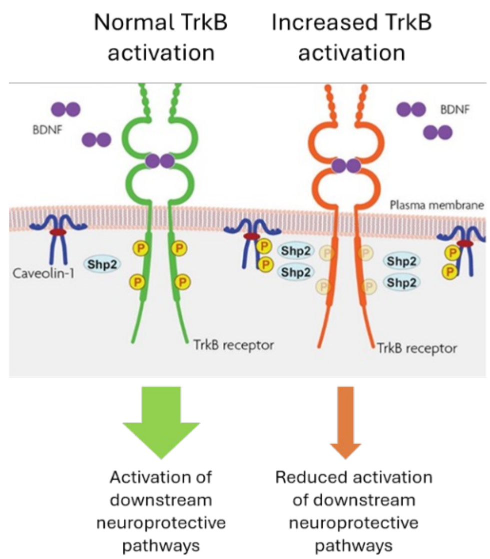

Figure 2. Increased TrkB activation can lead to shp2–mediated dephosphorylation of TrkB and reduced downstream activation of neuroprotective pathways. Modified from Abbasi et al., 2023

BDNF/ TrkB signalling – more than just neuroprotection of dopaminergic neurons

Most research into the potential of BDNF/ TrkB signalling as a therapeutic target in PD has focussed on neuroprotection of dopaminergic neurons in the substantia nigra. However, BDNF and TrkB are widely expressed throughout the CNS and are known to provide neuroprotection to a wide variety of neuronal cell types, including cortical neurons, dopaminergic neurons, hippocampal neurons, sensory neurons, and spinal motor neurons. This broad neuroprotection may be very important in PD, where it is known multiple neuronal cell types, such as cholinergic and monoaminergic neurons, as well as dopaminergic neurons undergo neurodegeneration.

In addition to its neuroprotective effect, BDNF/ TrkB signalling also has neurotrophic effects, such as modulating synaptic plasticity and neurotransmitter release. For instance, BDNF is known to enhance dopamine release in the striatum and modulate the expression of striatal dopamine receptors, effects that would be beneficial in PD irrespective of any neuroprotective effects. Thus, when studying therapeutic approaches aimed at modulating the BDNF/ TrkB signalling pathway it is important to consider that any efficacious response may, at least in part, be due to neurotrophic, and not neuroprotective, effects.

Interaction between α–synuclein and BDNF/ TrkB signalling

In 2017 it was reported that the neurotrophic activities of BDNF/ TrkB signaling were blocked by α -synuclein. It was shown that α-synuclein selectively interacts with TrkB, but not other neurotrophin receptors (TrkA and TrkC). This interaction suppresses the neurotrophic/ neuroprotective activities of BDNF/ TrkB signalling leading to an increased vulnerability of dopaminergic neurons to degeneration. Interestingly, this interaction is bidirectional, with activation of TrkB by a small molecule agonist (7,8-dihydroxyflavone) able to reduce expression of α-synuclein in the striatum and substantia nigra. A full understanding of the interaction between α-synuclein and TrkB is not yet known, however, given the bi-directional nature of this interaction, and the fact that BDNF is known to decrease with age, it is possible that as an individual ages BDNF/ TrkB activity is reduced, allowing increased α-synuclein aggregation to occur. This process would be self-reinforcing, leading to increased α-synuclein aggregation and the inhibition of one of the most important neurotrophic and neuroprotective systems in the brain.

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3. Disappointment of early clinical trials

The earliest clinical trials focused on continuous infusion of BDNF into the brains of people with ALS. The largest of these, a Phase II, double–blind, placebo–controlled trial, failed to show any significant clinical benefit in patients with advanced ALS. The primary endpoints were not met, and the treatment was associated with side effects, including weight loss, sensory disturbances, and pain at the infusion site.

The reasons for these failures were likely multifactorial, with poor diffusion of the BDNF protein within the brain tissue, a short half–life of BDNF, and complex biology of BDNF, including its potential to bind to the p75 neurotrophin receptor, which can mediate apoptosis or cell death, may have contributed to the lack of efficacy and the observed side effects.

