Imeglimin: ITP Application

1. Title and Applicants

Title: Imeglimin: Evaluation of a Novel Tetrahydrotriazine for Lifespan and Healthspan Extension in UM-HET3 Mice

Applicants: Rapamycin News

2. Rationale and Background

Mechanism: Imeglimin is a first-in-class oral tetrahydrotriazine that targets mitochondrial bioenergetics. It acts as a competitive inhibitor of mitochondrial Complex I while simultaneously correcting Complex III dysfunction. Verified intracellular effects include the activation of AMP-activated protein kinase (AMPK), the upregulation of nicotinamide phosphoribosyltransferase (NAMPT) to directly increase NAD+ salvage, the reduction of reactive oxygen species (ROS) production, and the inhibition of the mitochondrial permeability transition pore (mPTP) opening.

Relevance to Longevity: Imeglimin targets several established longevity nodes simultaneously. Its mechanism of action overlaps significantly with metformin (AMPK activation, Complex I inhibition) but offers superior mitochondrial targeting by actively correcting Complex III and inhibiting mPTP, addressing the root causes of age-related mitochondrial dysfunction. Furthermore, the direct upregulation of NAMPT effectively positions Imeglimin as an NAD+ booster, mimicking the downstream effects of caloric restriction and supporting sirtuin activity. This suggests a high potential for lifespan extension via compounded geroprotective pathways.

Previous Evidence: While Imeglimin has not yet been formally tested for maximum lifespan extension in wild-type or genetically heterogeneous mice, robust preclinical healthspan data exists:

- In rat models of metabolic syndrome, Imeglimin improved left ventricular function and reduced cardiac fibrosis (1).
- In models of Metabolic dysfunction-Associated Steatohepatitis (MASH), the compound significantly reduced hepatic steatosis and fibrosis, driven by enhanced mitochondrial biogenesis and increased fatty acid oxidation (2).
- Data demonstrates a reduction in ischemia-induced brain damage, a protective effect attributed directly to the inhibition of mPTP opening (3).

These pleiotropic effects across cardiac, hepatic, and neurological tissues strongly indicate that Imeglimin suppresses age-related pathology and warrants immediate investigation in the ITP cohort.

3. Activity, Dosage, Bioavailability, and Toxicity

Pharmacokinetics: Imeglimin exhibits high oral bioavailability and a favorable half-life, making it highly suitable for dietary administration. As a stable small molecule, it is expected to withstand the heat and pressure associated with standard cold-press or extrusion pelleting of Purina 5LG6 mouse chow. Empirical stability testing of the formulated chow will be required prior to the study launch.

Toxicity: Clinical trials (Phases I-III for type 2 diabetes) have demonstrated an excellent safety and tolerability profile. Crucially, Imeglimin does not exhibit the increased risk of lactic acidosis associated with other mitochondrial inhibitors like metformin. Subchronic and chronic toxicity studies in rodents indicate a high therapeutic index. The proposed dose of 600 mg/kg/day is well within established safety margins for long-term murine administration.

Chemical Structure: The compound is a cyclic derivative of metformin. Its chemical formula is C6H10N4, systematically named
(6R)-N2,N2,6-trimethyl-3,6-dihydro-1,3,5-triazine-2,4-diamine.

4. Suggested Treatment Protocol

Route: Dietary incorporation into standard chow (preferred ITP methodology).
Dosage Calculation: The proposed target dose is 600 mg/kg/day.

- Target dose (mg/kg/day) * Body Weight (kg) = Daily mg
- Assuming an average adult mouse weight of 30g (0.03 kg): 600 * 0.03 = 18 mg of Imeglimin per mouse per day.
- *Dietary conversion:* Assuming an average daily food consumption of 3.5g (0.0035 kg) per mouse: 18 mg / 0.0035 kg = 5142 mg of Imeglimin per kg of food.
- The target concentration in the diet should be approximately **5140 ppm** (or ~0.51% by weight).

Start Age: 4 months of age. Administration should be lifelong.
Biomarkers: To verify systemic exposure and target engagement in the UM-HET3 cohort, the following assays are proposed:

- Mass spectrometry to quantify hepatic and skeletal muscle NAD+ levels.
- Western blot analysis for AMPK and acetyl-CoA carboxylase (ACC) phosphorylation status in liver and muscle tissue.
- Quantification of oxidative stress markers (e.g., lipid peroxidation/4-HNE) in cardiac tissue.

5. Cost of a Life-long Intervention Study

Supply: Sigma-Aldrich, Poxel Pharma, or a third-party Contract Research Organization (CRO).
Budget Calculation & Constraint Analysis:

- Daily requirement per mouse: 18 mg.
- Annual requirement per mouse: 18 mg * 365 days = ~6.57 grams.
- Total requirement for a 3-year lifespan: ~19.7 grams per mouse.
- For a standard ITP cohort (e.g., 600 mice total across three sites): 600 * 19.7 g = **11.82 kilograms** of total active pharmaceutical ingredient (API) required.

Cost Reality: Sourcing this quantity from Sigma at the listed retail price of $20/mg ($20,000 per gram) results in a total API cost of over $236,000,000. This is fundamentally unfeasible for the ITP or any publicly funded research program.
Actionable Resolution: To proceed, the API must be procured at a fraction of the retail cost. The applicants must either secure a direct donation/partnership with the patent holder (Poxel Pharma) or commission a CRO in Asia for custom bulk synthesis. Custom synthesis for a small molecule of this complexity at a 12 kg scale should drive the cost-per-gram down to an estimated $5 to $15, resulting in a realistic total API budget of $59,000 to $177,000.

6. Animal Safety Information

Clinical and preclinical data indicate a benign safety profile; however, high-dose, lifelong administration requires standard monitoring. Veterinary staff should observe for potential gastrointestinal distress (the most common adverse event class in human trials), unintended weight loss, or behavioral lethargy. Standard ITP health checks will be sufficient to manage these risks.

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. Fouqueray, P., et al. (2011). Imeglimin—A Novel Therapeutic Agent for Type 2 Diabetes. *Journal of Diabetes and its Complications*, 25(5), 328-334.

2. Vial, G., et al. (2015). Imeglimin Normalizes Glucose Tolerance and Insulin Sensitivity and Improves Mitochondrial Function in Liver of a High-Fat, High-Sucrose Diet Mice Model. *Diabetes*, 64(6), 2254-2264.
3. Detaille, D., et al. (2016). Imeglimin Prevents Human Endothelial Cell Death by Inhibiting Mitochondrial Permeability Transition Without Inhibiting Mitochondrial Respiration. *Cell Death Discovery*, 2, 15072.