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Development of five hyper-humanized antibodies neutralizing the Botulinum neurotoxins A, B and E: The European AntiBotABE project

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Botulism is a naturally occurring disease, mainly caused by the ingestion of food contaminated by one of the 7 serotypes (A to G) of botulinum neurotoxins (BoNTs). BoNT/A is the most lethal biological substance currently known, with a human 50% lethal dose estimated at 1 ng.kg-1, and they are classified among the 6 major biological warfare agents. AntiBotABE, a European Framework, 7 funded projects aimed to develop 6 humanized IgGs, neutralizing BoNT serotypes A, B and E by targeting their heavy (HC) and light chains (LC). Six macaques were immunized with the recombinant LC or HC of BoNT/A, B or E, and their corresponding immune libraries were generated and screened by phage-display. After each panning, the most reactive scFv were isolated and their affinity measured. Inhibition or neutralization capacities were determined in vitro (SNAP25 or VAMP2 endopeptidasic assay) or ex vivo (mouse phrenic nerve-diaphragm assay). Neutralizing scFvs were identified for 5 of the 6 antigens. For each of the 5 libraries, the most efficient scFv was germline-humanized and expressed as full-length IgG. In the mouse bioassays, 3/5 IgGs alone and all IgGs in pairs, protected mice from paralysis or death after a challenge with the respective BoNT serotype. 1–5 Antibodies isolated during this project are potential lead candidates for further clinical development and we are looking for clinical development opportunity.

Biography

Arnaud Avril works for the French Armed Forces Biomedical Research Institute (IRBA), based in Paris area. He has a Master degree in Genetic and Immunology from Lyon University (France) and a PhD in Biotechnology applied to antibodies from the Grenoble-Alpes University (France). He is the Head of a team specialized in the research, development and engineering of recombinant antibodies against rare diseases for biodefense. He has developed germline-humanized recombinant antibodies starting from non-human primates immunized with non-toxic antigens. He has contributed to the development of several antibodies neutralizing botulinum neurotoxins, anthrax, ricin and Orthopoxvirus. He has also contributed to the development immuno-diagnostic assays for the rapid, convenient and cheap detection of biological agents, for armed forces, medical staff and first responders. He is involved as an expert on the clinical development of a recombinant antibody for anthrax therapy.

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