Center for Strategic Prophylaxis and Vaccine Development

Novel class of superior Th1 polarizing glycolipids valuable as vaccine adjuvant or adjuvant therapy in oncology

Technology

Potent alfa galactosyl ceramide analogues targeting invariant natural killer T-cells (iNKT) for selective boosting of cellular immunity.

Introduction

Invariant natural killer T cells (iNKT) are a unique subset of peripheral blood cells that play a **pivotal role in the activation of the adaptive immune system** through the rapid release of Th1 and Th2 cytokines. This cytokine release is initiated by the interaction of the T cell receptors (TCR) of iNKT cells with an MHC class I-like molecule (CD1d) on antigen-presenting cells (e.g. dendritic cells (DC)) complexed with self- and foreign lipids and glycolipids.

The prototypical **antigen for iNKT cells** is α-galactosyl ceramide (aGalCer or KRN7000), a synthetic analogue of glycolipids originally isolated from a sponge.

This compound has sparked drug discovery efforts to identify analogues capable of skewing the adaptive immune response in a Th1 or Th2 direction (“polarisation”).

Team

The groups of Prof. Serge Van Calenbergh (Ghent University, Medicinal Chemistry) and Prof. Dirk Elewaut (Ghent University Hospital, Molecular Immunology) have extensive experience in the development of innovative aGalCer analogues with a clinical focus. They identified a novel class of **aGalCer analogues with a superior Th1-skewing profile**.

