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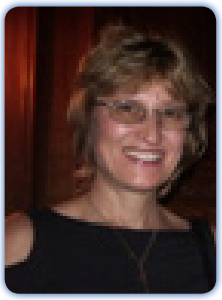

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Neutralizing antibodies directed against Botulinum A and B toxin heavy and light chains

Purpose of Study: The antiBotABE is a collaborative consortium project with an aim to generate an oligoclonal cocktail of protective recombinant super-humanized IgGs against neurotoxins secreted by Clostridium botulinum A, B, and E strains. A new strategy has been implemented involving germline-humanized antibodies of macaque (Macaca fascicularis) origin, which already proved successful to generate neutralizing antibodies against ricin and anthrax toxins, as well against encephalitis viruses. These drug lead candidates could become available for biodefense primarily, but also for treatment of natural and iatrogenic cases of botulism.

Methods: The recombinant form of the corresponding heavy (HC) and light (LC) chains of botulinum neurotoxin (BoNT) A and B were used to immunize macaques, from which an immune antibody phage-display library was built. The best antibody fragments (scFvs) isolated from that library were selected according to their affinities, and the best binders against the LC and HC were tested against BoNT holotoxin for their in vitro inhibition properties in an endopeptidase assays and ex vivo neutralization in mouse phrenic nerve-hemidiaphragm assay respectively. The most effective scFvs were humanized using human germline sequences as template, expressed as full size IgG and tested individually and in combination for neutralization properties in local flaccid paralysis as well as in lethality bioassay in vivo.

Summary of Results: The best scFvs or scFv-Fcs against the LC, selected by inhibition of endopeptidase studies in vitro and subsequently by mouse phrenic nerve-hemidiaphragm assay were SEM120-IIIC1 and BLC3 against BoNT/A and B respectively. The best scFvs or scFv-Fcs against the HC were selected by highest neutralization capacity in the mouse phrenic nerve-hemidiaphragm assay and were AHc38 and B2-7 against BoNT/A and B respectively. When these antibodies were expressed as IgGs and tested in the mouse protection assay AHc38 and BLC3 alone protected mice from toxin induced paralysis, whereas combinations of SEM120-IIIC1 and AHc38 as well as combinations of BLC3 and B2-7 fully protected mice in vivo at doses where protection was not observed by each antibody alone.

Conclusions: AntiBotABE project has developed promising germline-humanized IgGs confirming the success of a strategy, based on targeting the HC and LC domains and the use of NHP hyper-immune libraries. These antibodies are potential lead candidates for further clinical development.

Biography

Thea Sesardic has over 35 years' experience in biomedical research with 25 years' experience at NIBSC on regulatory research focusing on the 3Rs - replacement, reduction and refinement of animals in the field of biological products derived from bacterial toxins. Over 10 methods have been developed and implemented as part of the batch release function of the group for toxins, antitoxins and toxoid vaccines at NIBSC, reducing the use of animals by 1,000 a year at NIBSC alone. Several of the methods have also gone through international validation and are now regulatory standards. In her capacity as UK delegate on the European Pharmacopoeia group of experts, she has introduced new monographs and method chapters (eg. potency of human tetanus IgG, safety and potency of DT vaccines, replacing toxin challenge methods and replacing LD50 assays for Botulinum toxin for therapy) that continue to impact animal use in Europe and globally. She has contributed to several major revisions and manuals of methods to assess quality, safety and efficacy of DT vaccines as part of a WHO working group.

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