1. Dapansutrile: ITP Application

Applicants: Rapamycin News

2. Rationale and Background

Mechanism: Dapansutrile (OLT1177) is an orally active beta-sulfonyl nitrile compound. It acts as a direct, selective inhibitor of the NOD-like receptor protein 3 (NLRP3) inflammasome. It blocks the ATPase activity of the NLRP3 protein, halting its oligomerization and the subsequent processing of pro-caspase-1. This action selectively prevents the maturation and release of the pro-inflammatory cytokines interleukin-1-beta (IL-1-beta) and IL-18.

Relevance to Longevity: Chronic, sterile, low-grade inflammation (inflammaging) is a validated hallmark of biological aging that drives systemic metabolic decline and tissue degeneration. Sustained NLRP3 activation is a primary mediator of this process. Dapansutrile dampens IL-1-beta-mediated sterile inflammation without broadly suppressing the immune system (e.g., it does not inhibit TNF-alpha or other inflammasomes like NLRC4 or AIM2). Consequently, it is a mechanistically logical candidate for mitigating age-related metabolic decline and preserving tissue integrity in late life.

Previous Evidence:

- **Healthspan and Lifespan (Verified Facts):** Preclinical data demonstrate that dapansutrile preserves neuronal integrity and rescues cognitive impairment in APP/PS1 mouse models of Alzheimer's disease by normalizing neuroinflammation and metabolic profiles (Lonnemann et al., 2020). Furthermore, dapansutrile reduces the secretory phenotype of senescence and extends the lifespan of progeroid mice (LmnaG609G/G609G model) while preserving body weight and reducing kyphosis (Bárcena et al., 2024).
- **Clinical Data (Verified Facts):** Phase 2 human trials for acute gout flare demonstrate short-term safety and targeted reduction of joint pain and systemic inflammatory markers with doses up to 2000 mg/day (Jansen et al., 2020).
- **Informed Speculation:** Attenuating baseline inflammaging over a lifespan via NLRP3 suppression will likely delay the onset of multiple age-related morbidities in wild-type models.
- **Knowledge Gaps:** There are currently no long-term lifespan or late-life healthspan data for dapansutrile in genetically heterogeneous, wild-type mammals. The proposed ITP study aims to directly address this deficit.

3. Activity, Dosage, Bioavailability, and Toxicity

Pharmacokinetics: Dapansutrile is orally bioavailable and readily crosses the blood-brain barrier. It has a plasma half-life of approximately 24 hours in humans.

- **Critical ITP Constraint:** Empirical data confirming the stability of dapansutrile during the high heat and pressure pelleting process of standard Purina 5LG6 mouse chow are currently lacking and must be established prior to study initiation.

Toxicity: Short-term clinical and preclinical data indicate adequate tolerability. In Phase 2 human trials, no severe adverse metabolic or hematological changes were observed. However, lifelong toxicity data are absent. The primary theoretical risk is an impaired acute response to specific bacterial or viral pathogens due to chronic IL-1-beta suppression.
Chemical Structure: The compound is a beta-sulfonyl nitrile. Its chemical formula is C14H17NO2S.

4. Suggested Treatment Protocol

Route: Dietary administration via compounded mouse chow.
Dosage Calculation:

- **Target Dose:** 1000 mg/kg/day.
- **Assumptions:** Average adult UM-HET3 mouse body weight is 0.030 kg. Average daily food consumption is 0.004 kg.

Math:

- Daily target mass per mouse: 1000 mg/kg/day * 0.030 kg = 30 mg/day.
- Dietary inclusion rate (parts per million): 30 mg / 0.004 kg = 7500 mg per kg of food, or 7500 ppm.

Start Age: 4 months. The intervention must be lifelong to adequately evaluate its efficacy in preempting the cumulative accumulation of sterile inflammation.
Biomarkers: Target engagement must be empirically verified during the study.

1. **Serum concentration:** Liquid chromatography-tandem mass spectrometry (LC-MS/MS) to quantify circulating dapansutrile.
2. **Pharmacodynamics:** Enzyme-linked immunosorbent assay (ELISA) to measure systemic reductions in IL-1-beta and IL-18 in peripheral blood or tissue homogenates.

5. Cost of a Life-long Intervention Study

Supply: Sigma
Cost per unit: $15.80 per mg.
Budget Calculation (per cohort of 100 mice):

- Daily consumption per mouse: 30 mg.

- Total consumption per day for 100 mice: 3,000 mg (3 grams).
- Duration: 3 years (1095 days).
- Total compound required: 3,285,000 mg (3.285 kilograms).
- **Estimated Cost at Retail:** 3,285,000 mg * $15.80/mg = $51,903,000.

Constraint: Sourcing this compound at retail catalog prices is financially impossible for the ITP budget. Execution of this study strictly requires establishing a Material Transfer Agreement (MTA) with the patent holder (Olatec Therapeutics) to secure industrial-scale quantities, or outsourcing custom bulk synthesis to a Contract Research Organization (CRO), which typically reduces costs by several orders of magnitude.

6. Animal Safety Information

Chronic inhibition of the NLRP3 inflammasome carries a known theoretical risk of blunting acute immune responses to infections. The animal care protocol must incorporate routine screening for opportunistic infections. Technicians should monitor for sudden weight loss or lethargy that may indicate subclinical infection rather than normal aging. Necropsies must clearly distinguish between pathogen-induced mortality and age-related pathology.

7. Statement of Understanding

"I understand all information presented in the proposal can be freely shared with members of the ITP Steering Committee... I understand the ITP intends to submit the results of all ITP-supported studies... regardless if they produce data showing positive or negative effects..."

8. References

1. Lonnemann, N., et al. (2020). "The NLRP3 inflammasome inhibitor OLT1177 rescues cognitive impairment in a mouse model of Alzheimer's disease." *Proceedings of the National Academy of Sciences*, 117(50), 32145-32154. https://www.pnas.org/doi/10.1073/pnas.2009680117
2. Jansen, T., et al. (2020). "Dapansutrile, an oral selective NLRP3 inflammasome inhibitor, for treatment of gout flares: an open-label, dose-adaptive, proof-of-concept, phase 2a trial." *The Lancet Rheumatology*, 2(11), e673-e681. https://pubmed.ncbi.nlm.nih.gov/33005902/
3. Bárcena, C., et al. (2024). "The NLRP3 inhibitor Dapansutrile improves the therapeutic action of lonafarnib on progeroid mice." *Aging Cell*, 23(10), e14290. https://pubmed.ncbi.nlm.nih.gov/39192596/