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DISCOVERY SERIES — EMERGING TARGETS IN PARKINSON'S DISEASE

#1 — D1 PAM

The Potential of D1 Dopamine Receptor Positive Allosteric Modulators

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D1 PAMs represent a promising, yet understudied approach, potentially improving motor control and cognitive function while minimizing side effects associated with current treatments. Better understanding D1 PAMs could significantly advance how we treat both motor and non–motor PD symptoms.

D1 dopamine receptors (D1Rs) are a critical subtype of dopamine receptors involved in numerous physiological processes including motor control, cognition, and reward mechanisms.[1] The D1 dopamine receptor plays a significant role in the pathophysiology of PD, impacting both motor and non-motor symptoms, such as cognitive dysfunction.[2] Positive allosteric modulators (PAMs) represent a novel class of compounds that enhance the receptor's response to its endogenous ligand, dopamine, without directly activating the receptor.[3, 4] In this first installment of our Discovery Series exploring encouraging new targets and therapeutics for Parkinson's disease, we review how D1 PAMs have emerged as a promising therapeutic class, offering several advantages over traditional orthosteric agonists, such as improved selectivity, reduced side effects, and enhanced physiological relevance.

Why now?

The dopamine D1 receptor, and specifically positive allosteric modulators (D1 PAMs), have become an area of considerable academic and industry attention as potential treatments for Parkinson's disease (PD). Major pharmaceutical companies such as UCB, Eli Lilly, and Boehringer Ingelheim have recently moved their D1 PAM compounds into clinical trials.

An under–studied approach to PD

Enhancement of D1 signaling in PD represents an attractive approach and could have benefits: as monotherapy to reduce parkinsonian motor symptoms; in an L-DOPA-sparing strategy; as an adjunct to existing dopamine replacement therapy to reduce motor complications; and, as monotherapy to reduce cognitive deficits.

Mechanism of action

D1 PAMs bind to multiple allosteric sites on the D1 receptor. These sites are distinct from the orthosteric site where dopamine binds. This allosteric modulation enhances the receptor's affinity for dopamine, increasing the efficacy of dopamine without directly activating the receptor, thus offering a more physiologically relevant modulation. PAMs can also enhance agonist efficacy and efficiency of G-protein coupling.

Selectivity

Compounds like DETQ and UCB0022 have shown high selectivity for D1 receptors over other dopamine receptor subtypes, including D2, D3, D4, and only marginal activity at D5 receptors. This selectivity reduces the likelihood of side effects commonly associated with broader dopamine receptor activation.

Pharmacokinetics

D1 PAMs such as DETQ and UCB0022 are orally bioavailable and demonstrate good brain penetration. These pharmacokinetic properties are crucial for their potential therapeutic application in central nervous system (CNS) disorders.

Preclinical efficacy

In preclinical studies, D1 PAMs have shown efficacy in models of Parkinson's disease. For example, UCB0022 reportedly improved motor function in MPTP-treated macaques with reduced dyskinesia compared to traditional therapies like L-DOPA. D1 PAMs have also shown cognitive enhancing properties across a range of preclinical animal models.

Safety profile

The preclinical safety data for D1 PAMs are encouraging, with favourable safety margins observed in studies. Compounds like UCB0022 and LY3154207 (mevidalen) have progressed to first-in-human studies, indicating a good emergent safety profile.

Clinical efficacy

Of the limited Phase 2 studies conducted thus far, mevidalen has shown promise in treating both motor (improvements in parkinsonian symptoms) and some non-motor (e.g. fatigue, hallucinations / psychosis and daytime sleepiness) symptoms in people with PD.

Challenges and considerations

Despite promising data, challenges remain, such as the potential for species-specific differences in receptor binding (e.g., DETQ's lower potency in rodent models). These factors must be carefully considered in the ongoing development of D1 PAMs.

Future directions

Ongoing development of D1 PAMs should be focused on optimizing their efficacy, safety, and pharmacokinetic profiles.

