4"-O-ALKYLATED α-GALACTOSYLCERAMIDE ANALOGUES AS *i*NKT-CELL ANTIGENS: SYNTHETIC, BIOLOGICAL AND STRUCTURAL STUDIES

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INTRODUCTION

 α -Galactosylceramide (α -GalCer or KRN7000; 1), an optimized synthetic analogue of selected agelasphins that were isolated from the marine sponge *Agelas mauritianus*,¹ is an antigenic glycolipid acting as a bridging element between CD1d and the T-cell receptor (TCR) of *I*NKT-cells, thereby forming a ternary complex.² This leads to the release of cytokines by this subset of T-



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Typically, *i*NKT-cells secrete two types of cytokines: Th1- and Th2-cytokines. Since these two types antagonize each other, clinical effectiveness of α -GalCer is limited and, thus, research for analogues with an improved cytokine release profile proves to be highly important. Although a lot of α -GalCer analogues have been disclosed in literature, and consequently the SAR of the majority of this glycolipid has been established, the importance of the 4"-OH functionality remains understudied.³



SYNTHESIS OF THE ANALOGUES⁴

CYTOKINE DATA (MICE)

- Intraperitoneal injection in male C57BL/6 mice
- Kinetic cytokine measurements (ELISA) for selected set
- Lower antigenicity as compared to α-GalCer
- Th1-skewing response by aromatic modifications

PROTEIN CRYSTALLOGRAPHY

- High-resolution crystal data of ternary complex
- Conserved binding mode as compared to α -GalCer
- Loss of hydrogen bond with 4"-O
- Benzyl-type modifications: extra Van der Waals interaction with Gly155 (CD1d)

CONCLUSIONS

- Fast diversification of common precursor (2)
- Th1-response in mice favoured by benzyl moieties at the 4"-position
- Loss of hydrogen bond partly compensated by Van der Waals interaction with glycine residue

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Ghent University and the Research Foundation Flanders (FWO) are acknowledged for financial support to this research.