To–date, no clinical trials examining the effect of direct brain infusion of BDNF in people with Parkinson's disease have been performed.

Challenges to the development of a BDNF/TrkB therapeutic

The journey of developing BDNF and TrkB-based therapies for Parkinson's disease has been hugely instructive, highlighting the immense complexity of the human brain and the formidable challenges of translating basic science into clinical practice. Several key challenges have emerged as major roadblocks to success.

1. The Blood–Brain Barrier (BBB): The BBB remains the single most significant obstacle for delivering large molecules like BDNF to the brain. While direct infusion and gene therapy have been explored as ways to circumvent the BBB, they come with their own set of risks and limitations. The development of strategies to temporarily and safely open the BBB, or to engineer BDNF to be transported across it, remains an active area of research. Small molecule TrkB agonists that can cross the BBB offer the most promising solution to this long-standing problem.

2. Delivery and Distribution: Even with direct brain delivery, achieving widespread and therapeutic concentrations of a neurotrophic factor throughout the affected brain regions is a major challenge. The diffusion of large proteins is limited and ensuring that the therapy reaches all the vulnerable neurons is critical for its efficacy. Gene therapy offers a more localized and sustained delivery but optimizing the spread of the vector and the expressed protein is an ongoing challenge.

3. The Complexity of Neurotrophic Factor Signaling: The biological effects of BDNF are not always straightforward. The existence of the p75NTR, which can mediate opposing effects to TrkB, adds a layer of complexity. The balance between pro-BDNF and mature BDNF, and their differential binding to TrkB and p75NTR, is another important consideration. Future therapeutic strategies may need to be more sophisticated, aiming to selectively activate the pro-survival TrkB signaling pathways while avoiding the potentially detrimental effects of p75NTR activation. In addition, direct activation of TrkB can increase Shp2 activation, which can lead to dephosphorylation and inactivation of TrkB. Thus, approaches that circumvent this negative feedback loop may be a more optimal therapeutic approach.

4. Interactions between α-synuclein and BDNF/ TrkB: Recent research has shown that α-synuclein can bind to the TrkB receptor and impair the intracellular signalling cascades that support the neuroprotective and neurotrophic effects of BDNF, and this may be one mechanism by which α-synuclein is neurotoxic. Conversely, enhanced BDNF/ TrkB signalling can reduce α-synuclein aggregation and protect against neuronal cell death. The development of therapeutics targeting BDNF/ TrkB signalling should take these findings into consideration when planning preclinical and clinical studies.

5. Clinical Trial Design and Patient Heterogeneity: Parkinson's disease is a heterogeneous disorder with a long and variable clinical course. This makes it challenging to design and conduct clinical trials that can definitively demonstrate a disease-modifying effect. The selection of appropriate patient populations, the timing of intervention, and the choice of meaningful clinical endpoints are all critical factors for success. Earlier intervention in the disease process, before significant neuronal loss has occurred, may be more likely to yield positive results. The development of reliable biomarkers to track disease progression and therapeutic response is also urgently needed.

6. The Comparison with Other Neurotrophic Factors: The extensive research on GDNF for Parkinson's disease provides a valuable comparative framework for the development of BDNF-based therapies. Both neurotrophic factors have shown immense promise in preclinical models, and both have faced similar challenges in clinical translation, particularly with regards to delivery. The successes and failures of the GDNF trials have provided important lessons for the entire field of neurotrophic factor therapy. While BDNF and GDNF have distinct receptors and signaling pathways, the overarching challenges of delivering these large proteins to the brain and demonstrating a clear clinical benefit are shared.

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4. Gene therapy

To circumvent the BDNF delivery problem, researchers turned to gene therapy to deliver the gene encoding for BDNF directly into the brain. Transfected cells would continuously produce and secrete BDNF in the vicinity of the degenerating dopaminergic neurons. Preclinical studies using this approach in rodent and primate models of Parkinson's disease were highly promising and provided a compelling rationale for pursuing gene therapy as a more clinically viable strategy for BDNF delivery.

