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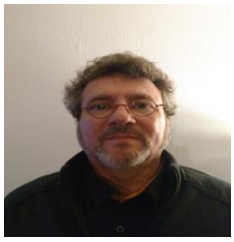
iNKT Activation by Potent Alpha-Galcer Analogues and anti-EGFR-Antibody Glycoconjugates as Useful Tool for Onco-Immunotherapy



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Abstract

CD1d restricted T lymphocytes, a subclass of human lymphocytes, appears to be major players of the immune response. A subpopulation of the CD1d restricted lymphocytes, called *i*NKT cells, bears a TCR receptor and reacts against □-galactosylceramides (□-GalCer). Recognition of □-GalCer (KRN7000) bound to CD1d molecule of an antigen presenting cell, leads to the fast and strong secretion of a large panel of cytokines. These cytokines can stimulate the maturation of dendritic cells, activate the proliferation of IFN□ synthesis and stimulate cytotoxic CD8 lymphocytes. These mechanisms contribute to the control of tumor progression.

In view to highlight the potency of deoxy-analogues of □-GalCers to modulate the iNKT response, we evaluated the effect of combined alterations of the sphingoid base devoid of both 4-OH[1] and 3-OH groups by substitution with one or two fluorine atoms.[2,3] We shown that, despite suppression of the H-bond donating capacity with CD1d, electron isoelectronic effect of one or two fluorine atoms, *vs.* oxygen, can modulate the lack of the sphingosine 3-OH on the destabilisation of the CD1d/GalCer/TCR complex by reinstating favourable interactions.

In our continuing efforts to improve iNKT activation, we recently discovered novel α-GalCer analogues proved to be more potent by several orders of magnitude than α-GalCer for IFN-□ secretion. Intriguingly, unlike α-GalCer, they also proved to be active when loaded on several human cancer cell lines known as not expressing CD1d. This latter result reveals a paramount effect of modified α-GalCer on CD1d/TCR complex stabilization that occurs on cancer cell bed without recruitment of usual APCs. With the aim to mediate a local immune response close to tumour environment, selected α-GalCer derivatives have been associated to the anti-EGFR monoclonal antibody. We found that monoclonal antibody glycoconjugates are able to restore iNKT stimulation at a nM range while keeping antibody cytotoxicity

Biography:

Didier Dubreuil has completed is PhD in 1989 at the ICSN (Institut de Chimie des Substances Naturelles, Gif/Yvette France). He is currently a full professor at the University of Nantes in CEISAM laboratory (CNRS 6230) working at the interface of chemistry and biology. He has over 85 publications and 14 international patents.

Speaker Publications:

1. "3,4-Dideoxy-3,3,4,4-tetrafluoro- and 4-OH epimeric 3-deoxy-3,3-difluoro-α-GalCer analogues: Synthesis and biological evaluation on human iNKT cells stimulation";Researchgate, 2020, 10.1016/j.ejmech.2019.05.069

2. "Synthesis of Ribonucleosidic Dimers with an Amide Linkage from D-Xylose"; The Journal of Organic Chemistry, 2016, 10.1021/acs.joc.6b01822

3. "1,10-Phenanthroline and Non-Symmetrical 1,3,5-Triazine Dipicolinamide-Based Ligands For Group Actinide Extraction"; Chemistry, 2014, 10.1002/chem.201402266

12th International Conference on Medicinal Chemistry and Drug Discovery; October 14-15, 2020, webinar.

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