Project Summary/Abstract

Current COVID-19 vaccines fail to induce strong cross-reactive neutralizing antibodies against circulating SARS-CoV-2 variants, which have undergone extensive mutation in the neutralizing epitopes of spike protein. Booster vaccinations with variant-matched vaccines primarily strengthen immunity towards epitopes shared with the original strain, leading to poor neutralizing activity against variants and failing to induce strong protection. This biased immune response towards the ancestral strain is termed “original antigenic sin”. It results in repeated infections with new variants regardless of vaccination status.

The overall goal of this proposal is to develop an improved SARS-CoV-2 vaccine that can induce broadly cross-reactive neutralizing antibody responses against current and future variants by targeting a highly conserved epitope in the heptad repeat 1 (**HR1**) region of the spike protein. When presented on spike protein, it is poorly immunogenic and anti-HR1 antibodies rarely form naturally. Dr. Stampfer has developed an engineered antigen, composed only of the HR1 epitope, that induces high titer anti-HR1 antibodies in mice. This immunogen also functions as a scaffold when linked to an additional epitope, the receptor binding motif (**RBM**), which mutates frequently between different SARS-CoV-2 variants and can induce very potent neutralizing antibodies. The HR1 portion of such a vaccine has the potential to induce broadly neutralizing antibodies against all variants, while the RBM portion can function as a seasonal component targeting current circulating strains, all without boosting non-neutralizing cross-reactive epitopes on spike protein. Three Aims are proposed. **Aim 1** investigates the immunogenicity and protection of the HR1 and RBM-HR1 vaccines against the current circulating SARS-CoV-2 variants in naïve mice, while **Aim 2** evaluates their efficacy as boosters in mice with prior mRNA COVID-19 vaccination. **Aim 3** will isolate vaccine-induced HR1-specific B-cells to generate broadly-active anti-HR1 monoclonal antibodies for prophylactic and therapeutic evaluation in mouse challenge experiments. **Long term,** this lays the groundwork for future larger projects testing the optimized vaccine and anti-HR1 therapeutics in nonhuman primates and humans, and in designing HR1-based vaccines for other viruses.

The research will be conducted at the Emory Vaccine Center, with multiple vaccinology labs whose close proximity encourages new collaborations and the sharing of methodology and equipment, along with on-site nonhuman primates for future preclinical vaccine testing. Dr. Stampfer’s **career goal** is to develop better vaccines for viral pathogens by using protein structure data to design antigens that induce strong immunity to critical epitopes. His career development plan includes hands-on training in vaccine development, neutralization assays, and monoclonal antibody isolation, along with didactic and online courses in immunology, antibody engineering, biostatistics, and grant-writing. The mentorship team of physician-scientists and viral vaccinologists will ensure productive research and training, helping him launch his career as an independent researcher.