University of Massachusetts Medical School

eScholarship@UMMS

May 8th, 12:30 PM - 1:30 PM

Identification of a Human Monoclonal Antibody to Replace Equine Diphtheria Anti-toxin for the Treatment of Diphtheria

Leila M. Sevigny
University of Massachusetts Medical School

Et al.

Let us know how access to this document benefits you.

Follow this and additional works at: https://escholarship.umassmed.edu/cts_retreat

Part of the Amino Acids, Peptides, and Proteins Commons, Bacterial Infections and Mycoses Commons, Immunoprophylaxis and Therapy Commons, and the Translational Medical Research Commons

Identification of a Human Monoclonal Antibody to Replace Equine Diphtheria Anti-toxin for the Treatment of Diphtheria

Leila M. Sevigny, Brian J. Booth, Kirk J. Rowley, Brett Leav, Peter S. Cheslock, Kerry A. Garrity, Susan E. Sloan, Gregory J. Babcock, William D. Thomas, Jr, Mark Klempner, Yang Wang

Department of Medicine, MassBiologics of UMMS
Yang.wang@umassmed.edu

Abstract

Diphtheria anti-toxin (DAT) has been used to treat *Corynebacterium diphtheriae* infection for over one hundred years. While the global incidence of diphtheria has declined in the 20th century, the disease remains endemic in many parts of the world and significant outbreaks still occur. Diphtheria anti-toxin is an equine polyclonal antibody with considerable side effects that is in critically short supply globally. A safer, more readily available alternative to DAT would be desirable.   In the current study, we cloned human monoclonal antibodies (HuMabs) directly from *antibody secreting cells* of human volunteers immunized with Td vaccine. We isolated a diverse panel of HuMabs that recognized diphtheria toxoid and recombinant protein fragments of diphtheria toxin. Forty-one unique HuMabs were expressed in 293T cells and tested for neutralization of diphtheria toxin in *in vitro* cytotoxicity assays. The lead candidate HuMab, 315C4 potently neutralized diphtheria toxin with an EC_{50} of 0.65 ng/mL. Additionally, 25 µg of 315C4 completely protected guinea pigs in an *in vivo* lethality model. In comparison, 1.6 IU of DAT was necessary for full protection resulting in an estimated relative potency of 64 IU/mg for 315C4. We further established that our lead candidate HuMab binds to the receptor binding domain of diphtheria toxin and blocks the toxin from binding to the putative receptor, heparin binding-epidermal growth factor like growth factor. The discovery of a specific and potent neutralizing antibody against diphtheria toxin holds promise as a potential human therapeutic and is being developed for human use.