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# AN INTEGRATED APPROACH TO TACKLE FABRY DISEASE

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**Pharmacological therapy with small molecules is a transversal approach and can be applied when instability of a protein is the first cause of pathology. Small molecules can act by direct interaction with the affected protein, and in this case are defined pharmacological chaperones or stabilizing mutants indirectly. A large proportion of Fabry mutations destabilize lysosomal α-galactosidase (AGAL). A pharmacological chaperone, 1-deoxygalactonojirimycin, is already in clinical trial. In order to test the effects of drugs on different mutations, a cell based assay has been developed. Expression vectors encoding mutant AGAL are transiently transfected into mammalian cells and the residual activity of the enzyme is measured in the extracts of cells that had been treated or not treated with the drug. These data offer the unique possibility of associating a numerical value that correlates to the severity of the damage to hundreds of mutations. 1-deoxygalactonojirimycin is a promising drug, but, regrettably, it is an inhibitor of the enzyme. The therapy needs a precise regimen to balance the stabilizing effect of the drug, which is required, versus the inhibitory effect, which is detrimental. Allosteric ligands might act as pharmacological chaperones, and in this case they might prove to be more effective than reversible inhibitors, since they would play their stabilising action without competing with the natural substrate. A pilot study of our laboratory demonstrated that non inhibitory small molecules can be found for Fabry disease.**

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