Proof of concept

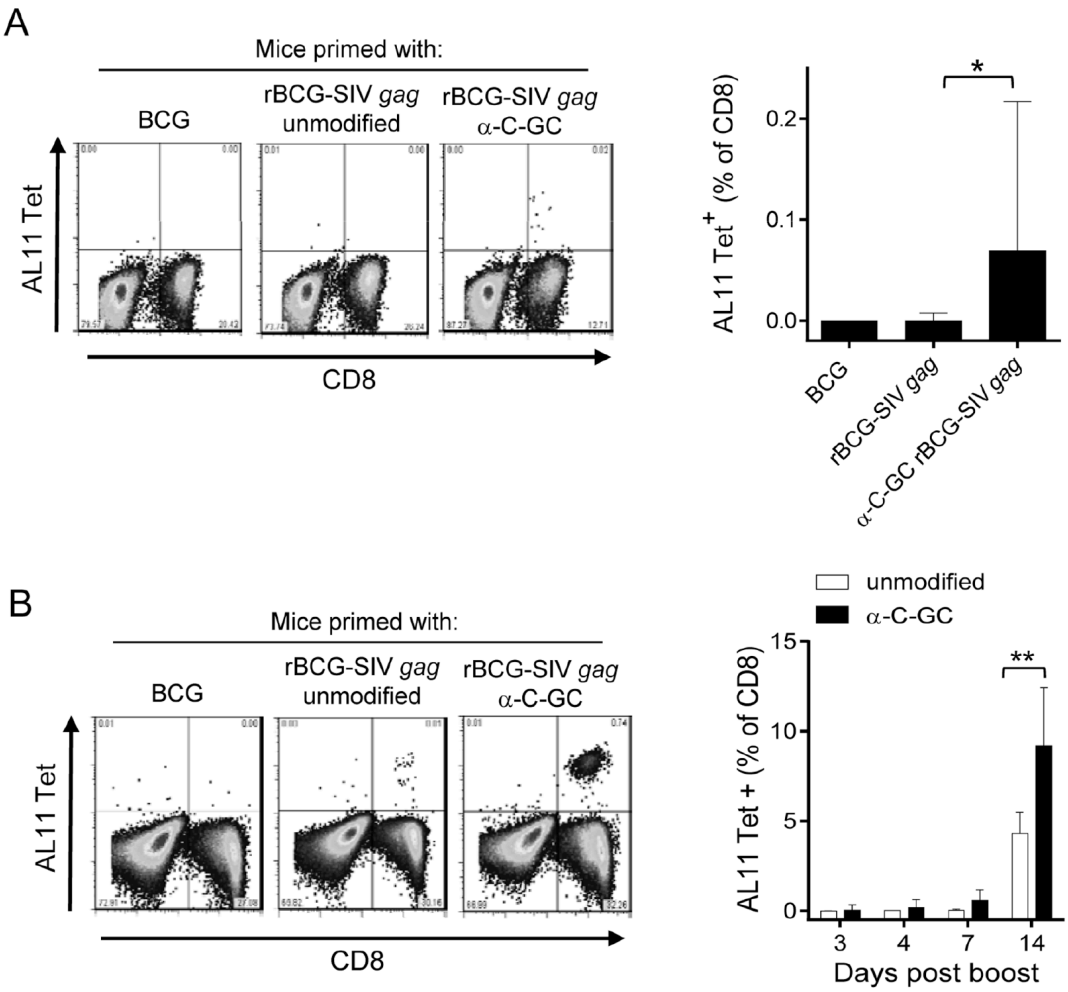

Figure 1. Enhanced primary and boosted responses to SIV Gag expressed in rBCG with incorporation of NKT cell activating glycolipids. C57BL/6 mice were primed i.v. with 107 CFU of M. bovis BCG, rBCG-SIV gag, or rBCG-SIV gag modified by incorporation of a-C-GC. CD8+T cells specific for SIV Gag in peripheral blood samples were enumerated by flow cytometry of lymphocytes stained with H2Db/AL11 tetramers specific for an immunodominant Gag epitope.
(A) Primary responses were analyzed at 14 days after priming. Plots on left show representative profiles of tetramer staining of CD8+ T cells (for complete gating strategy, see supplementary Fig. S2). Graph on right shows medians and interquartile ranges for groups of similarly immunized mice (n = 5 mice per group). *P,0.05 (Kruskal-Wallis followed by Mann-Whitney test with Bonferroni correction).
(B) Secondary responses to SIV Gag in mice boosted with rAd5-SIV gag (107 VP i.m.) eight weeks after priming. Plots on left show representative tetramer staining on day 7 after boosting. Graph on right shows medians and interquartile ranges at the indicated day after boosting for groups of mice (n = 5 per group) primed with rBCG-SIV gag without glycolipid modification (unmodified, open bars), or with rBCG-SIV gag with incorporation of a-C-GC
(filled bars). **P,0.01 (Mann-Whitney test).

Advantages

- Boost of a strong and effective cellular immune response *in vivo*
- Best-in-class when benchmarked to other Th1-skewing Galcer analogues (IL-12/IFNg/IL-4 profiles). Less IL-4 production compared to aGalCer.
- Ghent University lead is as effective in soluble form as when loaded on a DC
- No acute toxicity.
- Ghent University glycolipids have a druggable profile and have been optimized for easy synthesis. Availability of SAR data for rational design strategies.
- Patent protected with a broad claim scope anticipating chemical optimization processes and a broad range of immune-modulatory applications.
- *In vivo* proof-of-concept in two tumor models: B16 lung metastasis model (incl. independent repeat study) and a 4T1 breast cancer metastasis model (orthotopic). In all studies, a strong reduction of metastases was observed after one administration of the Ghent University lead compound (both soluble and DC-loaded).

IP position

International patent application PCT/EP2013/062941 filed on 20/06/2013.

Partnering

We are actively seeking partners to develop or co-develop the Ghent University GalCer molecules to applications in the vaccine and/or oncology field.

Evaluation batches are available for in-house evaluation.

University and regional innovation funds allow for risk sharing collaboration models.

Target market

Potent Th1 polarizing GalCer analogues have a potential as

- a vaccine adjuvant (bacterial, viral or tumor vaccines)
- in cancer therapy (adjuvant therapy): immuno-oncological strategies targeting aggressive cancer types in a combination therapy (adjuvant setting).

References

1. Venkataswamy, MM.; Ng, TW.; Kharkwal, SS.; Carreno, LJ.; Johnson, AJ. et al. Improving Mycobacterium bovis Bacillus Calmette-Guérin as a Vaccine Delivery Vector for Viral Antigens by Incorporation of Glycolipid Activators of NKT Cells. *PLoS ONE* **2014**, 9(9): e108383.
2. Janssens, J.; Bitra, A.; Wang, J.; Decruy, T.; Venken, K.; Van der Eycken, J.; Elewaut, D.; Zajonc, D .; Van Calenbergh, S. 4"-O-Alkylated α-galactosylceramide analogues as iNKT-cell antigens : synthetic, biological, and structural studies. CHEMMEDCHEM **2019**, 14(1), 147–168.