Engineering enzyme replacement therapies for Mucopolysaccharidosis Type IV

Abstract

Metabolic enzymatic deficiencies (MEDs) disrupt cell physiology, either by preventing the production of essential metabolic intermediates or by causing the accumulation of toxic levels of substrates. Lysosomal storage diseases (LSDs) are among the most devastating MEDs [Parenti et al., EMBO Mol. Med., 2021]; they are caused by the deficiency of enzymes responsible for the catabolism of lipids and glycoproteins, which lead to irreversible damage of many organs. Enzyme inactivation is caused by inherited loss-of-function mutations; thus, they cannot be cured, but they can be treated using Enzyme Replacement Therapies (ERTs), which consist in the injection of a recombinant version of the affected enzymes into patients [Brady, Lancet, 2004].

ERTs are currently standard of care for many LSDs, including Gaucher's and Fabry disease, but are not yet available for many others. In fact, developing ERTs is challenging, since enzymes are less catalytically active in blood, can cause immune response, have poor cellular uptake, and are extremely expensive to manufacture. For example, current treatment for Mucopolysaccharidosis Type IV A (MPS IVA), an LSD causing life threatening muscoskeletal alterations, can cost up to $6M per year per patient. Taken together, these factors are currently limiting the number of treatments available and have unsustainable costs for patients and many healthcare systems.

Research challenge

Here we want to engineer new therapies for MPSIVA using generative artificial intelligence and engineering biology. Our goal is to design, build and test new, recombinant galactosamine (N-acetyl)-6-sulfatase (GALNS) enzymes in Chinese Hamster Ovary (CHO) cell lines, as a more effective and sustainable treatment for MPS IV. The project will be part of the broader program of the Stracquadanio lab on engineering ERTs for LSDs [Lobzaev et al, 2022] and will be part of the Engineered Genetic Control Systems for Advanced Therapeutics Hub at the University of Edinburgh, and in close collaboration with Dr Eve Miller-Hodges, a world-renown clinical expert in LSDs and leading the Inherited Metabolic Disease clinic in Scotland.

Data and Methodology

The student will develop generative artificial intelligence models, either diffusion or variational autoencoder models, using sequence and structural information from large biological databases (e.g. Uniprot, PDB) to generate variants for downstream computational validation (e.g. structure prediction, molecular dynamics analysis) and laboratory testing.

RRI/Ethical considerations

There are no RRI or ethical concerns to carry out the project but, importantly, we will seek feedback from patients, as part of the Edinburgh Kidney Network, to inform and explain how AI can help the drug discovery process, especially for underfunded, low prevalence diseases, like LSDs.

Expected outcome and impact

The student will receive training in generative and geometric deep learning, protein language models as well as bioinformatics methods to analyse proteomic datasets. Computational training will be complemented with wetlab experience, if desired, including mammalian cell culture and enzyme analysis techniques. The student will also learn how to write reproducible scientific pipelines and research software. We expect the successful candidate to build a competitive profile in machine learning and protein engineering, which ultimately will support a career in academia or industry.

We will finally seek advice from Edinburgh Innovation (EI) to protect any new enzyme with therapeutic potential that might be discovered during the project.

References:

- Parenti, Giancarlo, et al. "The rapidly evolving view of lysosomal storage diseases." *EMBO molecular medicine* (2021).
- Brady, Shiffman. Enzyme-replacement therapy for metabolic storage disorders. The Lancet Neurology, 2004.
- Lobzaev, Evgenii, et al. "Designing human Sphingosine-1-phosphate lyases using a temporal Dirichlet variational autoencoder." bioRxiv (2022).