Title:

A Broadly Applicable Therapeutic Platform that Employs a Simple VHH-Based Neutralizing Agent (VNA) and a Universal Effector Antibody (efAb) to Replicate the Pathogen Neutralization and Serum Clearance Functions of Polyclonal Antibodies

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Abstract:

We have developed and successfully tested a novel therapeutic platform that performs two major effector functions of conventional polyclonal antibodies, pathogen neutralization and pathogen serum clearance. Our platform performs both of these functions by administering two simple recombinant proteins. One component is a “VHH-based neutralizing agent”, or VNA, that binds pathogens at two or more unique sites and potently neutralizes their activity. Each VNA is a heteromultimer of camelid heavy-chain-only antibody (Ab) V_H (VHH) binding domains. Linking VHHs into VNAs commonly results in major improvements in pathogen neutralization potency compared to the monomer VHHs. The second component is the “effector Ab” (efAb), a monoclonal Ab that binds to multiple copies of an epitopic tag present on each VNA. Co-administration of the VNA and the efAb results in decoration of the pathogen with multiple mAbs which, in addition to neutralization, promotes rapid pathogen clearance from serum. The same efAb can be used in all therapeutics developed using this platform. Our platform has been successfully used in animal models to protect animals from many different pathogen targets, including: C. difficile infection (CDI); exposure to C. diff toxins TcdA and TcdB; Shiga toxin-producing E. coli (STEC) infection; exposure to Shiga toxins Stx1 and Stx2; exposure to two serotypes of Botulinum neurotoxin (BoNT); exposure to ricin, and; exposure to anthrax. In some animal models, employing the VNA alone has proven fully protective in the absence of efAb. VNAs containing up to four linked VHHs have

successfully been used to treat exposures to two different pathogens with a single, easily-produced protein. Genetic delivery using a single treatment with an adenovirus that promotes in vivo VNA expression protects mice from lethal BoNT/A challenge for more than two months and protects gnotobiotic pigs from the lethal sequela of STEC infection. Use of this platform should permit rapid development of economic therapeutics for virtually all pathogens responsive to antibody treatments, including many microbial and viral pathogens. The resulting products should have much improved safety and shelf-life properties compared to conventional serum-based products. Genetic delivery options should permit protection from multiple pathogen risks for long periods with a single treatment and make possible oral delivery for treating enteric diseases.