First-in-class non-carbohydrate inhibitors of sialic acid-binding immunomodulatory-type lectin-7 (Siglec-7) discovered from genetically encoded bicyclic peptide libraries

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Sialic acid-binding immunoglobulin-type lectins (Siglecs) are a class of immunoinhibitory cell signaling proteins with significant implications in cancer. Hypersialiation of cancer cells activates Siglecs, and this activation suppresses the immune recognition of these hyper-sialylated cells and promotes cancer-cell survival. Although Siglecs' natural substrates are gangliosides (a class primarily composed of glycoprotein with terminal sialic acid residues), Siglec proteins have a low affinity for these substrates. Hence, high-affinity inhibitors are a highly desirable focus of research.

Using genetically encoded libraries, we identified a group of bicyclic peptides with a strong affinity for Siglec-7 and Siglec-9. Specifically, we used bicyclic genetically encoded libraries modified by two-fold symmetric linkers (BiGEL2) to screen against these two targets, employing next-generation sequencing (NGS) analysis for hit nomination.

We synthesized approximately 100 peptides to explore their binding towards the Siglec targets using ELISA, BLI, and SPR. This study led to the discovery of low micromolar binders to Siglec-7 with IC_{50} & K_i <10 μM. Additionally, we preformed a preliminary structure-activity relationship profile using alanine scans to assist in the future development of highly potent, bioavailable, and immunosuppressive peptide binders of Siglec-7 and Siglec-9.