# Brain-Selective Inhibition of LRRK2 as a Novel Therapeutic Strategy for Parkinson's Disease

Rishi Rakhit[1], Zachary B. Hill[1], Randall Chin[1], Roy Y. Kim[1], Jennie Phung[1], Nadia Khan[1], Alex Laihsu[1], Jessica Li[1], Steven Hansberry[1], Nicholas T. Hertz[1]

[1] Montara Therapeutics, Inc. San Francisco, CA, USA

## Abstract

Therapeutic inhibition of LRRK2 remains a compelling strategy for Parkinson's Disease (PD), but development has been limited by poor CNS exposure and dose-limiting peripheral toxicities, particularly in the lung and kidney. To overcome these challenges, we are advancing a brain-selective approach using the BrainOnly™ platform, which combines CNS-active LRRK2 chimeras with a novel peripheral blocker, MT1062.

BrainOnly chimeras are a small molecules that consist of an FKBP-binding moiety, a linker, and a LRRK2 inhibitor. In cell-based assays, these chimeras exhibit potent LRRK2 inhibition at single-digit nanomolar $IC_{50}$ values, which are attenuated by >100-fold in the presence of MT1062. In vivo, chimeras inhibit LRRK2 in lung and kidney, but co-dosing with MT1062 completely blocks this peripheral activity while preserving LRRK2 inhibition in the brain. Notably, co-dosing also enhances brain exposure of the chimeras.

This approach effectively decouples central and peripheral pharmacology and has been validated across multiple LRRK2 scaffolds, supporting broad applicability. Our ongoing efforts focus on optimizing brain-penetrant chimeras with strong CNS efficacy and a favorable safety profile. By resolving key limitations of prior LRRK2 inhibitors, BrainOnly has the potential to deliver a best-in-class therapeutic for LRRK2-driven PD with the potential to expand to other neurodegenerative disorders.

## BrainOnly™ Platform Overview

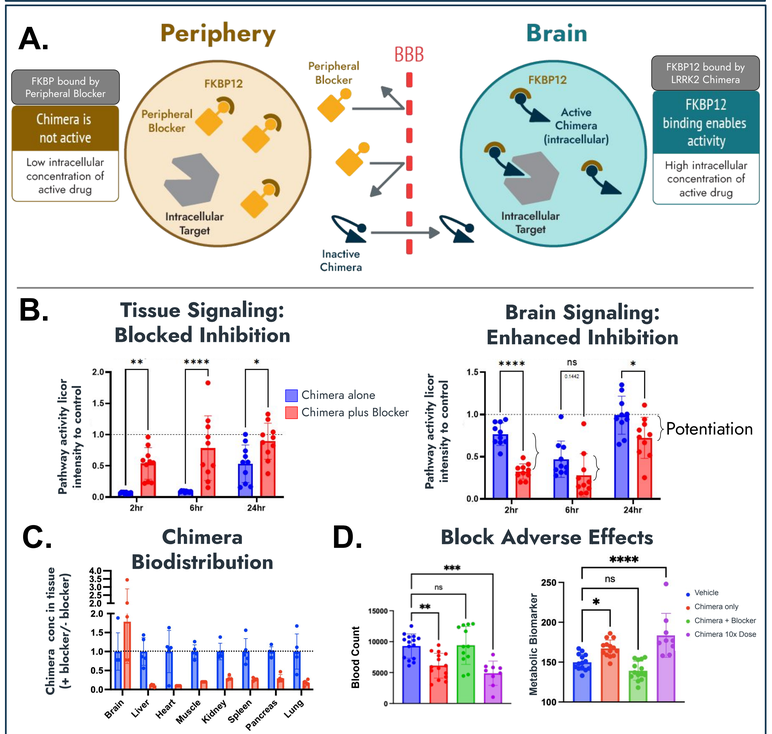


**Figure 1. Overview of the BrainOnly Platform.** (A) Schematic illustrating the brain-selective pharmacology enabled by the BrainOnly Platform. (B) In mice, co-treatment with a peripheral blocker and a Chimera enhances inhibition of signaling in the brain while preserving signaling in peripheral tissues.(C) Restoration of peripheral signaling correlates with exclusion of the chimera from peripheral tissues. (D) Blocking peripheral inhibition suppresses adverse effects.

## A LRRK2 Targeting BrainOnly Chimera

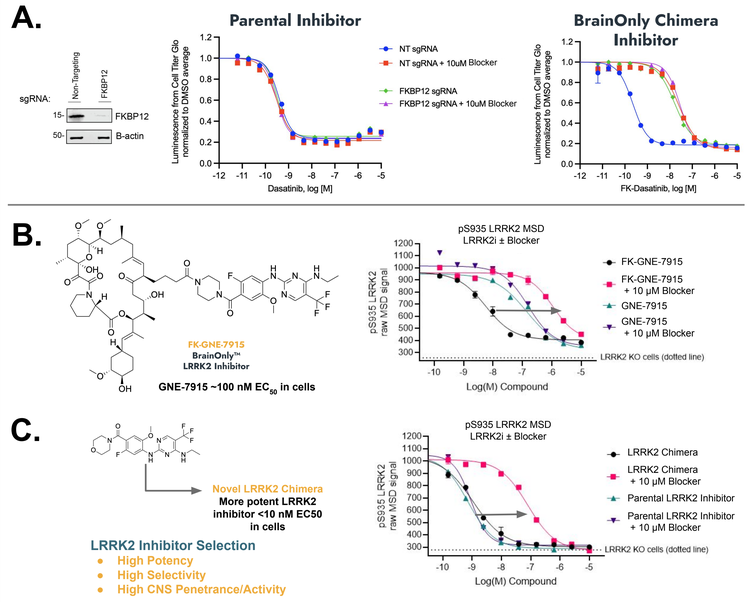


**Figure 2. Application of the BrainOnly Platform to LRRK2 Inhibitors.** (A) BrainOnly platform data showing the dependency chimera potency on FKBP12. (B) The BrainOnly Platform example compound FK-GNE-7915 exhibits FKBP12 dependency, blocking ratio of >150X. (C) Novel Montara-generated LRRK2 Chimera with improved potency, that exhibits 80X blockability in cells.

