The repertoire of naturally occurring proteins is finite and many molecules induce multiple confounding effects, limiting their efficacy as therapeutics. Recently, there has been a growing interest in redesigning existing proteins or engineering entirely new proteins to address the deficiencies of molecules found in nature. Researchers have traditionally taken an unbiased approach to protein engineering, but as our knowledge of protein structure-function relationships advances, we have the exciting opportunity to apply molecular principles to guide engineering. Leveraging cutting-edge tools and technologies in structural biology and molecular design, our lab is pioneering a unique structure-based engineering approach to elucidate the mechanistic determinants of protein activity, in order to inform therapeutic development. Our group is particularly interested in engineering immune proteins, such as cytokines, growth factors, and antibodies, to bias the immune response for targeted disease treatment. Despite the recent explosive growth of protein drugs within the pharmaceutical market, limitations such as delivery, acquired resistance, and toxicity have impeded realization of the full potential of these therapeutics, necessitating new approaches that synergize with existing strategies to address clinically unmet needs. This talk will highlight ongoing work in our lab that spans the discovery, design, and translation of novel molecular immunotherapeutics for applications ranging from cancer to autoimmune disorders to regenerative medicine.