Continued research is essential to fully understand their therapeutic potential in PD, particularly in building a good understanding of the relative motor and non-motor benefits that might be anticipated with appropriate target engagement. Such understanding will not only define clinical potential of the class but will define a route through development to market.

Care must also be taken to carefully design clinical trials to optimally translate preclinical efficacy findings.

Motor symptoms and complications

D1Rs are highly concentrated in the striatum, an area that experiences a loss of dopaminergic tone as dopaminergic neurons in the substantia nigra degenerate in Parkinson's disease.[2] This loss of stimulation contributes to the motor symptoms characteristic of Parkinson's disease. The reduction of D1R stimulation is associated with underactivity in the direct pathway connecting the striatum to the internal segment of the globus pallidus. This underactivity leads to reduced inhibition and thereby excessive output from the basal ganglia, contributing to motor symptoms.[5] Enhancement of signalling at striatal D1Rs, is a well-validated target for symptomatic therapy for motor aspects of in Parkinson's disease.

Historically, a range of D1R family agonists have been shown to provide benefit as monotherapy in alleviating Parkinson's motor symptoms in rodent and non-human primate (NHP) models, in particular using the MPTP-lesioned NHP model. A model that is well-suited for generating data that allow translation to Phase 2 clinical proof-of-concept.[6] However, despite the data in NHP, currently, no pure D1 receptor agonists are used clinically for treating motor aspects of Parkinson's disease.[2] One reason for this failure to translate from NHP and Phase 2 through to the market, is the tendency of some D1R agonists to show tachyphylaxis,[7] where the therapeutic effect diminishes with continuous use, but more importantly perhaps, D1R agonists have been associated with eliciting dyskinesia, especially in patients who have been treated with L-DOPA. The dysregulation of D1R signaling through the direct pathway likely contributes to these motor complications.[8]

D1R PAMs offer a novel approach to motor symptoms by enhancing the effects of endogenous dopamine, which are reduced, though still significant in, at least in early and mid stage, Parkinson's disease. This mechanism may, in a monotherapy context, allow for a more balanced stimulation of the D1 receptors, potentially providing anti-parkinsonian benefits without inducing motor complications.

Another potential application of D1 targeting molecules is to be used as part of an L-DOPA-sparing strategy. By reducing the dose of L-DOPA to suboptimal or even subtherapeutic levels, where it minimizes side effects like dyskinesia, D1R stimulation could be used adjunctively to enhance the effect of endogenous dopamine and low doses of dopamine derived from L-DOPA metabolism. This could offer antiparkinsonian benefits while reducing the risk of motor complications. Indeed, this approach has been validated not

only in MPTP-lesioned NHPs[9] but recently at Phase 3 by Cerevel's tavapadon, a partial D1/D5 agonist.[10] In an analogous manner, D1 PAMs can be envisaged as an approach to fine tune dopaminergic stimulation to a level where D1 stimulation drives activity in the direct pathway at a level to reduce parkinsonism without driving dyskinesia.

Cognitive symptoms

In addition to motor symptoms, Parkinson's disease is often accompanied by cognitive deficits, indeed such may precede motor symptoms.[5] In an implementation of the MPTP-lesioned NHP model, that replicates cognitive deficits seen in Parkinson's without motor symptoms[11], D1R stimulation can improve cognitive performance. For example, the administration of a D1R agonist, dihydrexidine, improved performance on the variable delayed response task in MPTP-lesioned macaques.[12] This suggests that D1 PAMs could also have therapeutic potential in improving cognitive function in early-stage Parkinson's disease, where dopaminergic innervation is relatively intact.[4] In addition, the D1 PAM, DETQ, was shown to improve spatial working memory and cognitive function in rhesus macaques[13] and UCM-1306 enhances memory in a novel object recognition test (NORT) in mice.[14]

Although these approaches have not yet been clinically validated, the availability of robust animal models including the very well established chronic low-dose (CLD) MPTP macaque model[15] offers a promising path for future research and drug development as the pharmacology of D1 PAMs continues to evolve.