## *In vitro* and Cell Screening of LRRK2 Chimeras

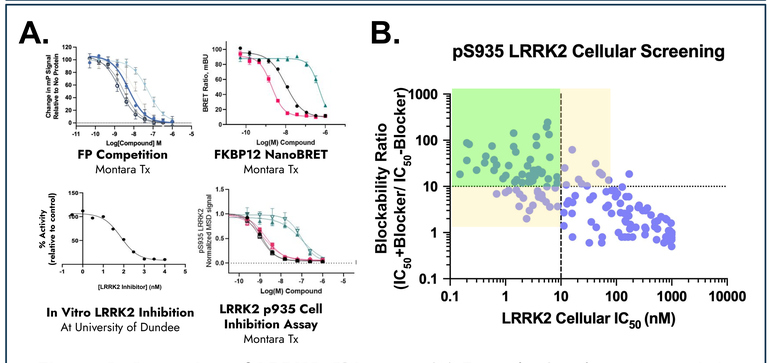


**Figure 3. Screening of LRRK2 Chimeras.** (A) Example data from Montara's *in vitro* screening cascade (B) More than 170 chimeras were evaluated for inhibition of pS935-LRRK2 ± Blocker in cells. Hits demonstrating both high potency and effective blockability were selected for subsequent *in vivo* testing.

## Thanks!

Grant support from the Michael J. Fox Foundation LITE program

Financial Disclosures:
The presenters are employees and shareholders of Montara Therapeutics, Inc. Accordingly, the data presented here could influence the value of the company's shares.

## Potent and Blockable LRRK2 Inhibition *in vivo*

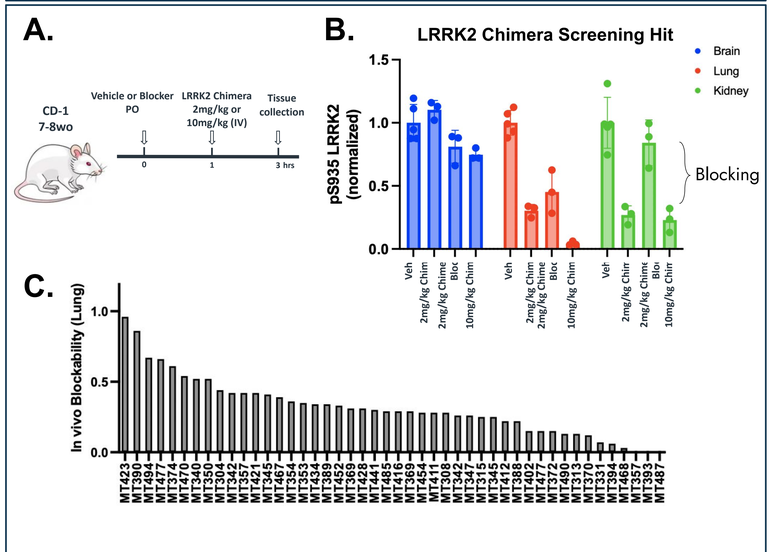


**Figure 4. *In vivo* Screening Identifies LRRK2 Chimera Hits with Blockable Peripheral Activity.** (A) Schematic of the *in vivo* screening protocol. (B) Peripheral and brain pS935-LRRK2 levels after dosing with the chimera ± peripheral blocker. (C) Rank order of LRRK2 chimera blockability in lung tissue.

## Brain Exposure of LRRK2 Chimeras

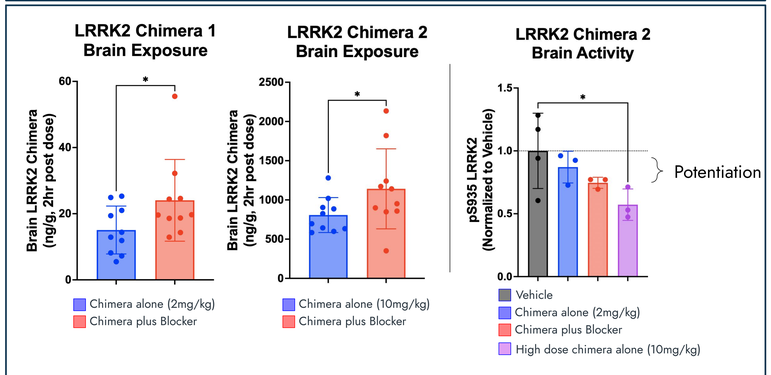


**Figure 5. Enhanced Brain Exposure of LRRK2 Chimeras with Peripheral Blocker Co-dosing.** Co-administration of a peripheral blocker with LRRK2 chimeras in mice increases chimera exposure in the brain. The data support FKBP12-mediated targeting, as the brain becomes the only site with unbound FKBP12 when the peripheral blocker is present.

## References

1. Zhang, Z., Shokat, K.M., et al. Brain-restricted mTOR inhibition with binary pharmacology. *Nature* 609, 822–828 (2022).
2. Simpson, C. et al. Prevalence of ten LRRK2 variants in Parkinson's disease: A comprehensive review. Parkinsonism & Related Disorders 98, 103–113 (2022).
3. Baptista, M. A. S. et al. LRRK2 inhibitors induce reversible changes in nonhuman primate lungs without measurable pulmonary deficits. Science Translational Medicine 12, eaav0820 (2020).