# β-D-ARABINOFURANOSYL CYCLITOL AZIRIDINES AS FIRST-IN-CLASS COVALENT AND SELECTIVE GBA2-BINDING SCAFFOLD

Rob F. Lammers, Qin Su, Max Louwerse, Johannes M.F.G. Aerts, Marta Artola

Department of Medical Biochemistry, Leiden Institute of Chemistry, Leiden University,
P. O. Box 9502, 2300 RA Leiden, the Netherlands
r.f.lammers@lic.leidenuniv.nl

Non-lysosomal glucocerebrosidase (GBA2) is a retaining β-glucosidase involved in glucosylceramide metabolism and cellular homeostasis. Although it is known that homozygous mutations in the GBA1 gene coding for the closely related lysosomal glucocerebrosidase GBA1 causes Gaucher disease, the relation between GBA2 and this disease remains poorly understood. In an attempt to find the first selective covalent GBA2 inhibitors, we screened our cyclitol aziridine-based ABP library as conformationally restricted cyclitols, armed with an electrophilic warhead suitable to intercept the Koshland double-displacement mechanism of GBA2. To our delight, we found that β-D-arabinofuranosyl cyclitol aziridines are selective and covalent GBA2 inhibitors. We harnessed this β-D-arabinofuranosyl cyclitol aziridine scaffold to develop new selective probes for visualizing GBA2 using confocal microscopy in cellular environments (Figure 1A) [1]. By connecting these cyclitol aziridines to lipophilic aglycons, we generated several potent and selective mechanism-based GBA2 inhibitors (Figure 1B). Finally, we connected several E3 ligase ligands to this scaffold using different linker lengths aiming to cause degradation of GBA2, a technique called proteolysis-targeting chimeras (Figure 1C). In summary, the new research tools presented herein hold promise for advancing our understanding of this enigmatic enzyme and exploring potential clinical applications.

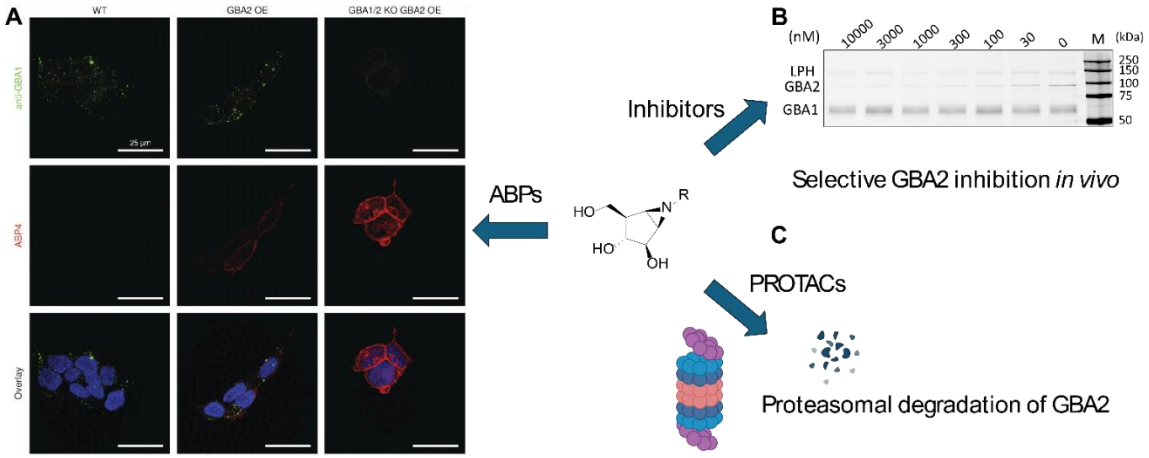


**Figure 1.** Exploitation of β-D-arabinofuranosyl cyclitol aziridine scaffold. **A**: Cellular imaging of GBA2 using ABPs. **B**: Selective inhibition of GBA2 in zebrafish embryos. **C**: PROTACs.

**References:**

1. Q. Su, M. Louwerse, R.F. Lammers, E. Maurits, M. Janssen, R.G. Boot, V. Borlandelli, W.A. Offen, D. Linzel, S.P. Schröder, G.J. Davies, H.S. Overkleeft, M. Artola, J.M.F.G. Aerts. *Chem. Sci.* **2024**, *15*, 15212-15220.