D1 PAM mechanism of action

D1 PAMs exert their effects by binding to allosteric sites on the D1R, which are distinct from the orthosteric site where dopamine binds.[16, 17] This binding increases the receptor's affinity for dopamine and/or enhances the efficacy of dopamine, leading to a potentiated response. Importantly, this mechanism allows for modulation of receptor activity only in the presence of dopamine, thereby preserving normal physiological regulation.

The advantages of D1 PAMs over orthosteric agonists are significant. PAMs reduce the likelihood of receptor desensitization and downregulation, common issues with continuous agonist exposure.[18] Additionally, PAMs help produce more physiological patterns of dopaminergic signaling, as they do not induce receptor activity in the absence of dopamine and offer the potential of greater selectivity of effect between the D1R and the other four dopamine receptors. Furthermore, as different allosteric modulators have been shown to bind to the D1R at distinctive sites, combinations of allosteric modulators may have advantages over single agents. For instance, PAMs that act at different sites have the potential to be effective at lower doses than either agent administered separately, thereby circumventing pharmacokinetic limitations or non-mechanism-related toxicity.[19] PAMs can also enhance agonist efficacy response by increasing the time for which a G-protein-coupled receptor is in the active state.[20]

Key compounds and their profiles

Several D1 PAMs are currently under development (Table 1), a selection of which are summarized below.

DETQ

DETQ is a selective allosteric modulator of the human D1R developed by Boehringer Ingelheim.[18] It increases cAMP production in HEK293 cells expressing the human D1R with an EC50 of 5.8 nM. DETQ is considerably less potent at rat and mouse D1R and shows no activity at the human D5 receptor.

DPTQ

DPTQ has been studied for its effects on spatial working memory in rhesus monkeys.[13] Although detailed data on its pharmacokinetic profile is limited, DPTQ has demonstrated potential in cognitive enhancement, making it a subject of interest for continued research.

UCB0022

UCB0022, developed by UCB Pharma, is a brain-penetrant D1 PAM with promising preclinical data.[21] It selectively binds to D1Rs with nanomolar affinity and significantly enhances the potency of dopamine. In MPTP-treated cynomolgus monkeys, UCB0022 improved motor function and reduced dyskinesia when administered alone or in combination with a low dose of L-DOPA.

Mevidalen

Mevidalen (LY3154207)[7], a D1 PAM developed by Eli Lilly, has shown efficacy in enhancing wakefulness and cognitive function in preclinical models. Its selectivity for D1Rs and favorable pharmacokinetic profile made it a candidate for the treatment of disorders like Parkinson's disease and schizophrenia. See Page 10 for a summary of clinical investigations utilizing mevidalen.

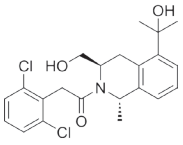
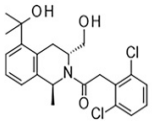
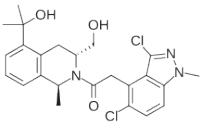
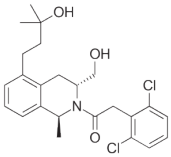
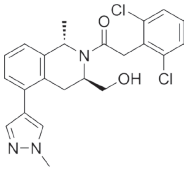
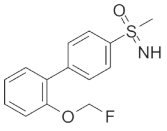
LY3154885

LY3154885[22], a more recently developed D1 PAM, was developed following clinical assessment of mevidalen for the treatment of Lewy body dementia due to Parkinson's disease or dementia with Lewy bodies.[23] Preclinical data show that mevidalen was eliminated principally by CYP3A4-mediated metabolism and was therefore at risk of drug–drug interactions (DDI) with CYP3A4 ligands. Lilly identified LY3154885 as a D1 PAM with comparable pharmacologic properties to mevidalen, but which is metabolized principally by UDP-glucuronosyltransferase (UGT), suggesting it could potentially offer reduced DDI risk when used clinically.

UCM–1306

UCM-1306[14] increases the endogenous dopamine maximal effect both in human and mouse D1 receptors. It has been shown to not induce D1R desensitization and exhibits no agonist activity or subtype selectivity. UCM-1306 is orally active and can enhance L-DOPA-evoked activity in reserpinized mice. UCM-1306 also enhances memory in a novel object recognition test (NORT), suggesting potential for use in PD patients with cognitive impairment.

Table 1. D1 Dopamine Receptor Positive Allosteric Modulators (D1 PAMs).

NAME	COMPANY	CHEMICAL STRUCTURE	BIOLOGICAL ACTIVITY	REFERENCE
DETQ	Boehringer Ingelheim		Selective D1R PAM; increases cAMP with an EC50 of 5.8 nM in HEK293 cells expressing human D1 receptors.	18
DPTQ	Eli Lilly		Investigated for spatial working memory enhancement in rhesus monkeys.	13
UCB0022	UCB Pharma		Selective D1R PAM; enhances dopamine activation by ~10–fold; effective in MPTP–treated macaques with reduced dyskinesia.	21
Mevidalen	Eli Lilly		PAM at human D1R; demonstrated wakefulness and cognitive enhancement in preclinical models.	7
LY3154885	Eli Lilly		Displays equivalent *in vitro* and *in vivo* pharmacologic properties to LY3154207, but with potential for reduced drug–drug–interaction risk.	22
UCM–1306	Universidad Complutense de Madrid		PAM targeting D1R; efficacy in various models discussed.	14

Preclinical and clinical data

Preclinical studies in rodents and non-human primates have provided valuable insights into the efficacy and safety of D1 PAMs and potential application in PD and other indications (see Table 2 and Table 3). For example, DETQ enhances motor activity in mice and in MPTP-treated cynomolgus monkeys, UCB0022 significantly improved motor function with reduced dyskinesia compared to L-DOPA. Similarly, mevidalen has shown promise in enhancing wakefulness and cognition in rhesus monkeys.

Table 2. Select rodent studies with D1 PAMs

PAM NAME	SPECIES	DOSE(S) USED (MG/KG)	ROUTE OF ADMINISTRATION	EFFECTS OBSERVED	REFERENCE
DETQ	Mouse	3–20 mg/kg	Oral	Enhanced motor activity; increased cAMP production; species–specific lower potency compared to humans.	4, 18, 24
Mevidalen	Mouse	3–100 mg/kg	Oral	Mevidalen dose–dependently enhanced wakefulness (latency to fall asleep) in the hD1 mouse. Mevidalen also promoted wakefulness in mice after prior sleep deprivation and delayed sleep onset.	25
UCM–1306	Mouse	1–2.5 mg/kg	Oral	Potentiated cocaine–induced locomotion and enhanced L–DOPA effects on activity in reserpinized animals.	14
DETQ	Mouse	3–30 mg/kg	Oral	Rescued novel object recognition deficit in aged mice.	24

Table 3. Select non–human primate studies with D1 PAMs

PAM NAME	NHP SPECIES	DOSE(S) USED	EFFECTS OBSERVED	REFERENCE
DETQ	Rhesus (Macaca mulatta)	3–10 mg/kg, IM	Increased spontaneous eye–blink rate (a measure known to be depressed in PD).	26
UCB0022	Cynomolgus (Macaca fascicularis)	Single oral doses: specific doses not detailed in the abstract.	Improved motor disability in MPTP–treated macaques, reduced dyskinesia compared to L–DOPA.	21
DPTQ	Rhesus (Macaca mulatta)	0.1 – 10 mg/kg, SC	Improvement in spatial working memory.	13

These preclinical successes have led to the initiation of early-phase clinical trials for some D1 PAMs, with a focus on assessing their safety, tolerability, and efficacy in humans (Table 4).