The challenges for BDNF gene therapy include ensuring the safety and long–term expression of the transgene, optimizing the viral vector and delivery method to achieve targeted and efficient transduction of the desired cell populations, and managing potential immune responses to the viral vector or the expressed protein. In addition, direct stimulation of the TrkB receptor may be a sub–optimal strategy (Figure 2).Despite these hurdles, gene therapy remains a viable and actively pursued strategy for delivering BDNF to the parkinsonian brain. Ongoing research is focused on developing more efficient and safer viral vectors, such as novel AAV serotypes with improved brain penetration and reduced immunogenicity. The lessons learned from the other CNS–based gene therapy trials will undoubtedly inform the design and execution of future BDNF gene therapy trials for Parkinson's disease.

Despite these formidable challenges, the future of BDNF and TrkB-based therapies for Parkinson's disease is far from bleak. The field is characterized by persistent innovation and a growing understanding of the complexities involved. Several promising future directions are emerging:

- Next-Generation TrkB Agonists: The development of more potent, selective, and brain-penetrant small molecule TrkB agonists is a major focus of current research. Medicinal chemistry efforts are underway to optimize the pharmacological properties of existing compounds and to identify novel chemical scaffolds with improved efficacy and safety profiles.
- Modulation of the BDNF/ TrkB Pathway: Rather than directly targeting BDNF or TrkB, a range of other approaches that modulate this pathway are being explored. These approaches include; altering the proBDNF: BDNF ratio, inhibit TrkB dephosphorylation, TrkB positive allosteric modulators, and approaches that target upstream processes to increase BDNF availability. Some of these programs have completed Phase I/ II clinical trials in people with Alzheimer's disease and have demonstrated efficacy in preclinical models of Parkinson's disease
- Advanced Gene Therapy Vectors: The continuous evolution of gene therapy technology is leading to the development of safer and more efficient viral vectors. Novel AAV serotypes with enhanced ability to cross the BBB after systemic administration are being explored, which could eliminate the need for invasive brain surgery.
- Personalized Medicine: As our understanding of the genetic and molecular subtypes of Parkinson's disease improves, it may be possible to develop personalized therapeutic strategies. For example, patients with specific genetic mutations that affect BDNF signaling might be particularly good candidates for a BDNF-based therapy.
- Harnessing Endogenous Mechanisms: Continued research into the mechanisms by which exercise and environmental enrichment boost endogenous BDNF levels could lead to the development.

Therapeutic landscape of BDNF/ TrkB based therapies

The landscape of therapeutics targeting BDNF/ TrkB continues to evolve. Gene therapy and small molecule TrkB agonists approaches continue to be refined and an improved understanding of the complex biology of BDNF-TrkB signalling is revealing new ways of targeting this pathway. A summary of TrkB and BDNF approaches that have been evaluated in any indication is shown in Table 2. Across CNS disorders (notably ALS), direct infusion of the BDNF protein has been advanced the furthest in clinical development, although, as discussed above, this approach has been largely discontinued due to issues with protein delivery. Of the AAV-based, antibody, and small molecule therapeutics, aimed at overcoming the delivery issues of direct protein infusion, the most advanced are in Phase I testing with several more approaches still in preclinical testing.

Table 2. Summary of BDNF/ TrkB based therapies that are, or have been, in preclinical, Phase I, or Phase II development

MODALITY	TEST ITEM	INDICATION(S)	ROUTE	STAGE	TOPLINE OUTCOME
Phase II or III					
Recombinant BDNF protein	r–metHuBDNF (systemic)	ALS	s.c. injection	Phase II/III	Failed efficacy; poor PK/ tolerability
Recombinant BDNF protein	r–metHuBDNF (intrathecal)	ALS	Pump infusion	Phase I/II	Feasible, safe; no efficacy established
Local protein delivery	OTO–413 (sustained BDNF)	Hearing loss	Intratympanic	Phase I/II	Lower dose: benefit in speech–in–noise; higher dose: no benefit
Cell therapy	NurOwn® (MSC–NTF)*	ALS, progressive MS	Intrathecal	Phase II/III	Safe; mixed efficacy (ALS Phase III negative)
Phase I					
Gene therapy (AAV–BDNF)	AAV2–BDNF	Alzheimer's disease	Intracerebral	Phase I	Safety being tested, no efficacy yet
Agonist antibodies	BI 754132 (TrkB agonist mAb)	Geographic atrophy (AMD)	Intravitreal	Phase I	Feasible, data pending
Small molecules	ACD856 (Trk PAM)	Cognitive disorders	Oral	Phase I	CNS exposure, qEEG changes; Phase II planned
Preclinical					
Gene therapy (AAV–BDNF)	AAV–BDNF, AAV–TrkB (various vectors)	AD, PD (preclinical)	Intracerebral, intranasal	Preclinical	Restored synapses, rescued behavior in rodents

