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Title of Presentation: IVIG Induced Regulatory Macrophages Reduce Dextran Sodium Sulfate Induced Intestinal Inflammation

Abstract

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disease characterized by inflammation along the intestinal tract. Current treatment for IBD relies on non-specific immune suppression but up to 40% of people are, or will become, refractory to current therapies. Macrophages are key mediators of inflammation initiating the innate immune response. However, macrophages can be skewed to a regulatory phenotype (Mregs) that plays an equally important role in turning off the inflammatory response. Intravenous immunoglobulin (IVIG) is a blood product composed of pooled polyclonal IgGs from more than 1000 donors. High doses of IVIG are used to treat autoimmune diseases and may work, in part, by skewing macrophages to a regulatory phenotype.

My **overarching hypothesis** is that Mregs can be used to reduce intestinal inflammation, like that which characterizes IBD. To address this hypothesis, I propose two specific aims:
Aim 1. To assess the anti-inflammatory properties of Mregs primed with IVIG *in vitro*
Aim 2. To determine whether Mregs can reduce intestinal inflammation *in vivo*.

Methods: Macrophages were derived from mouse bone marrow aspirates. Macrophages were primed to create an Mreg phenotype with high dose IVIG. Inflammatory responses of Mregs were measured *in vitro* and the potential of Mregs to block inflammatory responses was assessed *in vivo* using the dextran sodium sulfate (DSS)-induced mouse model of intestinal inflammation.

Results: Mregs stimulated with high doses of IVIG produce low levels of pro-inflammatory IL-12/23p40 and high levels of anti-inflammatory IL-10 in response to inflammatory stimuli. Importantly, adoptive transfer of *in vitro*-derived Mregs reduces inflammation and clinical disease activity in mice during DSS-induced colitis.

Conclusions: These studies demonstrate that Mregs have potent anti-inflammatory activity that can be used to reduce intestinal inflammation *in vivo*. Skewing macrophages to an Mreg phenotype *in vivo* or adoptive transfer of *in vitro*-derived Mregs may provide a novel immunotherapeutic strategy to treat intestinal inflammation. In future studies, we will investigate the mechanism(s) by which macrophages change their phenotype to become Mregs to determine whether macrophages can be skewed *in situ* to dampen down inflammation in people with IBD.