Table 4. Select clinical studies with D1 PAMs

PAM NAME	PHASE	TRIAL NAME AND CLINICALTRIALS.GOV ID	PARTICIPANTS	SUMMARY
Mevidalen	1	A study of LY3154207 in healthy participants. NCT02365571	64 healthy controls	Single ascending dose study. Tolerability up to 200 mg; doses above 75 mg caused acute increases in blood pressure and pulse rate.
Mevidalen	1	A study of LY3154207 in healthy participants and participants with PD. NCT02562768	48 healthy volunteers and 25 PD patients	No serious AEs reported. Dose–related increases in blood pressure and pulse rate resolved after two weeks. PD patients showed improvement on the UPDRS motor score.[27]
Mevidalen	1	A study of LY3154207 on sleep in healthy male participants. NCT02603861	16 healthy men	Promoted wakefulness, delayed sleep onset in sleep–deprived men.[25]
Mevidalen	1	Study of LY3154207 in healthy participants. NCT03616795	8 healthy men	Disposition of [14C]–LY3154207 following oral administration.[27]
Mevidalen	1	A drug interaction study of LY3154207 in healthy participants. NCT03942029	36 healthy adults	Formulation comparison and interaction with fluconazole. No serious adverse events; secondary outcomes included changes in blood pressure, pulse rate, and assessment of plasma PK.
Mevidalen	1	A study to evaluate LY3154207 on the brain of healthy participants. NCT04258826	16 healthy adults	Assessed change from baseline in intrinsic Functional Connectivity among resting–state networks of the brain.
Mevidalen	2	A Study of LY3154207 in participants with dementia due to Lewy body dementia associated with idiopathic PD or dementia with Lewy bodies (PRESENCE). NCT03305809	344 patients with mild to moderate LBD or DLB	A randomized placebo–controlled trial to evaluate the safety and efficacy of three doses of study drug LY3154207 treated for 12 weeks in participants with mild–to–moderate dementia associated with LBD (PDD or DLB). No change in primary endpoint of cognition. Improvements in Clinical Global Impression of Change, UPDRS, and daytime sleepiness, especially at 75 mg. Common adverse events included dizziness, nausea, hallucinations, headache, insomnia. The 75 mg dose was discontinued mid–study due to serious cardiovascular adverse events.[23]
Mevidalen	1	A study of LY3154885 in healthy participants. NCT04014361	36 healthy adults	Single– and multiple–ascending dose, safety, tolerability, and PK study with LY3154885. Study was terminated early due to a business decision.
UCB0022	1	A study to test the safety, tolerability, and blood levels of UCB0022 in healthy participants and participants with PD. NCT04867642	100 healthy adults	Outcomes not reported.
UCB0022	2	A study to evaluate the efficacy, safety, tolerability and PK of UCB0022 in study participants with advanced PD (ATLANTIS). NCT06055985	189	Still recruiting (as of Sep 2024). Primary aims to demonstrate the effect of UCB0022 as adjunct to a 'stable' dose of standard–of–care (including at least L–DOPA therapy) over placebo with regard to motor fluctuations including OFF time in advanced PD patients.

Notes on preclinical and clinical data

Of note, although the Phase 2 assessment of LY3154207 (mevidalen)[23] did not show any significant effect of treatment on the primary cognitive endpoints, there was a significant improvement of MDS-UPDRS total score (sum of Parts I-III) and in MDS-UPDRS Part I (non-motor) from baseline to week 12.

There are a number of potential reasons for the lack of improvement in cognitive measures in this trial. First, subjects were selected for inclusion into the trial based on the presence of mild or moderate dementia, not on the basis of presence or severity of any particular cognitive impairments. Second, the primary endpoint was a Continuity of Attention (CoA) composite score, obtained from the Cognitive Drug Research Computerized Cognition Battery (CDR-CCB), that primarily reflects ability to sustain attention. As subjects weren't selected based on presence or severity of the cognitive dysfunction assessed by the primary endpoint measure, it is not surprising that the average baseline CDR-CoA score was near the scale's ceiling, reducing the ability to detect a treatment effect on this primary outcome measure.[23] Additionally, the CDR-CCB was administered at every follow-up visit for a total of 11 times throughout the study period.

