Dissertation Defense - Dana E. Austin, PhD Biosciences

April 28, 2022 2:00 - 4:00 PM

All are invited to attend the defense. For more information please contact Graduate Coordinator at

dstgerma@gmu.edu

Candidate: Dana E. Austin

Program: PhD, Biosciences

Date: Thursday, April 28, 2022

Time: 1:00 PM

Meeting Location: https://gmu.zoom.us/j/99238488008?pwd=d0lKdEkwL0Z3Ni9vSmJxbjJBSEtYdz09

Title: Developing Low-Density Lipoprotein Receptor–Related Protein-1 Agonists as a Therapeutic Strategy in Allergic Inflammatory Diseases

Dissertation Director: Dr. Cohava Gelber

Committee Chair: Dr. Alessandra Luchini

Committee Members: Dr. Lance Liotta, Dr. Kylene Kehn-Hall, Dr. Mikell Paige

ABSTRACT:
Allergic inflammatory diseases such as atopic dermatitis, eosinophilic esophagitis (EoE) and asthma are a consequence of persistent exposure to allergens leading to impaired innate immune mechanisms and dysregulated immune responses. A large unmet need exists for an effective treatment that is devoid of potentially serious side effects and without immunosuppressive effects. We have previously developed a family of first-in-class drugs derived from naturally occurring Serine Protease Inhibitors (SERPINS) that target Low-Density Lipoprotein Receptor-Related Protein-1 (LRP-1), a homeostatic receptor that regulates a multitude of critical functions of the immune response. The lead peptide, SP16, is a short (17mer) modified peptide derivative of Alpha-1 Antitrypsin (AAT). Recent work has shown that both AAT and LRP-1 play a role in alleviating allergen-driven inflammation. We have now designed a series of several SP16-derivative analogs modeled off of the putative LRP-1 binding site, with the goal of developing these peptide therapeutics for inflammatory diseases. We have methodically screened these analogs for their ability to inhibit inflammation, refining the analog design based on structure-activity relationships, ultimately increasing potency, with dramatically improved effective concentrations (EC50s) compared to SP16, and no toxicity, increasing the potential therapeutic window. In-vitro LRP-1 binding assays show target engagement. Lead analogs, screened in a rapid in-vivo mouse model of acute inflammation, exhibit significant anti-inflammatory function comparable to SP16. The analogs demonstrate improved pharmacokinetic properties and potential for a wider range of administrative techniques, including oral. Finally, a few select analogs, alongside SP16, were tested for their ability to inhibit TH2 mediated responses in mouse models of atopic dermatitis and asthma. Both SP16 and analogs show significant amelioration of disease phenotypes, including TSLP inhibition. Overall, the developmental work has defined two new lead SERPIN-derived LRP-1 agonists for inflammatory diseases and provided a new avenue of development for SP16 in allergic inflammation.