Targeting alpha-L-iduronidase against mucopolysaccharidosis type I

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Mucopolysaccharidosis type I (MPS I) is a rare autosomal recessive lysosomal storage disorder caused by mutations in the **IDUA** gene, which encodes α-L-iduronidase.[1] This enzyme degrades glycosaminoglycans (GAGs) like dermatan and heparan sulfate.[2] Enzymatic deficiency leads to GAG accumulation in lysosomes, disrupting cellular function and causing multisystemic damage with clinical severity ranging from mild to severe.[3]

MPS I is classified into three phenotypes: Hurler syndrome (severe), Hurler-Scheie syndrome (intermediate), and Scheie syndrome (attenuated). Severe forms involve early neurodegeneration, skeletal abnormalities, and early mortality, while attenuated forms present later with milder symptoms like joint stiffness, corneal clouding, and cardiac issues, allowing longer life expectancy.

Among pathogenic IDUA variants, **L490P** and **P533R** are commonly linked to attenuated forms (Hurler-Scheie and Scheie). These mutations retain partial α-L-iduronidase activity, reducing systemic severity but still causing subtle neurological impairments, such as cognitive delays and attention deficits, due to GAG accumulation in the central nervous system (CNS).[3]

Current treatments, including enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT), manage somatic symptoms but are less effective for CNS involvement due to limited enzyme penetration across the blood-brain barrier (BBB). Emerging therapies like improved ERT and gene therapy (GT) offer promise but remain expensive and require further validation for MPS I.

We employed molecular docking calculations on the catalytic site of the protein to guide medicinal chemists into synthesizing weak inhibitors that would act as 1st generation pharmacological chaperons (PC). In parallel, molecular dynamics (MD) simulations were conducted to contrast the wild-type protein with the **L490P** and **P533R** mutants, aiming to uncover eventual micro-switches that lead to the misfolding of the protein. We are currently investigating these structural mechanisms to understand them from a structural point of view, and we hope to identify druggable cavities that we can target to stabilize the protein in an enzymatically active state using 2nd generation PCs.

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