*Talk*


# Inhibitors and effectors of the glycosidases as therapeutic tools

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## ABSTRACT

**Motivation:** The lysosomal storage disorders (LSDs) conforms a group of over fifty monogenetic diseases characterized by the dysfunction of a lysosomal enzyme, frequently a glycosidase, and the subsequent accumulation of the corresponding substrate, which gives rise to several pathological manifestations. Individually they are rare diseases, but taken together they affect at 1 in 7,000 newborns. For some of these conditions enzyme replacement and/or substrate reduction therapeutic strategies (ERT and SRT, respectively) are available. Yet, most LSDs course with neurological deterioration and are refractory to ERT and SRT, remaining orphan diseases, sice the respective active principles are unable to cros the blood brain barrier (BBB). Ironically, in most of the LSD patients the causative mutation leads to the expression of a mutated ezyme that retains catalytic activity, but it is unable to properly fold at the endoplasmic reticulum (ER) and undertake the secretory pathway to the lysosome. Small molecules capable of promoting the correct folding and restore traficking, termed pharmacological chaperones (PCs), represents therefore a promising therapeutic option that is, in principle, better suited than ERT and SRT to target the neuronopathic forms.

**Methods:** We have conducted research aiming at developing active site-directed pharmacologial chaperones for several LSDs based on glycomimetics (sugar lookaalikes). The molecular design implies a nitrogen-in-the-ring cycle bearing a hydroxylation profile that matches that of the monosaccharide cleave off by the target enzyme (Sánchez-Fernández et al. 2016). Such compounds can sit at the active site of the glycosidase, behaving as competitive inhibitors, subsequently inducing proper folding and trafficking. The chaperones are further elaborated to make them dissociate from the chaperone:enzyme complex at the lysosome, allowing substrate processing (Mena-Barragán et al. 2015).

**Results:** PCs acting as glycosidase effectors in Gaucher, Fabry and GM1 gangliosidosis LSDs have been prepared based on the above concept.

**Conclusions:** The ability of the PCs to cross the (BBB) and revert the accumulus of the substrate in the brain tissue (Takai et al. 2013) supports the promise of pharmacological chaperone therapy for a range of LSDs with neurological implications.

## REFERENCES

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