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Title: Design and Advancement of ***Gr***aft ***E***nabled ***A***ntibody ***T***herapies (GrEAT)

Executive Summary:
Membrane proteins such as ion channels, transporters or G-protein coupled receptors (GPCRs) are excellent but difficult drug targets involved in a large number of life-threatening diseases and conditions. These proteins, over-expressed and essential for disease onset and progression, are naturally targeted by toxins from venomous organisms. During evolution, these toxins have been optimized to efficiently target physiologically-relevant proteins involved in ion channel opening or closure, thus incapacitating the prey or defending against predators. We propose to generate synthetic antibody (Ab) libraries that integrate natural toxin-based polypeptides grafted in place of one of the complementarity determining regions as a scaffold. Such libraries will be a formidable resource for discovery and subsequent directed-evolution of graft-enabled antibodies against pharmacologically challenging or previously thought as "undruggable" targets, as well as be a starting point for further biological therapeutic lead development and commercialization, in line with the vision and mission of the partner organization, CCAB.