ENGINEERING NEXT GENERATION THERAPEUTICS TO COMBAT INFECTIOUS DISEASES

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Of the 56 therapeutic monoclonal antibody products currently marketed in the US, four now target infectious disease indications. An additional 40 recombinant antibodies are in clinical trials for infectious indications, with 29 in phase II or III trials. The evolution of antibiotic-resistant bacteria, the emergence of new pathogens, and a growing population of immunocompromised individuals means that in many cases antibodies are an increasingly attractive therapeutic option. Next-generation antibody formats, including antibody-drug conjugates and single-domain antibodies as well as antibody mixtures and bispecific antibodies provide access to novel therapeutic mechanisms and allow for targeting a wider range of epitopes. This talk will provide an overview of recent advances in the field and highlight two on-going projects in my lab. First, to address a resurgence in pertussis in high resource countries and continued high rates of morbidity and mortality in low resource countries, we have developed and antibody therapeutic neutralizing the toxin primarily responsible for symptoms. This antibody has been engineered for high affinity binding, reduced immunogenicity and extended serum half-life. We have also characterized its mechanism of action, using biochemical, structural and cellular assays. We have shown hu1B7 is protective against disease in mouse and adolescent baboon models of disease. Moreover, a single dose can prevent disease symptoms in a neonatal baboon model when administered five weeks before experimental challenge. Second, to address issues with recurrent cytomegalovirus infection in immuno-suppressed individuals, we envision a bispecific antibody able to redirect any passing T cells toward CMV suppression. In our first iteration of this therapeutic, we aim to target infected cells via a T cell receptor (TCR) binding the immuno-dominant peptide-HLA complex. Since TCRs are typically low affinity and express poorly as soluble molecules, we have used a novel eukaryotic-based cell display system that allowed us to rapidly identify variants with higher affinity and enhanced stability. We have generated TCR variants with up to 100-fold improved affinity that retain exquisite peptide selectivity. We will report our initial efforts to use this modified TCR to target CMV-infected cells.