Galectin-3 – a novel target for treatment of atopic dermatitis

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Partnering goals

1. Further validation of Galectin-3 as a target for atopic dermatitis and asthma
2. Advancement of novel drugs for atopic dermatitis (eczema) and asthma based on inhibition of Galectin-3

Introduction/Business Opportunity

Eczema affects a wide population age group, and prevalence of the disease has increased two- to three-fold during the past three decades in industrialized countries, where the current incidence in children is estimated to be 15-20%. Various studies suggest that eczema is a complex disease, with involvement of multiple immunologic and inflammatory pathways that include T cells, dendritic cells, mast cells and eosinophils, as well as keratinocytes. Treatment of eczema continues to be a challenge, especially in patients with severe conditions.

Current therapies include topical application of glucocorticoids and calcineurin inhibitors (immunomodulators), and systemic use of glucocorticoids, immunosuppressants and calcineurin inhibitors. Due to significant health concerns of long-term use of glucocorticoids and immunosuppressants, topical immunomodulators gained wide acceptance. However, safety issues raised by the FDA may limit use of these immunomodulators.

A family of animal lectins, called *galectins*, are beta-galactoside-binding animal lectins with conserved carbohydrate-recognition domains (CRD). They are evolutionarily highly conserved (found in nematodes and mammals). Some show wide tissue distribution, while others are more selectively expressed by tissue. Galectins have no signal sequence and no transmembrane domain and are found in the cytosol and nucleus, but also in extracellular spaces. Galectin-3 is unique among others in possessing chimeric structure consisting of an N-terminal region that contains 9-14 tandem repeats PGAYPG(X)\(^{1-4}\) and a C-terminal carbohydrate-recognition domain. Through its N-terminal domain galectin-3 forms oligomers upon binding to multivalent saccharides. Extracellular and intracellular functions of galectin-3 are very different. Galectin-3 is present in epithelia and inflammatory cells, and demonstrated in vitro to activate many cell types (mast cells, neutrophils, monocytes, T cells), and influence adhesion of neutrophils to laminin.

Pro-inflammatory and anti-apoptotic properties of galectin-3 have been confirmed in galectin-3 knockout (gal3\(^{-/-}\)) mice developed at UC Davis\(^5\). gal3\(^{-/-}\) animals exhibit the following phenotypes:
- reduced mast cell mediator release and cytokine production \(^5\)
- reduced airway inflammation in a model of atopic asthma \(^6\)
• attenuated contact hypersensitivity due to impaired dendritic cell migration
• diminished allergic skin inflammation in a model of atopic dermatitis

We have demonstrated the suitability of targeting galectin-3 to treat inflammatory disease in vivo using an inhibitory monoclonal antibody (B2C10) in a mouse model of peritoneal inflammation. A single treatment with galectin-3 antibody significantly suppressed macrophage infiltration induced by zymosan. In a mouse model of atopic dermatitis using the gal3-/- mice, disease severity was significantly reduced, accompanied by lower inflammatory infiltrates of eosinophils and mononuclear cells (Fig. 1).

Core Technology

Aptamers, a class of novel drugs, have recently been approved for treatment of age-related macular degeneration (Pegaptinib). We chose aptamer strategy, partly because experimental small molecule inhibitors of galectins typically target only one of the galectin functions. Multivalency of galectin-3 requires targeting of multiple activities. Currently reported small molecule inhibitors of galectin-3 also inhibit other galectins and exhibit low inhibitory properties. The advantages that aptamers include the following:

i) Higher affinities for galectin-3 due to larger contact areas with their targets
ii) Higher specificity for galectin-3.
iii) Ability to target any region of a protein molecule including the N-terminal region of galectin-3, the region is essential for oligomerization. None of the currently reported compounds selected from screening combinatorial chemistry libraries target this region.
iv) Ability to target either extracellular or intracellular galectin-3.

Stage of Technology Development

Completed Milestones

Extensive aptamer library screening has been performed from an N60 library encompassing 21 serial rounds of screening (solid phase). Individual clones are being obtained.

Anticipated Milestones

1. Characterize RNA clones identified via a solid-phase assay by galectin-3 domain with which they interact, i.e. lectin (glycan-inhibiting and non-inhibiting), N-terminus, N-terminal repeats, ser6 and ser12, and other identifiable motifs using galectin-3 truncated mutants
2. Validate inhibitory abilities of the clones by the mast cell histamine release assay
3. Further validate the candidate clones in mouse model of atopic dermatitis. Detailed analyses will be performed with regard to acanthosis, eosinophil and mononuclear cell infiltration, IgE levels in circulation, and Th cytokine profiles at affected skin sites.
4. Identifying minimal sequences that effect demonstrated inhibition.

Figure 1. OVA-sensitized skin sites of gal3-/- mice show significantly reduced inflammation. Gal3+/+ and gal3-/- mice were sensitized with OVA. Immunohistochemical staining for galectin-3 (brown color) (A), H&E staining for epidermal thickness measurement (B), and Giemsa staining for quantification of the skin cellular infiltrates (C) were performed. Bars represent mean cell numbers ± SEM. *P <0.05.
Intellectual Property

**UC Case#: 2007-373-1. Patent Application:** Galectin-3 as target for treatment of atopic dermatitis

**UC case # 2006-236.** Patent application (A1 20060148712) published July 6, 2006:

Monocyte Chemoattractant activity of galectin-3

Selected Publications

Peritoneal macrophage infiltration is inhibited by galectin-3 antibody.

Peritoneal inflammation was induced in mice with zymosan (0.1 mg/g) for 18 h. PBS, irrelevant isotype-matched IgG (N.S) or B2C10 anti-galectin-3 IgG was administered subcutaneously, 30 min prior to zymosan. * P < 0.05.