STRUCTURE-ACTIVITY RELATIONSHIP OF MODIFIED AMPHIPHILIC CATIONIC CYCLODEXTRINS FOR RNA DELIVERY

Kristóf Felegyi[a], Francisca Soares[b], Miguel Ramôa[b], Tamás Sohajda[a], Piotr S. Kowalski[b], Milo Malanga[a], Caitriona M. O'Driscoll[b]

[a] CarboHyde Zrt, Berlini street 47-49. Budapest, Hungary
milo.malanga@carbohyde.com
[b] School of Pharmacy, University of College Cork, Ireland

The success of mRNA vaccines has validated RNA-based therapies for non-infectious diseases as well like neurodegenerative and inflammatory disorders. While viral vectors are common, safety and scalability concerns drive the search for non-viral alternatives. Lipid nanoparticles excel in liver delivery, but broader use demands novel biomaterials for RNA stability and efficient targeting [1].

Cyclodextrins (CDs), cyclic oligosaccharides with tunable chemical properties, offer a promising platform for RNA delivery (Figure 1). A library of amphiphilic CDs was synthesized and systematically modified to enhance stability and gene delivery efficiency. Structural variations including modifications in lipid tail length, branching, ionizable group substitution (primary vs. tertiary amines), and linker chemistry. The resulting compounds were characterized using nuclear magnetic resonance spectroscopy and mass spectrometry, confirming successful synthesis.

As part of the GENEGUT project, these modified CDs were screened for physicochemical properties and gene silencing efficiency in undifferentiated and differentiated Caco-2 cell models. The four most effective candidates were selected for further evaluation in biorelevant media, assessing their resistance to enzymatic degradation and potential for oral RNA delivery.

Our findings establish amphiphilic CDs as a viable alternative to conventional nanocarriers, with implications for non-viral gene therapy applications.

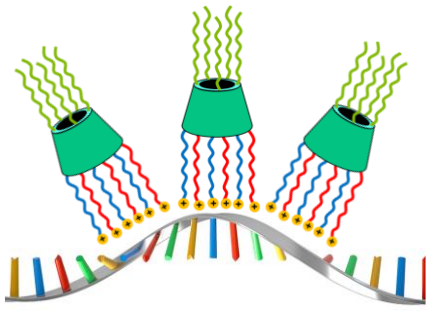

Figure 1. Cyclodextrin-Nucleic Acid complex.

Acknowledgements: Funded by the European Union (GENEGUT, GA 101057491).

References:

1. J. R. Androsavich, *Nature Rev. Drug Discov.* 2024, 23, 421–444.