opnMe by Boehringer Ingelheim

opn2EXPERTS – Harness futile cycles to find new anti-obesity approaches

Question How would you propose to identify and characterize novel futile cycle molecular mechanisms to counteract obesity, using innovative *in vitro* assay systems, or *in vivo* models?

Answers to this question including a proposal for collaboration can only be considered if they arrive no later than December 16, 2023, 11:59 pm PST.

Boehringer Ingelheim

Table of contents

What is the context of the problem that we would like to solve?

Obesity is a serious medical condition characterized by excess adiposity that affects 39% of the adult population worldwide, resulting in numerous comorbidities that reduce lifespan. Unfortunately, lifestyle interventions like diet and exercise often fail to sustain long-term weight loss. Thermodynamically, obesity occurs due to an imbalance in energy homeostasis due to increased energy intake and/or reduced energy expenditure. Currently, the most effective anti-obesity medications are glucagon-like-peptide (GLP-1) receptor agonists (semaglutide, tirzepatide) which have centrally mediated satiety effects, reducing food intake. While promising, these drugs' unfavorable gastrointestinal side-effects limit their widespread use[1]. Furthermore, these drugs do not increase energy expenditure, which remains an attractive physiological mechanism for counteracting obesity. Recently, the pancreatic peptide glucagon was shown to increase energy expenditure, demonstrating the pharmacological feasibility of exploiting energy expenditure mechanisms for obesity[2].

Futile cycles are metabolic reactions whereby the products of one step are substrates in the subsequent step, which occur in a cycle until the original substrate is regenerated. One or more steps in these reactions can consume ATP, and result in the net utilization of energy. Thus, futile cycles offer an attractive strategy to target energy-expending mechanisms to treat obesity that are independent of mitochondrial uncoupling. Examples of futile cycles include glycolysis/gluconeogenesis, the Cori cycle, and the glycerolipid-free fatty acid cycle[3].

Based on the urgent need to introduce new approaches for treating obesity, there is high interest in identifying and characterizing novel targets (genes, proteins, or pathways) that act through futile cycle mechanisms to increase energy expenditure, and result in weight loss.

What potential solutions could be in scope?

- Novel, innovative in vitro models/assay systems that enable the identification and/or validation of potential inter- or intracellular modulators (genes, proteins, pathways) of futile cycles that could be developed into anti-obesity therapies.
- Studies leveraging human tissue and -omics approaches to identify or characterize novel futile cycle mechanisms.
- Approaches ranging from biological matrices such as primary cells, cell lines, organoids, fluids, and tissues to animal studies (including rodents, pigs, or other mammalian species) with comments on translatability to humans provided.
- Any already identified futile cycling targets which are not yet public or described in the context of obesity, provided they have translatability to humans with clear evidence in metabolically relevant cellular or animal models.

What potential solutions would be out of scope?

- Approaches that are not based on testable hypothesis, e.g. proposals that are purely based on technologies that require upfront substantial establishment and validation (no previous hands-on experience).
- Repurposing existing therapies or combinations with GLP-1-based therapies (semaglutide).
- Proposals referring to well-studied futile cycle targets (e.g., SERCA, creatine kinase, miR-378).
- Proposals that are mitochondrial membrane potential-dependent (such as mitochondrial uncoupling/UCP-1).
- Proposals that focus on known chemical uncouplers such as 2,4-dinitrophenol (DNP).
- Proposals focusing on models from non-human species that lack a clear link to the human disease condition.
- Purely computational approaches.

What benefits do we offer to you in exchange for having submitted a solution?

If your project is selected, you will have the opportunity to directly collaborate with the Cardiometabolic Diseases Research team of Boehringer Ingelheim. You can expect appropriate funding for the prospective collaboration period. Your exact funding request should be outlined in your proposal. As a framework, we suggest that your initial funding request is structured in milestones and does not exceed 200,000 euros per submitted project in total (including direct, indirect, and overhead costs).

Our collaboration agreement will provide full transparency about each partner's rights & obligations (including intellectual property rights). As part of the agreement, you will be encouraged to publish following the collaboration agreement (to be negotiated in good faith).

To maintain the highest degree possible in an open innovation environment, we plan to announce the winner(s) publicly and feature them on opnMe.com and our social media channels.

What are the key success criteria on which we base our selection for the best answer?

We are seeking research collaboration proposals that contain:

- A well-structured proposal outlining a new and compelling scientific approach including an experimental plan that will be used to test your hypothesis.
- A novel, testable working hypothesis distinct from those previously published.

- A thorough validation that includes an in-depth analysis package consisting of biochemical, and biophysical analyses.
- Outlining of the technical feasibility, and potentially existing data or previous publications that support feasibility / experience with outlined technology, based on existing techniques and established assays.
- Potentially includes (non-confidential) existing data and results.
- Your exact funding request should be outlined in your proposal based on a well-thought-through project. The project should be structured in milestones and planned with key decision points (clear Go/No-Go criteria). The funding request for the initial milestones resulting in a Go/No-Go decision should not exceed 200,000 euros per submitted project in total.
- Proven track record in the required field of expertise.
- Ability to implement the outlined solution as part of a scientific collaboration project with Boehringer Ingelheim including access to a laboratory.
- Anything considerably longer than 2 years will be excluded.

What information should be included in your answer submission?

Please use our answer submission template to provide a 2–3 page non-confidential proposal (available for download on the following site).

If confidential data exists that would strengthen the proposal, please indicate that information is available to share under a Confidential Disclosure Agreement (CDA). If we find the non-confidential concept proposal sufficiently interesting, we will execute a CDA for confidential discussions.

Anticipated Project Phases or Project Plan

Phase 1	Please complete your submission by **December 16, 2023, 11:59 pm PST at** the very latest.
Phase 2	Our review of all proposals will be completed around mid-February 2024 and scientists will be informed after that.
Phase 3	Potential collaboration starting date in Q2/2024.

Submitting a collaboration proposal

- Check the outline of the opn2EXPERTS "Harness futile cycles to find new anti-obesity approaches" on opnMe.
- Alternatively, you may click the "Get Submission Template" banner to access the material transfer template.
- Follow the instructions to upload your submission document (requires login or registration).
- The upload allows you to attach additional application files if desired.
- You will be able to access your final submitted collaboration proposal in your personal dashboard and follow its review status.
- Please also visit the FAQ section on opnMe.com to learn more about our opn2EXPERTS program.

References

1. Wilding J. P. H., Batterham R. L., Calanna S., Davies M., Van Gaal L. F., Lingvay I., McGowan B. M., Rosenstock J., Tran M. T. D., Wadden T. A., Wharton S., Yokote K., Zeuthen N., Kushner R. F., STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity *N Engl J Med*. **2021**, 384(11):989-1002. Epub 2021 Feb 10. DOI: 10.1056/NEJMoa2032183, PubMed.
2. Kleinert M., Sachs S., Habegger K. M., Hofmann S. M., Müller T. D. Glucagon Regulation of Energy Expenditure. *Int J Mol Sci.* **2019**, 20(21):5407. DOI: 10.3390/ijms20215407, PubMed.
3. Brownstein A. J., Veliova M., Acin-Perez R., Liesa M., Shirihai O. S. ATP-consuming futile cycles as energy dissipating mechanisms to counteract obesity. *Rev Endocr Metab Disord.* **2022**, 23(1):121-131. Epub 2021 Nov 6. DOI: 10.1007/s11154-021-09690-w, PubMed.