MODALITY	TEST ITEM	INDICATION(S)	ROUTE	STAGE	TOPLINE OUTCOME
Agonist antibodies	BBB–shuttled agonist mAbs	CNS disease (PD, AD models)	i.v.	Preclinical	Cross–BBB, activate TrkB in rodents
Small molecules	BBB–shuttled agonist mAbs LM22A–4, 7,8–DHF, deoxygedunin	AD, PD, depression (models)	Oral/i.p.	Preclinical	Functional rescue in models; TrkB agonism debated
Intranasal BDNF	Various formulations & EVs	Stroke, SCI, PD (models)	Intranasal	Preclinical	Neuroprotection, behavioral recovery in rodents

* Although this cell–based approach involves BDNF, the relative contribution of BDNF vs. other neurotrophic factors is unknown.

Small Molecule and antibody TrkB Agonists

The development of small molecule TrkB agonists and antibodies that stimulate the TrkB receptor has opened an exciting new avenue for developing a BDNF-based therapy for Parkinson's disease. These compounds, which can cross the blood brain barrier, are dosed systemically (oral, i.p., or i.v.) and thus offer a much more patient-friendly and less invasive alternative to direct protein infusion or gene therapy.

While the preclinical data for small molecule TrkB agonists, like 7,8-DHF and its derivatives, have been encouraging, their development has not progressed beyond preclinical efficacy studies. To the best of our knowledge, there have been no large-scale, randomized controlled trials of small molecule TrkB agonists in people with Parkinson's disease. The most advanced small molecule approach directly targeting the TrkB receptor is the positive allosteric modulator (PAM) ACD856, which has been tested in Phase I clinical trials (see next section).

The development of TrkB agonists is not without its own set of challenges. One major concern is the potential for off-target effects and unforeseen toxicities, especially with long-term administration. The TrkB receptor is widely expressed throughout the body, not just in the brain, and chronic activation of this receptor could have unintended consequences. Furthermore, the precise pharmacological properties of these compounds, including their ability to cross the BBB in humans and their affinity and selectivity for the TrkB receptor, need to be thoroughly characterized.

Compared to small molecule approaches, there are fewer approaches using BDNF monoclonal antibodies (mAb).

Theoretically, mAbs have greater target specificity, better receptor engagement, and fewer off-target effects compared to small molecules. However, they are harder to synthesise and cannot be administered orally. The most advanced BDNF mAb was BI 754132, which was assessed in a Phase I study in people with geographic atrophy, an advanced stage of dry age-related macular degeneration. However, development on this compound has been discontinued.

Despite challenges, the development of small molecule TrkB agonists, and BDNF mAb agonists, represents a highly promising and rapidly evolving area of research. The ability to effectively engage TrkB signaling with an oral medication could be a game-changer for the treatment of Parkinson's disease and other neurodegenerative disorders.

Approaches to modulate BDNF/ TrkB signalling

Whilst direct targeting of the TrkB receptor is promising, approaches that modulate this pathway, rather than directly stimulating it, are also being explored. Potentially, these approaches can offer a more selective way of engaging the BDNF/ TrkB pathway and can avoid some of the potential issues that might occur with direct stimulation, such as dephosphorylation, and subsequent inactivation, of the TrkB receptor in response to continuous stimulation. Most of these approaches are not targeted at Parkinson's disease, although several have entered clinical development for other disorders.
A summary of these approaches is shown in Table 3.

