PROGRESS REPORT for Mizutani Foundation Research Grant

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Grant Title: Defining Anti-Anaphylactic N-Linked Glycan Structures

Progress Report:

(a) Abstract: (within 1 page)

IgE is required for allergic disease, yet it remains unclear why some individuals with allergen-specific IgE develop allergic symptoms while others do not. Differences in IgE affinity, epitope diversity, mast cell numbers, FcεRI expression, Syk signaling, and allergen-specific IgG or anti-IgE antibodies likely all contribute. A factor that has received little attention is IgE glycosylation: IgE is the most heavily glycosylated monomeric antibody in humans, with seven N-linked sites across its constant chains. One site is unoccupied, one bearing an oligomannose glycan, and five bearing complex biantennary glycans. We previously found that IgE from non-allergic adults carries less sialic acid on these biantennary glycans than IgE from peanut-allergic adults, and that removing sialic acid from IgE markedly reduces anaphylaxis in both human and murine models. Our *long-term goal* is to define how antibody glycosylation regulates, and is regulated by, immune responses. Our *central hypothesis* is that a glycan exposed on IgE by loss of sialic acid engages an inhibitory receptor that attenuates mast cell and basophil degranulation, a model supported by preliminary data presented here. Identifying how desialylated IgE is attenuated should reveal new pathways and therapeutic targets in allergic disease and establish IgE glycosylation as a disease biomarker. Here we characterize the immunomodulatory activity of asialylated IgE and its effect on degranulation of mucosal and connective-tissue human mast cells.

Methods: Sialic acid was enzymatically removed from IgE, confirmed by lectin blotting, and the resulting asialylated IgE was tested in models of passive systemic anaphylaxis *in vivo* and primary mast cell degranulation assays *in vitro*.

Results: Asialylated IgE was anti-anaphylactic in vivo, attenuating anaphylaxis induced by sialylated IgE, and produced differential degranulation in primary mast cells relative to sialylated IgE.

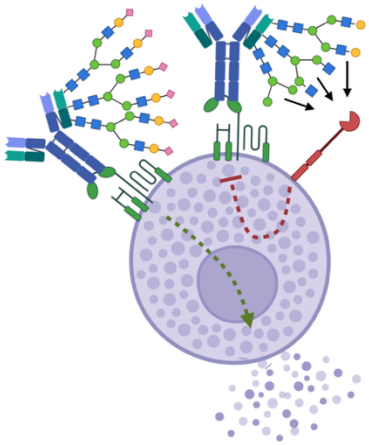

Figure 1. Defining Anti-Anaphylactic N-Linked Glycan Structures. Sialylated IgE (top left) and asialylated IgE (top right) bind to FcεRI on mast cells. Sialylated IgE triggers mast cell activation upon allergen exposure, while asialylated IgE attenuates mast cell activation.