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Discovery of positive allosteric modulators for the treatment of mannosidosis

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Alpha-mannosidosis (MANSA) is a human genetic disease characterized by a deficiency in the lysosomal ?-mannosidase. Three major clinical subtypes exist from a mild form showing skeletal abnormalities, myopathy, and slow progression to severe form manifesting as prenatal loss or early death. MANSA belongs to the lysosomal storage disorders (LSDs) and there is no cure for it. The two available treatments so far are bone marrow transplantation (BMT) and enzyme replacement therapy (ERT). However, they are not without drawbacks and can cause serious complications. Thus, novel therapeutic options are urgently needed. MANSA is caused due to the expression of defective human lysosomal ? -mannosidase (hLAMAN) variants. hLAMAN catalyzes the cleavage of end-terminal mannosidic linkages ?(1?2), ?(1?3), and ?(1?6) from glycoproteins. The main goal of my PhD project is the discovery of small molecules (positive allosteric modulators) to rescue the activity of defective hLAMAN variants within the lysosome as a novel therapeutic approach. I will present the first work package of my PhD project, where the wild-type hLAMAN and the three MANSA-relevant defective variants D159N, R229W, and E402K will be expressed in Origami E. coli 2(DE3) and Komagataella phaffii (aka. Pichia pastoris) X33 cells and purified using liquid chromatography. One of the main open scientific questions is the impact of the glycosylation in the expressed hLAMAN variants on the standardized enzymatic assay as well as the setup of the in vitro screening platform. Further workpackages will involve the screening of chemical libraries previously identified in silico on the in vitro activity of hLAMAN variants and on the binding to the enzyme.. Additionally, we will collaborate to determine the 3D structure of hLAMAN in complex the best candidates. Overall, this project is committed to discover for the first time positive allosteric modulators of hLAMAN to rescue the enzymatic activity in defective variants.