IMMUNOTHERAPEUTICS DC TARGETING ANTIBODIES THAT ELICIT IMMUNE TOLERANCE

Dendritic cells (DCs) are major antigen presenting cells that can induce and control host immune responses toward either immunity or tolerance. In addition to linking innate and adaptive immunity by inducing T cell responses, DCs also play crucial roles in the induction and activation of humoral responses. DCs can also trigger unwanted types of immune responses, including inflammation, autoimmunity and transplant rejection. Scientists at the Baylor Institute for Immunology Research (BIIR) have discovered novel antibodies against several key receptors expressed on DCs that favor tolerance over immunity, including dendritic cell asialoglycoprotein receptor (DC-ASGPR) and Dectin-1.

**DC-ASGPR, a Novel Target for the Treatment and Prevention of Graft-versus-Host Disease and Autoimmune Disease**

The BIIR team has demonstrated that DC-ASGPR may provide a promising treatment or prevention for graft-versus-host disease (GVHD), a major cause of transplant rejection that affects approximately 5,500 patients in the US each year, representing a serious unmet medical need. In one approach to inducing immune tolerance, activation of DCs with a novel anti-DC-ASGPR monoclonal antibody induced an expansion of alloantigen-specific regulatory T cells and IL-10 production, improving allograft survival. This effect has been successfully demonstrated both in vitro in a mixed lymphocyte reaction (MLR) assay using human peripheral blood mononuclear cells (PBMC) from two human donors, and in vivo in a GVHD mouse model in which human PBMC are injected into immunodeficient NOG mice. Most significantly, in addition to treating GVHD, the induction of immune tolerance through activating DC-ASGPR may have implications for treating and preventing a wide range of autoimmune diseases.

In a second approach to inducing tolerance, novel fusion proteins at BIIR may be used to deliver relevant antigens to DCs in a preventative or therapeutic vaccine approach. Anti-DC-ASGPR antibodies fused to antigen induce in vitro expansion of IL-10-producing CD4+ regulatory T cells (Tregs) capable of dampening the inflammatory response of IFNγ-producing effector T cells. This effect has also been demonstrated in nonhuman primates treated with anti-DC-ASGPR fused to prostate specific antigen (PSA) or influenza hemagglutinin-1 (HA1). Importantly, antigens targeted to other DC receptors such as LOX-1 do not have this tolerogenic effect.
Dectin-1, a Potential Target for the Treatment and Prevention of Allergic Diseases

Allergen-induced Th2-type T cells are major effectors of allergic diseases, including allergic rhinitis, allergic asthma and dermatitis. Allergic rhinitis alone affects 10 to 30 percent of people globally, including approximately 65 million Americans each year. Although the pathophysiology of such allergic immune disorders is complex, these diseases share common major cellular and effector mechanisms. Consequently, therapeutic modulations of the Th2 pathway represents a rational strategy for the treatment of allergic diseases.

BIIR scientists have discovered that activating the DC cell surface receptor Dectin-1 induces robust IL-10 production and uniquely downregulates Th2-type T cell responses by interfering with the TSLP and OX40L pathways. Treatment with a Dectin-1 ligand, β-curdlan, significantly downregulated Th2 responses in vitro in PBMC from asthma patients. To enhance this program, BIIR has novel agonistic anti-Dectin-1 antibodies for use in efficacy studies in animal models of Th2-mediated disease.

Opportunities

Patent applications have been filed for each of these innovations, including novel targets and compositions for the treatment and prevention of autoimmune disease, and are available for licensing. In addition, there are opportunities for partnering and collaboration to further advance these technologies and translate them to the clinic.

Selected Publications:
