A Novel Immunomodulatory Glycolipid Derived From A Prominent Human Commensal Microbe

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TECHNOLOGY DESCRIPTION

BACKGROUND:

Natural Killer T-cells (NKT cells) are a growing area of preclinical and clinical research, and modulation of these cells has therapeutic applications in various diseases with immunological, infectious, or oncologic components.

DESCRIPTION:

Investigators at UCSF and Harvard have identified, isolated, purified, and characterized a novel chemical composition – a glycolipid molecule, from a prominent commensal bacterium. The glycolipid is an analog of a known synthetic class of compounds that are known to activate natural killer T-cells. This new glycolipid compound is also a close analog of a previous clinical candidate for cancer and viral infections, and a current clinical candidate for autoimmune disorders, including graft-versus-host disease. However, the other known NKT activators are synthetic and are thus non-physiological. By contrast the new glycolipid is a fully natural glycolipid produced by resident microbes of the human GI tract.

The investigators have demonstrated the ability of the new glycolipid to activate NKT cells and classical NKT-cell cytokine response in cellular experiments (via administration to immune cells) and *in vivo* (via application of glycolipid-pulsed dendritic cells to conventional mice, and variable expression of the relevant synthetic pathway in gnotobiotic mice).

Interestingly, the glycolipid appears to have a subtle but significant difference in *in vitro* affinity for NKT cells as well as a different cytokine activation profile from known, synthetic NKT activator. Our study implies that the co-evolved human gut microbiome might specifically produce this physiological glycolipid as a natural ligand that modulates the NKT subset of immune cells relevant to pathogen response and autoimmune disease. Given that the compound is significantly different in structure and activity than the previously studied compounds, this new glycolipid and the surrounding chemical space should be useful as therapeutics as well as research tools.

APPLICATIONS

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OTHER INFORMATION

KEYWORDS

glycolipid, gut microbe, natural killer cells, NKT

CATEGORIZED AS

- Biotechnology
  - Food
- Medical
  - Disease: Autoimmune and Inflammation
  - Disease: Cancer

RELATED CASES

2012-069-0

- pro-inflammatory therapeutic (anti-cancer, anti-viral) or anti-inflammatory therapeutic (wide range of autoimmune diseases)
- potential for medical foods
- Diagnostics of a microbiome-related immune disease or susceptibility to a disease based on endogenous levels of the glycolipid
- Research tools and reagents for NKT activation
- Patient stratification for therapy choice/dose based on a patient's resident level of the glycolipi

ADVANTAGES

▶ The new glycolipid seems to be the first known natural ligand for the activation of NKT-cells harboring the invariant T-cell receptor. Additionally, as commensal microbes have evolved for thousands to millions of years inside humans, the molecules that they produce are likely biased towards both activity and tolerability for modulating human physiology. Thus, this compound and its derivatives may be a relatively safe therapeutic due to its previous exposure to humans.

▶ The glycolipid appears to have a subtle but distinct NKT activation pattern the other known, synthetic NKT activator and clinical candidate. This candidate has been brought into the clinic for various indications, but has been discontinued in many of those indications due to efficacy and/or safety issues. Therefore, it is important for any new analog to have a difference in NKT activation profile that may be of more clinical relevance.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	10,227,290	03/12/2019	2012-069
Germany	Issued Patent	60 2013 035 737.4	04/11/2018	2012-069
France	Issued Patent	2811831	04/11/2018	2012-069
United Kingdom	Issued Patent	2811831	04/11/2018	2012-069

STATE OF DEVELOPMENT

The new molecule has been isolated, purified, structurally-characterized, chemically synthesized, and assessed in initial physiological systems. A few validation steps that would add significant value are:

▶ Further in vivo experiments to 1) confirm a physiological effect when dosed exogenously to a mouse, validating the potential of the purified molecule as a potential therapeutic, and 2) determine the full physiological profile in mice

▶ Confirmation of the potential utility of the compound in diseases in various animal disease models.

▶ Search and discovery of additional ligands from other commensal microbes

RELATED MATERIALS

▶ Wieland Brown LC, Penaranda C, Kashyap PC, Williams BB, Clardy J, Kronenberg M, Sonnenburg JL, Comstock LE, Bluestone JA, Fischbach MA. Production of a-galactosylceramide by a prominent member of the human gut microbiota. PLoS Biol. 2013 Jul;11(7):e1001610.

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