ORFORGLIPRON CITP Nomination

1. Background and Rationale

Describe concisely the reason why the proposed intervention deserves to be evaluated in Caenorhabditis for potential effects on lifespan and aging phenotypes.

The following questions should be addressed:

• What is the conceptual basis in support of testing this compound in Caenorhabditis?

GLP1 receptor agonists have shown incredible promise for longevity and healthspan but until orforglipron we have only had peptides which require injection which is a serious increase in cost and work to test in animals compared to orally bioavailable compounds.

Now with the advent of orforglipron we have access to a small molecule orally bioavailable GLP1 receptor agonist, and if we can show promising lifespan benefits in worms this will encourage tests to be performed in higher order species.

• What is known about the chemistry of the compound to be tested? -Note that the compound identity/chemical structure must be disclosed to the CITP team.

Orforlipron, aka LY-3502970.

CAS number 2212020-52-3

PubChem CID 137319706

Formula C48H48F2N10O5

Molar mass 882.974 g·mol−1

Elimination half-life 29–49 hours

• What is known about the compound safety profile?

As of now the only known adverse effects are very similar to other GLP1RA, which are gastrointestinal. These are diarrhea, nausea, upset stomach, and constipation. This is usually commensurate to dosage, and as people adjust to a dosage these tend to go away.

• What effects on lifespan, disease(s) of aging, hallmarks of aging, or pathways involved in aging are known?

Assuming this has similar effects to semaglutide, liraglutide and other singular GLP1RA drugs it will impact mTOR and have a wide range of positive metabolic regulatory effects which are correlated with increased longevity and healthspan.

This section should include the following if available:

• Preliminary data showing the ability of the compound to either a) extend lifespan in worm/other model organisms, b) prevent disease in humans/other model organisms, c) target one or more of the hallmarks of aging, d) modulate a biological pathway involved in aging, or e) any other data in support of testing the proposed compound.

- *GLP1RA's improve mitochondrial ATP production by utilizing more glucose and fatty acids, promote the growth and division of mitochondria, reduce ROS and protect against mitochondrial damage. https://doi.org/10.1089/ars.2021.0113*
- *A study on liraglutide showed that it modulated cellular senescence and autophagy which may serve as a potential therapeutic agent for liver cancer. https://doi.org/10.1016/j.ejphar.2017.05.015*
- *Stimulates autophagy by AMPK/mTOR pathway. https://doi.org/10.1152/ajpendo.00195.2019*
- *GLP1 has positive effects on stem cells including proliferation, differentiation, migration and more. https://doi.org/10.1038/nrendo.2009.285*

- *Improves cardiovascular disease risk factors such as dyslipedemia, weight and hypertension. Potentially improves endothelial function and mitigates heart failure. https://doi.org/10.1155/2018/4020492*
- *Improves hypertension https://doi.org/10.1016/j.bbrc.2009.01.003*
- *May have a positive impact on the cognitive impairment brought on by diabetes or obesity, enhancing memory and learning https://doi.org/10.3389/fnins.2019.01112*
- *Long term use of GLP-1 should reduce prostate, colon and lung cancer risk https://doi.org/10.1080/07435800.2021.1955255*
- *Counterintuitively, liraglutide administration combatted skeletal muscle atrophy in rodents, leading to enhanced muscular function https://doi.org/10.1016/j.metabol.2019.154044*
- *Liraglutide reduced cartilage degradation through anti-catabolic effect at in-vitro, and in-vivo it targets cartilage inflammation, its breakdown and reduced pain https://doi.org/10.1038/s41598-022-05323-7*
- *Liraglutide reduced neuroinflammation, decreased AMD symptoms and protected retinal ganglion cells https://doi.org/10.1038/s41598-019-52295-2*
- *Improved cognitive and non-cognitive function within the central nervous system https://doi.org/10.1016/j.bcp.2020.114187*
    - *No association was observed between cognitive changes and alterations in body mass index, blood pressure, or glycemic control. This means these effects were independent. https://doi.org/10.1161 /JAHA.120.020734*
- *Neuronal differentiation and cell proliferation are caused by activating the GLP- 1R signalling pathway https://doi.org/10.1111/j.1471-4159.2010.06731.x and https://doi.org/10.1007/s00018-010-0398-3*
- *GLP-1RA were found to upregulate the expression of both mTOR and neurotrophic tyrosine kinase receptor type 2 (Ntrk2) in the hippocampus of mice fed a high-fat diet. These proteins play crucial roles in regulating LTP and, consequently, synaptic plasticity https://doi.org/10.1016/j.peptides.2014.08.014*
- *By stimulating the production of apurinic/apyrimidinic endonuclease 1 (APE1), activation of the GLP-1 receptor would improve DNA repair https://doi.org/10.7150/thno.15993*
- *GLP-1 reduces cellular senescence and DNA damage brought on by a range of oxidative stressors, mitigates H2O2-induced senescence, and modifies the antioxidant defence system https://doi.org/10.3390/antiox9090846*
- *Stimulation of GLP-1 Receptor Inhibits Methylglyoxal-Induced Mitochondrial Dysfunctions in H9c2 Cardiomyoblasts: Potential Role of Epac/PI3K/Akt Pathway https://pmc.ncbi.nlm.nih.gov/articles/PMC7274035/*
- *Cellular senescence is modulated by the DPP4-GLP-1 axis via the AMPK/SIRT1/ FOXO3a pathway https://doi.org/10.1038/s41392-021-00528-0*

