COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Chimeric Bait Receptor (CBR) For Reprogramming Of Myeloid Cells To Target And Eliminate Emerging Viral Infections

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In the face of the COVID-19 pandemic and growth of global biological threats, the need for proactive solutions against future infectious agents has become clear. To address this imminent threat, we have developed an off-the-shelf immunotherapy that could be utilized to prevent and combat infection by any known or emerging virus, preventing the next global pandemic and rendering potential virus-based bio-weapons ineffective.

Our innovation is three-fold: (1) an off-the-shelf mRNA-based therapeutic against viral infections – chimeric bait receptor (CBR). CBRs are modular synthetic receptors that are expressed on the surface of immune cells and can be rapidly reconfigured to attack almost any pathogen: virus, bacteria, or malignant cells; specifically, on macrophages in the upper respiratory tract to fight airborne viral infections. (2) Single therapeutics targeting multiple viral infections and insensitive to emerging mutations of the targeted viruses, preventing the development of resistance. (3) CBRs encoded by mRNA can be stored and deployed at ambient temperatures and administered by the end-user in the field using a standard atomizer/inhaler.
One of the ultimate threats to DoD personnel, and to society at large, is the uncertainty of biological threats, both natural and man-made. The first-in-class CBR platform allows for minimal lead time between first infection or preemptive intelligence and first response, providing protection for military personnel and civilians and eliminating the challenges to the global economy, health, and defenses.

Our initial CBR construct redirects macrophages to combat SARS-CoV-2 infection, it contains a portion of hACE2 receptor which is responsible for SARS-CoV-2 infection. We have successfully demonstrated that macrophages expressing this CBR specifically neutralize SARS-CoV-2 virus by phagocytosing live lentivirus displaying the spike envelope protein of SARS-CoV-2 virus (Spike-LV). We have also demonstrated that this CBR is insensitive to several variants of SARS-CoV-2. Briefly, the CBR construct was delivered to a macrophage cell line using lentivirus or delivered via mRNA transfection to primary macrophages that were differentiated from CD14+ monocytes isolated from peripheral blood. The modified cells were pre-incubated with either Spike-LV or with replicating SARS-CoV-2 strain WA1 virus (in a BSL-3 facility). After a 2-hour pre-incubation, the supernatant was collected and applied to pre-seeded hACE2-expressing cells. The infection level was evaluated by GFP signal on flow cytometry for the Spike-LV; and using a plaque assay for the replicating SARS-CoV-2 virus. The in-vitro neutralization assays showed superior phagocytosis and viral elimination by our CBR-expressing macrophages compared to un-modified control macrophages.

To determine the anti-viral activity of our CBR constructs in-vivo, hACE2-expressing mice were infected via intranasal route with an LD50 inoculum of SARS-CoV-2 (1E3 PFU) mixed with either CBR-expressing myeloid cells or with encapsulated CBR mRNA. We were able to demonstrate in-vivo delivery of our CBR using mRNA, allowing us to avoid ex-vivo cell modification and facilitate in-vivo treatment by mRNA administration.

Currently, we are developing a CBR-based treatment that simultaneously targets several families of viruses such as Filoviridae (Ebola, Marburg), Flaviviridae (Dengue, Zika), Togaviridae (Chikungunya), and Alphaviruses. Development of novel CBRs is facilitated and accelerated by in-silico simulations using AI-based tools and pipelines.

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