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Single-domain antibody-based therapeutics for *Clostridium difficile* infection

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Clostridium difficile continues to be one of the most prevalent hospital-acquired bacterial infections in the developed world, despite the recent introduction of a novel and effective antibiotic agent (fidaxomicin). Alternative approaches under investigation to combat the bacteria include fecal transplantation therapy, vaccines and antibody-based passive immunotherapies. By and large, inhibitory antibodies that recognize the primary *C. difficile* virulence factors, toxin A and toxin B, are the most popular passive immunotherapy under investigation, but antibodies to other targets, such as surface-layer proteins (SLPs), binary toxin, motility factors, and adherence and colonization factors may also have (complementary) therapeutic potential. Single-domain antibodies derived from camelid heavy chain antibodies and referred to as VHHs provide attractive therapeutic modalities against *C. difficile* infection (CDI). Some of their unique features compared to mAbs include their single-domain nature, small size (13-15 kDa), high chemical, thermal and proteolytic stability, high aggregation resistance, high level expression in microorganisms, high modularity, ability to access cryptic epitopes (e.g., cavities in receptors, enzymes, toxins and infectious agents), amenability to *in vitro* selection and engineering approaches for robust domains that are resistant to proteases (e.g., GI protease) and acidic pH-induced aggregation, denaturation and degradation. Moreover, high-affinity VHHs with KDs in the low-nM-pM range are readily obtainable. In my talk, I will describe our recent efforts to develop toxins A/B-specific and Ab-based therapeutics for CDI and how various antibody engineering approaches and structural data is used to improve their efficacy. Data on VHHs against another therapeutic target, *C. difficile* SLP are also presented.

Biography

Jamshid Tanha is a Senior Research Officer and Team Leader at National Research Council Canada (NRC), Human Health Therapeutics Portfolio and an Adjunct Professor at the University of Ottawa. He has completed his BSc and PhD in Biochemistry and Molecular Immunology from University of Saskatchewan, Canada. He has been a Research Officer since 2001 in the Antibody Engineering Group and more recently in the Antibody Libraries Team carrying out research on "The generation and optimization of camelid and human single domain antibodies for diagnostic and therapeutic applications". He has authored/co-authored ~60 articles in refereed journals and books.

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