• If data are unpublished, include enough information to permit its evaluation.

Though data specific to Orforglipron and longevity is currently lacking as it is still in clinical trials the GLP1RA class of drugs has more than enough promising scientifically validated longevity and healthspan data to warrant lifespan testing of its first small molecule orally bioavailable form.

2. Suggested Treatment Information

Provide a detailed description of and rationale for the proposed treatment. The following questions should be addressed:

• Is the compound soluble in water? If not, what solvent should be used and what should be the final dilution of the solvent? What are the recommended storage conditions for the stock and working solutions?

Direct water solubility data in published literature are not available as of now.

Commercial vendor data (e.g., SelleckChem) suggest Orforglipron is insoluble or poorly soluble in both water and ethanol at typical concentrations, with stock solutions often prepared in DMSO.

Final working concentrations in biological assays should keep DMSO ≤ 0.1 % to minimize solvent toxicity in Caenorhabditis.

• How stable is the compound in solution at room temperature (CITP testing is performed at or above 20°C)? Is it sensitive to light or heat?

No official data exists on stability. Suggested to store powder in airtight containers away from moisture, light and heat until it is mixed with solvent for study.

The fact that it is small molecule implies a reasonable room temperature stability.

• Is the median effective dose (ED50) in human or in animal models known?

There is currently no established ED50 in human or animal models. 0.1 to 10 mg/kg orally produced measurable glucose-lowering effects in mice and this range can be used as the basis for selecting C. elegans test concentrations.

• What dose(s) are recommended for testing?

• 1 µM
• 5 µM
• 10 µM
• 25 µM
• 50 µM

• Is there an assay to monitor the predicted effect of the intervention in Caenorhabditis? If the test requires specialized expertise or equipment, is this available in the compound nominator's laboratory?

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3. Toxicity

Describe what is known about potential harmful effects of the treatment in Caenorhabditis, including toxicity data obtained with doses of the compound other than the one(s) proposed for testing, or obtained when testing similar compounds. Note that if during the pilot/early phases of the CITP pipeline toxicity is observed in Caenorhabditis on plates at all concentrations tested, the testing will be terminated.

• If pilot toxicity data is available, describe the experimental conditions and any harmful side effects noted.

Worm studies have not been performed with Orforglipron. All studies have been in mice, primates and humans.

• Include information on the modality under which the side effect was observed (e.g., immediate or delayed), whether a dose reduction or more frequent dosing ameliorated the side effect (e.g., by preventing the accumulation of toxic metabolites).

NA

• Are the median toxic dose (TD50) and/or median lethal dose (LD50) in human or in animal models known?

No.

Clinical trial safety data do not report any deaths or serious adverse events attributed to Orforglipron at doses up to 24 mg daily in healthy adults, or at higher doses in type 2 diabetes patients, but they discuss mainly gastrointestinal side effects.

4. Costs

The CITP covers all costs for testing and statistical analysis. It also includes a limited budget for purchase or costshared purchase of test compounds. The following should be addressed in this section:

• What is the recommended source of the compound to be tested? If available commercially, which supplier(s) are suggested and why?

This is more affordable: https://invivochem.net/glp-1-receptor-agonist-1.html

Other options: https://www.medchemexpress.com/orforglipron.html

Other options: https://www.selleckchem.com/products/orforglipron-ly3502970.html

• If the compound can be purchased from commercial sources, provide an estimate of the cost of obtaining a sufficient supply to complete the test at all three CITP testing sites. Consider that the CITP will need to prepare a volume of approximately 350 ml of stock solution over the course of the study.

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• If the compound is not available commercially and cannot be provided to the CITP without charge, provide a cost estimate for a sufficient supply of the compound to test, and indicate if you can cover the cost in full or in part.

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