

Title: Maraviroc: ITP Application

Applicants: Rapamycin News

2. Rationale and Background

Mechanism: Maraviroc is an FDA-approved, small-molecule entry inhibitor that functions as a reversible, allosteric antagonist of the C-C chemokine receptor type 5 (CCR5), a G protein-coupled receptor (GPCR) ([Dorr et al., 2005](#)).

Relevance to Longevity: The CCL5/CCR5 axis is a critical driver of the senescence-associated secretory phenotype (SASP) in skeletal muscle. Maraviroc acts as a senomorphic agent. Unlike traditional senolytics (e.g., Dasatinib + Quercetin) that induce apoptosis in senescent cells, Maraviroc suppresses the toxic SASP phenotype without killing the cell. It breaks the inflammatory feedback loop, effectively "muting" the zombie cells and intervening directly in the Inflammation/NF-kappaB aging pathway.

Furthermore, CCR5 is widely expressed in the central nervous system (CNS). While historically studied for its role in HIV-associated neurocognitive disorder (HAND), recent data identifies CCR5 as a potent suppressor of synaptic plasticity, learning, and memory ([Joy et al., 2019](#)). Antagonizing this receptor offers a mechanism to mitigate age-related cognitive decline and neuroinflammation.

Previous Evidence: The current literature provides verified evidence that Maraviroc extends healthspan in mammalian models. Outcomes include the preservation of cognitive acuity, reversal of age-related sarcopenia, and mitigation of neuroinflammation. Recent single-nucleus multiomics research identifies the CCL5/CCR5 axis as a primary physiological driver of age-related sarcopenia, demonstrating that Maraviroc acts as a pharmacological senotherapeutic that improves muscle morphology, grip strength, and running endurance in aged mice ([Li et al., 2025](#)).

Knowledge Gap: Lifespan extension data in genetically heterogeneous UM-HET3 mice is currently absent from the literature. However, the profound healthspan benefits observed in specific organ systems strongly suggest informed speculation for systemic lifespan extension via the attenuation of SASP-driven inflammaging.

3. Activity, Dosage, Bioavailability, and Toxicity

Pharmacokinetics: Maraviroc exhibits adequate oral bioavailability in mammalian models. For ITP purposes, it must be administered via dietary admixture. The stability of Maraviroc in standard mouse chow post-pelleting (which involves heat and pressure) requires empirical verification prior to cohort initiation. The compound is highly stable under standard long-term storage conditions.

Toxicity: Maraviroc has a well-documented safety profile from long-term human clinical use, with a high LD50 in rodent models. Chronic, continuous administration is generally well-tolerated. Transient hepatotoxicity is the primary clinical monitoring endpoint. Because Maraviroc acts as a senomorphic rather than a senolytic, continuous dosing is required; pharmacokinetic clearance during "off" periods would allow the SASP inflammatory loop to rebound.

Chemical Structure: The chemical formula for Maraviroc is C₂₉H₄₁F₂N₅O. It is a cyclohexane-carboxamide derivative.

4. Suggested Treatment Protocol

Route: Dietary admixture (ITP standard preference).

Dosage Calculation: The proposed target dose is 200 mg/kg/day, administered continuously.

- **Formula:** Target dose (mg/kg/day) x Body Weight (kg) = Daily mg
- **Mouse Equivalent:** Assuming an average UM-HET3 mouse weight of 30 g (0.03 kg):
200 mg/kg/day x 0.03 kg = 6 mg/day.
- **Dietary Conversion:** Assuming an average daily food consumption of 3 to 4 g per mouse, the required concentration in the chow to achieve 6 mg/day is approximately 1500 to 2000 ppm.

Start Age: 8 months of age, continued lifelong. Given the mechanism of action here is related to build-up of senescent cells, starting at mid-life seems most appropriate for this intervention.

Biomarkers: In vivo efficacy and target engagement should be verified via transcriptomic analysis of skeletal muscle to confirm SASP suppression (e.g., downregulation of CCL3, CCL4, CCL5), and serum ELISA for downstream inflammatory cytokines (e.g., IL-6, TNF-alpha).

5. Cost of a Life-long Intervention Study

Supply: Currently available from MedChemExpress at \$2000 per 5 grams.

Budget Calculation: * Average daily dose: 6 mg/mouse/day.

- 6 mg x 100 mice x 365 days x 3 years = 657 grams required per site (per sex).
- Total estimated cost at MedChemExpress retail pricing: 657 grams x \$400/gram = \$262,800 per site, per sex.

Constraint: Relying on retail research-grade suppliers is not financially viable for a fully powered ITP study. Custom synthesis or a direct partnership with a generic pharmaceutical manufacturer is mandatory to bring the bulk compound cost within standard NIA ITP budget constraints.

6. Animal Safety Information

The primary safety concerns are mild immunosuppression (due to targeted CCR5 blockade) and potential hepatotoxicity. The specific pathogen-free (SPF) vivarium conditions standard to the ITP will effectively eliminate the risk of opportunistic infections. Potential hepatotoxicity will be monitored via standard physical health assessments, tracking of body weight trajectories, and necropsy pathology reports upon natural death.

7. References

[1] [Maraviroc \(UK-427,857\), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5... \(2005\).](#)

[2] [Joy, M. T., et al. \(2019\). CCR5 is a therapeutic target for recovery after stroke and traumatic brain injury. Cell.](#)

[3] “Multiomics and cellular senescence profiling of aging human skeletal muscle uncovers Maraviroc as a senotherapeutic approach for sarcopenia” Nature Communications, 2025

- STATEMENT OF UNDERSTANDING -

In submitting this proposal, I agree to the following:

- I understand that all information presented in the proposal can be freely shared with members of the ITP Steering Committee and Access Panel during their evaluation of proposals but will otherwise be considered confidential.
- If my proposal, or a modification of it (such as altered dosage or frequency of administration), is accepted for inclusion in a research protocol, I will be asked to help evaluate the data and to prepare the data for written and oral publications, on each of which I will be offered co-authorship. I understand the ITP intends to submit the results of all ITP-supported studies for publication – regardless of whether they produce data showing positive or negative effects on health status in mice.
- I understand that data generated by ITP-supported experiments using the compound/diet proposed will be made publicly available and can be used by anyone in applications for further research support. I also will be free to use ITP-generated data in the context of my applications for research support or for any other purpose.
- **If applicable:** The compound/diet proposed makes use of materials that are not yet freely available and whose production depends on proprietary or unpublished methods. If my application is approved for incorporation in the ITP, a mutually acceptable Materials Transfer Agreement that would permit me to provide the ITP with the compound(s) needed for the experimentation will be developed with the Institutions involved in this program.

Applicant Signature