Although this measure is believed to be "resistant" to learning effects, it is not immune to such effects, especially considering the frequency at which it was repeated. Also, as mevidalen has not been assessed for efficacy in non-demented patients with PD and mild cognitive impairment, it remains to be seen if improvements in cognition in this patient group can be achieved with this drug. The higher doses (30 mg and 75 mg) of mevidalen doses also showed statistically significant improvements in MDS-UPDRS Part II (motor experiences of daily-living), while only 75 mg mevidalen showed a significant improvement in MDS-UPDRS Part III (motor impairment). Furthermore, mevidalen treatment was also associated with significant positive changes from baseline in measures of fatigue, hallucinations / psychosis and daytime sleepiness. These latter effects are of particular interest as they are often poorly controlled or not addressed at all by many current symptomatic therapies for PD. Mevidalen was, however, found to cause an increase in ON time spent with dyskinesia ($P<0.01$ for 75 mg) although the severity of that dyskinesia and whether disabling or non-disabling in nature was not reported. Understanding such issues would clearly benefit from investigation in pre-clinical NHP models in which the effects of monotherapy and different L-DOPA combinations can be thoroughly examined in controlled and highly predictive settings.[28]

Challenges and future directions

D1 PAMs represent a promising new approach to modulating dopaminergic signaling with potential applications in treating a variety of neuropsychiatric and neurodegenerative disorders. Their unique mechanism of action, combined with encouraging preclinical data, suggests that D1 PAMs could offer significant advantages over existing therapies. Despite the promising data, several challenges remain in the development of D1 PAMs. In addition, there is the potential of D1 PAMs to address multiple indications (not merely motor symptoms of PD but also non-motor symptoms too, e.g. cognitive impairment, fatigue, hallucinations / psychosis and daytime sleepiness) there remains a challenge as to which translational goal(s) to pursue for maximum impact. Thus, the translation of preclinical findings to clinical success will require careful consideration of the translational goal, choice of appropriate clinical population for study, clinical trial design, dosing, safety, and long-term effects.

Future research should focus on optimizing the pharmacokinetic and safety profiles of D1 PAMs, exploring their potential in other neuropsychiatric conditions, and advancing our understanding of their long-term effects on receptor function and behaviour.

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About the Authors

Dr. Tom Johnston's research interests focus on optimizing the translation of advances in fundamental Parkinson's disease research into novel therapeutic strategies. His Ph.D. work in behavioral neuropharmacology ignited a passion for developing and utilizing rodent and non-human primate models to study Parkinson's disease, particularly relating to motor symptoms and motor complications. More recent interests include the development of models to enhance the translation of putative disease-modifying therapies for PD and other neurodegenerative disorders. His work has yielded over 60 publications and earned him an *h*-index of 37. In addition to his scientific leadership, Tom oversees Atuka's facilities in Toronto and Suzhou, PRC and has served as the company's Chief Operations Officer since 2003.

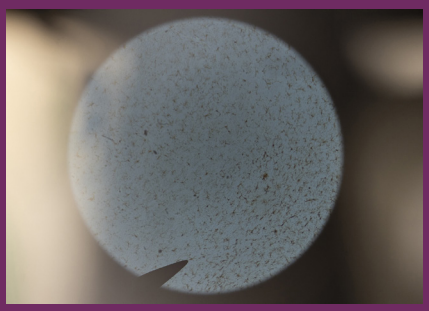
Dr. Jonathan Brotchie's research focuses on the intersection of basal ganglia function and Parkinson's disease. In both academia and industry, teams led by Jon have been global leaders in discovering and validating targets for potential treatments for PD and evaluating their pre-clinical efficacy. They have assessed over 300 drugs, biologics, and gene therapies, with more than 80 tested in non-human primates, and over 25 progressing to clinical development. Jon has collaborated with more than 100 pharmaceutical and biotech companies and acted as consultant to over 80 global organizations (commercial, academic, charitable, and governmental). A prolific contributor to academic literature, Jon's extensive body of work has been influential in defining the science of Parkinson's disease as we know it today. He is the founder of Atuka.











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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