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5. Alternative approaches

Other avenues of preclinical research focused on indirectly boosting endogenous BDNF levels, using small molecule approaches or physical exercise. In animal models of PD, we, and others, validated these approaches and demonstrated that small molecule and non–pharmacological interventions could play a supportive role in enhancing BDNF signaling and promoting neuronal health.

The advent of high–throughput screening technologies in the early 2000s led to the discovery of small molecule TrkB agonists. These were non–peptide molecules that could directly mimic the action of BDNF by binding to and activating the TrkB receptor. The most well–studied of these is 7,8–dihydroxyflavone, a flavonoid that can cross the BBB and exert potent neuroprotective effects in animal models of PD. The development of small molecule TrkB agonists represents a significant leap forward, offering the potential for a non–invasive, orally available therapy that could overcome the delivery challenges associated with the BDNF protein itself.

Table 3. Summary of approaches being used to modulate the BDNF/ TrkB signaling pathway that do not directly stimulate TrkB.

TARGET	COMPOUNDS/ PATHWAY	MECHANISM	STAGE	PRECLINCAL EFFICACY IN PD
↑ Conversion of proBDNF → BDNF	tPA activators / PAI–1 inhibitors (Tiplaxtinin, TM5441, TM5275)	Boost extracellular cleavage of proBDNF into mature BDNF	Preclinical (vascular/ neuro models)	No
	MMP–7/–9 upregulation	Cleave proBDNF extracellularly	Preclinical biology only	No
↓ proBDNF / p75NTR / sortilin signaling	LM11A–31 (C31)	Small–molecule p75NTR modulator; tilts balance toward TrkB	Phase II in AD; preclinical PD neuroprotection	Yes (in vitro)
	Sortilin antagonists (peptides, SMs)	Block proBDNF binding to sortilin	Preclinical	No
Prevent TrkB dephosphorylation	SHP2 inhibitors (SHP099, TNO155, RMC–4630)	Limit Shp2–mediated negative regulation of TrkB	Oncology Phase I/II; preclinical CNS	No
	STEP inhibitors (TC–2153)	Block STEP phosphatase, ↑TrkB–Y816 phosphorylation & PLCγ signaling	Preclinical (plasticity, AD)	No
	PTP1B inhibitors (MSI–1436/trodusquemine)	Reduce PTP1B RTK dephosphorylation; potential to ↑TrkB signaling	Preclinical; early human work in obesity	No
TrkB PAM	ACD856 (Trk PAM)	Orally available Trk positive allosteric modulator	Phase I completed (cognition disorders)	No
Boost endogenous BDNF availability	Exercise, ampakines, ketamine/(2R,6R)–HNK	Indirect ↑ BDNF release & signaling	Clinically assessed (exercise)	Exercise raises BDNF in people with PD and in animal models

Although there is currently a paucity of empirical evidence that these approaches are beneficial in animal models of Parkinson's disease, the fact that (i) several are in clinical development, (ii) all have been shown to modulate BDNF/ TrkB signaling, and (iii) the overwhelming preclinical evidence of the potential of BDNF as a treatment for Parkinson's disease, makes assessing some of the compounds in Table 3 attractive therapeutic candidates. Notably, LM11A-31 (↓ proBDNF / p75NTR / sortilin signaling), SHP099, TNO155, and RMC-4630 (Shp2 inhibitors), and ACD856 (Trk PAM) appear well placed to advance as potential Parkinson's disease therapeutics.

Summary

Overall, the complex biology of the BDNF/ TrkB signalling pathway, and the interaction between α-synuclein and TrkB, means that careful consideration needs to be given to preclinical and clinical studies during therapeutic development. For instance, continuous direct stimulation of the TrkB receptor may produce dephosphorylation, and subsequent inactivation, of TrkB. Another example is that performing preclinical work exclusively in toxin-based models of PD, such as MPTP-lesioned animals, may produce preclinical efficacy that does not translate to the clinic. Moreover, the use of BDNF/ TrkB therapies in people with late-stage PD, where α-synuclein levels in the brain will have been increasing for years, may be less effective than intervention much earlier in the disease process where there are more neurons that have not yet been exposed to pathologic α-synuclein. Thus, a careful preclinical program, that uses α-synuclein-driven models of PD, will be required to de-risk the translation from preclinical efficacy to clinical benefit.

