Medical University of Graz

Discovery of allosteric positive modulators for the treatment of mannosidosis

Summary

Otto Loewi Research Center (Physiological Chemistry), Medical University of Graz

Supervisor:	Dr. Pedro Alejandro Sanchez Murcia
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 15, 2022 00:00 and March 28, 2022 23:59 (Europe/Zurich)

Description

Background:

Human lysosomal a-mannosidosis and b-mannosidase are hydrolases responsible for breaking down terminal mannose residues attached to glycoproteins. Their deficiency leads to toxic mannose-riched oligosaccharide accumulation in the lysosome, what causes cell malfunctioning -eventually apoptosis- damaging tissues, and leading to characteristic pathological manifestations of different severity levels. These conditions are known as a- or b-mannosidosis[1,2] and are included in the family of lysosomal storage disorders (LSD). There is no cure for mannosidosis so far. Therapies like bone marrow transplantation (BMT) and enzyme replacement therapy (ERT) have been reported to relieve the symptoms in mannosidosis. However, possible benefits of BMT must be weighed against the risk of morbidity and mortality,[3] and ERT requires lifelong infusions, which can lead to autoimmune responses.[4] In addition, a recombinant enzyme as drug may not be properly distributed in the body, especially in tissues that are poorly vascularized or protected by a barrier. Besides that, BMT and ERT are expensive and involve specific hospital infrastructures, something only affordable in developed countries. Therefore, new effective therapeutic approaches are needed to treat mannosidosis.

Hypothesis and Objectives:

This PhD project is framed within our research line of **discovery** and **validation** of **small chemical molecules** as **positive allosteric modulators** of defective **human lysosomal a- and b- mannosidases** in order to rescue their activity.

Methodology:

The succesfull PhD candidate will join the wet-lab of our multidisciplinary research group (Computer-Aided Molecular Design Lab, CAMDgraz). The selected candidate will work back-to-back with our computational team. Her/his **PhD-thesis** will deal with the **screening** of **novel compounds as positive allosteric modulators** of the human lysosomal a- and b-mannosidases. In particular, the PhD candidate will be responsible of the **expression** and **purification** of the native proteins and the mannosidosis-relevant defective variants. She/he will lead and develop **enzyme** and **phenotypic screening assays** to mesure the effect of these modulators on the mannosidase activity. Computational techniques like molecular docking, molecular dynamics simulations and free energy calculations will broad her/his PhD training.

References:

[1] L. Borgwardt, A. M. Lund, C. I. Dali, *Pediatr. Endocrinol. Rev.* **2014**, *12 Suppl 1*, 185–191.

[2] D. A. Wenger, E. Sujansky, P. V Fennessey, J. N. Thompson, *N. Engl. J. Med.* **1986**, *315*, 1201–1205.

[3] D. Malm, Ø. Nilssen, *Orphanet J. Rare Dis.* **2008**, *3*, 1–10.

[4] M. Coutinho, J. Santos, S. Alves, *Int. J. Mol. Sci.* **2016**, *17*, 1065.

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