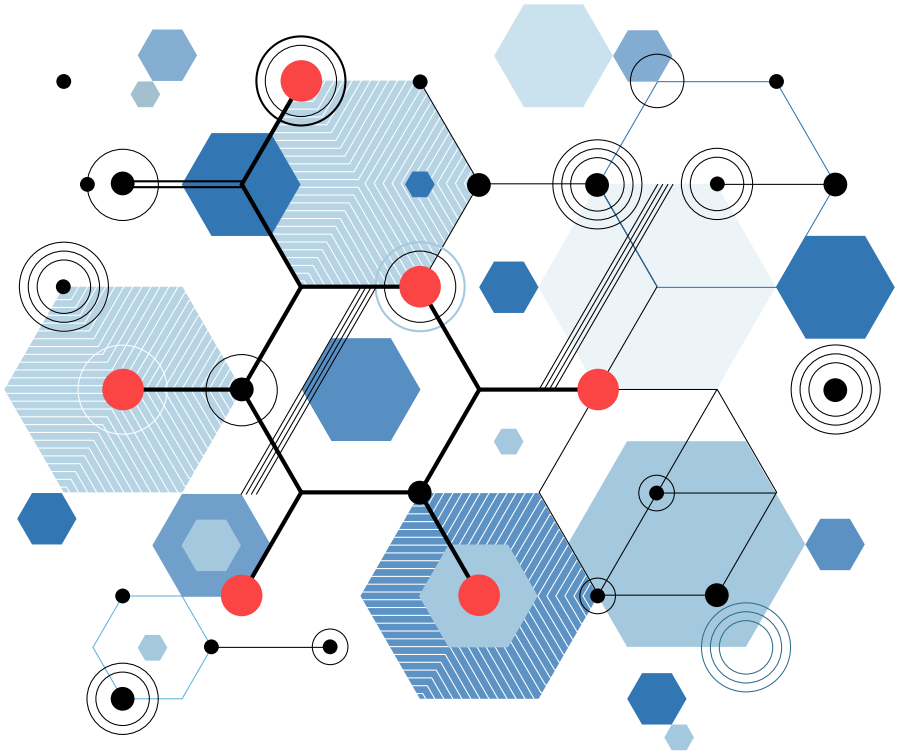

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POSTER ABSTRACTS

P200

Polyfluoroalkyl Glycolipid Mimetics as Immunomodulatory Agents

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α-Linked glycosphingolipids and their analogues, of which the synthetic glycolipid α-galactosylceramide (α-GalCer, KRN7000) is an archetypic example, exhibit intriguing immunostimulatory and immunomodulatory properties that have fueled the exploration of applicable treatments against tumors, microbial infections or autoimmune diseases [1]. The biological activities of α-GalCer have been mainly ascribed to its ability to activate invariant natural killer T (iNKT) cells, leading to the rapid discharge of cytokines [2]. Activation of other players of the innate and adaptive immune system, such as dendritic cells, macrophages and microglia has also been reported [3]. Unfortunately, pro-inflammatory and anti-inflammatory cytokines that antagonize each's other effects are simultaneously released, which is the main reason of the failures met in clinical trials. The discovery of metabolically stable glycolipid mimetics that favor either of the two biased cytokine profiles is, therefore, highly wanted. We previously found that some sp^2-iminosugar glycolipids (sp^2-IGLs) elicited an anti-inflammatory response in LPS-treated mouse microglia and human dendritic cells by interfering in the TLR-4 dependent mitogen activated protein kinase (MAPK) signaling route [4]. The fact that the same compounds exhibit anti-proliferative, anti-metastatic and anti-parasitic activities strongly suggests that they behave as context-dependent immunomodulators [5]. Computational docking supported that the mechanism of action involves binding of the sp^2-IGLs to the hydrophobic pocket of p38α MAPK, which induces self-phosphorylation and triggers cell polarization. Given the well-recognized capacity of fluorine atoms to affect drug-binding interactions with proteins, we have now prepared a series of fluorinated sp^2-IGLs related to nojirimycin and galactonojirimycin (Figure 1) and profiled their efficiency as anti-inflammatory, anti-proliferative and anti-leishmanial agents in vitro.

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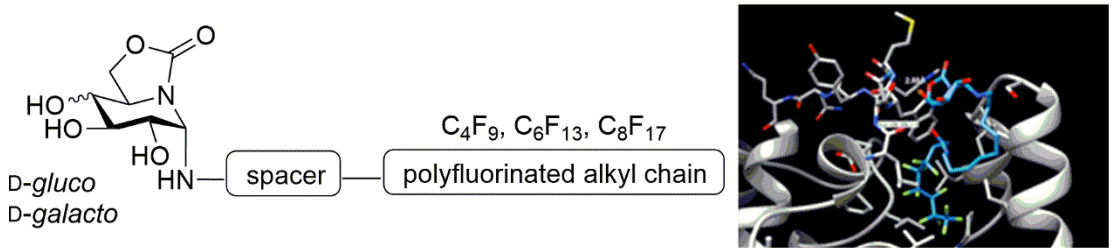

Figure 1. General chemical structure of the polyfluorinated sp^2-IGLs prepared in this work and the predicted binding mode to p38α MAPK.