Thus, for BDNF/ TrkB based therapies, maybe more than other potential therapies for PD, an in depth understanding of the biology of the intended clinical population, and an appreciation for which preclinical model(s) of PD most closely match the clinical cohort is required. Atuka has decades of experience of working with neurologists to understand the biology of PD and in creating and using animal models of PD to develop novel therapeutics, thus we are ideally placed to recognise the risks associated with developing BDNF/ TrkB therapeutics and to mitigate them through careful preclinical study design. We would be happy to answer any concerns you may have about developing BDNF/ TrkB based therapeutics for PD and look forward to helping de-risk these programs as they move toward clinical development.

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6. Conclusion

The development of therapeutic approaches targeting BDNF and TrkB in Parkinson's disease reflects decades of scientific discovery and the ongoing effort to translate neurotrophic biology into viable therapies. The initial hope, fueled by the potent neuroprotective effects of BDNF in preclinical models, has been tempered by a lack of clinical translation. The failures of the early protein infusion trials in ALS served as a crucial, albeit painful, lesson, highlighting the paramount importance of overcoming the BBB and achieving effective delivery to the target tissue.

While the clinical journey of BDNF and TrkB–based therapies has been fraught with challenges, the scientific rationale for this approach remains as strong as ever. The ongoing efforts in gene therapy and the exciting progress in the development of small molecule TrkB agonists offer renewed hope for the future. The road ahead is undoubtedly long and will require continued innovation, perseverance, and a deep understanding of the intricate biology of Parkinson's disease, animal models of Parkinson's disease, and BDNF/ TrkB. Research on BDNF illustrates both the promise and the challenges inherent in translating neurotrophic biology to the clinic. Every setback is a lesson learned, and every new discovery brings us one step closer to our goal: to not just manage the symptoms of Parkinson's disease, but to truly address the underlying pathology. The double–edged sword of BDNF, with its immense potential and its frustrating elusiveness, continues to be a driving force in the fight against PD.

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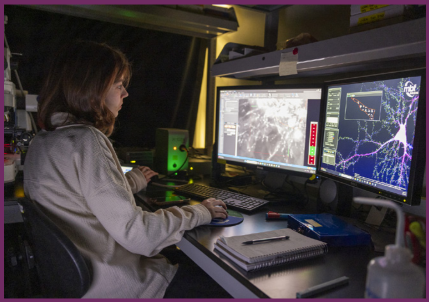
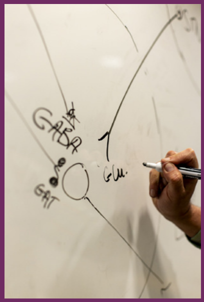
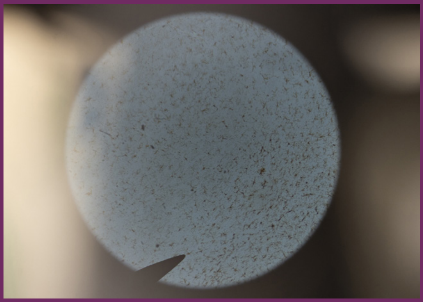
About the Author

Dr. Patrick Howson's primary research interest is in the development of disease-modifying therapies for neurodegenerative disorders. Patrick has a broad understanding of drug development through several years of working in virtual biotechs, where he has been responsible for research and development projects such as drug-screening programs, manufacture of GMP grade API, IND-enabling studies and Phase I and II clinical trials, including trials in Parkinson's disease. He uses this experience to help our partners develop preclinical programs suitable for their stage of development. Patrick is also experienced in the generation and management of intellectual property and is an inventor of several patents covering therapeutic approaches for Parkinson's disease. He has been with Atuka since 2013 and serves as the company's Chief Innovation 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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