Acid ceramidase inhibition as a mechanism to treat lysosomal storage disorders

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Lysosomal storage disorders (LSDs) are complex neurodegenerative disorders characterised by an abnormal build-up of toxic materials within lysosomes as a result of lysosomal enzyme defects. Due to the complex nature of these disorders, currently, there are no available treatments for the majority of LSDs. Acid ceramidase (ACase), a lipid hydrolase that cleaves ceramide, contributes to the pathology of LSDs by deacylating accumulating glycosphingolipids into lyso-glycosphingolipids, which are potent signalling lipids and are toxic to cells. Therefore, ACase makes a promising therapeutic target as a potential treatment for LSDs. The chemotherapeutic drug Carmofur is a potent, covalent inhibitor of ACase, however it is unsuitable as a treatment for LSDs as over-inhibition of ACase causes the development of Farber disease – an aggressive LSD. Therefore, our aim is to inhibit ACase to an extent that can alleviate the lysosphingolipid-induced pathology, but not induce Farber disease. We aim to do this by developing a non-covalent inhibitor of ACase. After establishing a fluorescent ACase activity assay in-house, we have tested numerous in house compounds for ACase inhibition. Currently, our most promising compound (compound A), inhibits ACase with an IC_{50} of 45 nM. Preliminary biophysical characterisation has also shown that compound A is a non covalent inhibitor of ACase. Compound A provides a promising starting point to find a compound that will inhibit ACase via a mechanism suitable for treating LSDs. Further work, including crystallisation of ACase and compound A, will help discover more potent and specific inhibitors of ACase for onward development towards the first therapy for several life-shortening and life-limiting LSDs.