SYNTHESIS AND EVALUATION OF MULTIVALENT CHAPERONES AGAINST POMPE DISEASE

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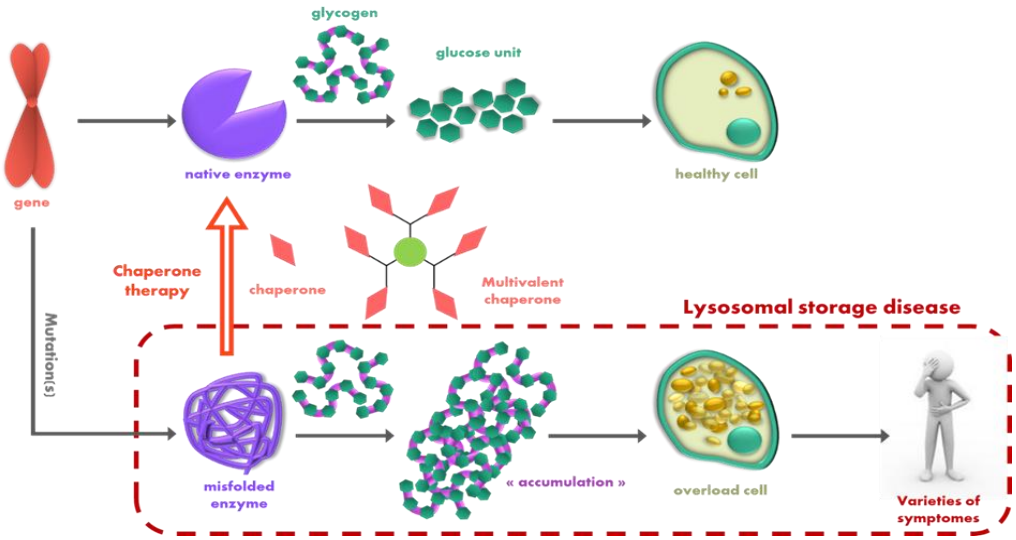
Lysosomal storage diseases (LSDs) are genetic disorders caused by defects in the activity of lysosomal proteins leading to an accumulation of metabolites in the lysosomes. Among them, Pompe disease (PD), caused by mutations in the *GAA* gene, results in a deficiency of acid alpha-glucosidase (GAA).[1] These mutations result in protein misfolding and early degradation by the proteasome. GAA catalyzes the hydrolysis of glycogen in the lysosomes, and the accumulation of glycogen leads to a variety of symptoms that can result in death (see figure below).

Recently, pharmacological chaperone therapy has emerged as a new therapeutic strategy through the use of so-called "chaperone" molecules that allow the correct folding and stabilization of the deficient enzyme in order to restore its activity.[2] Only a few pharmacological chaperones for GAA have been identified to date and most are competitive inhibitors of the enzyme. The synthesis of new multivalent chaperones is the method used to restore the enzyme activity. This strategy has already been developed for Gaucher disease[3], the most common LSD, but has never been explored for PD. Multivalent objects carrying several identical or different chaperone units of the protein will be prepared by click chemistry.

Among the small variety of pharmacological chaperones (almost exclusively inhibitory) of GAA listed, one family stands out for their activities, the imminosugars, widely studied for their inhibitory activities towards glycosidases, and more particularly the D-DNJ (D-deoxynojirimycin) derivatives. Recently its enantiomer, L-DNJ, has been shown to be a non-inhibitory chaperone (unlike the D-form) of GAA.[4] Multivalent derivatives were therefore synthesized, and their activities evaluated.

In 2017, a small molecule NAC (N-acetylcysteine) was co-crystallized in the presence of rhGAA and showed the existence of two "allosteric" sites of the enzyme. Multivalent analogues were therefore also synthesized, and their activities evaluated.



References

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