

## **NEXT-GENERATION ANTIBODY AND TCR THERAPEUTICS FOR INFECTIOUS DISEASE**

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Parasitic and infectious diseases cause over 9.5 million deaths worldwide annually, yet only 3 of the over 50 approved antibodies are for infectious conditions. This disparity can be attributed to the high costs of antibody development in the face of small molecule alternatives and effective vaccines; however, a growing niche of specialty applications and the emergence of antibiotic-resistant strains make antibody therapeutics a likely eventuality. Particular challenges for developing therapeutic proteins for pathogenic diseases are that high variability in circulating strains, mutability within the host, and immune escape mechanisms limits the efficacy of monoclonal antibody formats. Instead, next generation formats that can exhibit broader activity or induce novel immune mechanisms may be a viable approach.

T-cell receptors (TCRs) are membrane-bound molecules that bind peptide-MHC (pMHC) molecules displayed by host cells, and are experts at recognizing infected cells. We have replaced one arm of a bispecific antibody with a soluble TCR to make a novel TCR/Ig hybrid. To do this, we first developed a system which can display TCRs on the surface of CHO cells. After optimization of the TCR format, in particular constant region modifications, we replaced the transmembrane region of the construct with an IgG1 hinge and Fc to express and purify soluble fusions. By including a knob or hole mutation in the Fc region, we were able to make bispecific molecules. Our current format couples an anti-CD3 antibody specificity to a human TCR that is associated with cytomegalovirus (CMV). We hypothesize that this format may have unique ability to suppress CMV reactivation or infection in transplant recipients or pregnant women. Ongoing work includes affinity maturation of the TCR, as well as testing the bispecific in a cellular model of CMV.