**Specific Aims**

The immune system is a necessary and complex aspect of the human body, but when it fails to function properly the results affect the patient’s quality of life. Allergic rhinitis is a common affliction in the United States. Symptoms include sinus swelling, pressure, and sneezing.Allergic rhinitis is an antibody (IgE) mediated hypersensitivity reaction of the nasal mucosa. The antibody interacts an allergen to recruit phagocytic and cytotoxic cells [1]. These cells release cytokines, such as transforming growth factor beta isoform 1 (TGFB1). In allergic rhinitis patients, TGFB1 is overexpressed [2]. TGFB1 functions in the immune system as a cytokine which stimulates Th17 cells. [2] When stimulated, these Th17 cells secrete another cytokine, IL-17, which stimulates neutrophil recruitment and ultimately inflammation. [3] Losartan, a drug already approved by the FDA for high blood pressure treatment, acts as an angiotensin II receptor antagonist [4]. That results in a decreased amount of secreted TGFB1. In addition, neutropenia can be a side effect of losartan [5]. Losartan has the ability to target both TGFB1 secretion, as well as the resulting excessive neutrophil recruitment [4]. However, the drug has yet to be tested for its ability to treat the inflammation induced by TGFB1 that is associated with allergic rhinitis. This missing drug study may hold the key to treatment of allergic rhinitis.

**This experiment will test the hypothesis that losartan has the ability to decrease the inflammatory response found in allergic rhinitis.** This is based on the fact that allergic rhinitis is an inflammatory disease, and losartan targets the levels and the inflammatory effects of TGFB1. The **objective** of this study is to determine losartan’s ability to improve the inflammation associated with TGFB1 and the allergic rhinitis phenotype. This knowledge will apply to the **long-term goal** of the research, which is to therapeutically control the levels of TGFB1, eliminating the allergic rhinitis response.

**1. Compare homologs to solidify which domains or amino acids are important to the immunologic function of the protein.** TGFB1 is a widespread growth factor involved in countless biological processes. Phylogeny and domain analysis will allow me to deduce the domains and amino acids important for inflammation, by comparing species with diverse immune systems. These results will allow me to focus into certain areas of the protein which may be important during the drug study.

**2. Discover changes in gene regulation due to losartan and similar compounds.** Losartan’s ability to act as an angiotensin receptor antagonist is well documented. I will run a microarray with similarly structured compounds from a diversity screen to ensure losartan is the idea drug choice. I will then isolate the compounds which showed ability to act as an angiotensin receptor antagonist, and introduce them to transgenic inflammatory zebrafish via tank water. I will then use RNA sequencing to discover expression patterns of inflammatory cytokines before and after treatment. This information will be vital in determining which compound works best to inhibit inflammation and how it acts on several inflammatory cytokines including TGFB1.

**References**

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**[4]** Pesheva, E. (2013, July 24). Johns Hopkins researchers reveal genetic glitch at the root of allergies. *Johns Hopkins Medicine.*

**[5]** Losartan and Neutropenia – from FDA reports. <http://www.ehealthme.com/ds/losartan/neutropenia/> accessed 3/16/17.