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

Identification Of Host-targeting Nanobodies Disrupting New-world Arenavirus Receptor Binding

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A traditional approach for antibody-based anti-viral therapeutics is to identify high-affinity monoclonal or polyclonal antibodies that bind to viral entry proteins such as SARS-CoV-2 spike, RSV F protein, and Ebola virus glycoprotein. While this approach can generate potent virus-specific therapeutics, with multiple FDA approved examples, because they target viral entry proteins therapeutic effectiveness is limited by viral protein diversity and is susceptible to rapid viral evolution and escape. For the highly-pathogenic clade-B new-world arenaviruses, including Junin virus (JUNV), Machupo virus (MACV), Chapare virus (CHAPV), Sabia virus (SABV), Tacaribe virus (TCRV) and Guanarito virus (GTOV), some cross-reactive monoclonal antibodies have been identified for closely related viruses, but none have potent activity against all of clade-B.

An alternative therapeutic approach is to target cellular receptors implicated in viral entry, as with Ibalizumab, which targets cellular CD4 receptor to restrict HIV-1 replication. Clade-B arenavirus requires binding of the viral GP1 to the apical domain of the cellular transferrin receptor (TfR), suggesting that therapeutics targeting host TfR could be potent against all of the clade-B viruses, and would not be subject to viral evolutionary escape. Some examples of TfR decoys and TfR binding antibodies have been demonstrated to limit clade-B virus replication, with one example demonstrating some protective effect in in-vivo models against lethal JUNV challenge. Importantly, Fc effector function was dispensable for protection, with an Fc mutant mAb showing increased (although not complete) protection compared to the wild type TfR targeting mAb. This supports physical blocking of the GP1-TfR apical domain interaction as a protective mechanism and suggests that the additional functions of traditional antibody therapeutics (compliment and effector cell activation) are not involved in the observed protective effect.

At Sandia, we have utilized a phage-display bio-panning approach to identify a library of novel nanobody candidates which bind to human TfR. Preliminary screening suggests that a selection of our top candidates restrict VSV-JUNV (GPC) virus replication in culture, and we are currently further evaluating binding kinetics, epitope mapping, and in-cellulo potency of our top TfR interacting hits. Our platform allows for the discovery of novel nanobody sequences which have unique epitope profiles relative to traditional mAbs, are more flexible regarding multimerization and conjugation, and demonstrate improved stability and producibility.