AbTids: A new class of anti infective biologicals.

ABSTRACT

In response to the threat of antimicrobial resistance, we have developed a new platform technology called AbTids (Antibody + Antimicrobial peptides) built around a heavy chain antibody fragment derived from camels, attached to a linear antimicrobial peptide by a pathogen specific cleavable linker. These simple biologicals are extremely stable, with low immune signature and can be engineered and formulated for once a day dosing. Being small, they can penetrate tissues, destroy biofilms and access epitopes hidden deep inside the antigen pocket. This molecule is produced as a prodrug in a bacterial production system (*E. coli*) and is activated only in the presence of the pathogen. We have established the *in vitro* proof of concept against *Candida sp* and *Staphylococcus sp* and have tested the concept *in vivo* in carbapenem resistant *Pseudomonas aeruginosa*. The target of this molecule is extremely novel, a component of the C4 decarboxylase transporter, that has been found to be present in all the pathogens of the ESKAPE group but absent in human host and is responsible for uptake of essential metabolites in the facultative aerobic as well as anaerobic conditions. The Pseudomonas molecule, ABG 14, has a MIC 99 value of 3.5 µg/ml (175 nM) comparable with the other small molecule anti bacterials in the market, a single dose of 5 mg/kg of which wiped out a clinically multidrug resistant *P.aeruginosa* in a systemic infection mouse model. We extended these findings by isolating an antibody fragment binding to all the ESKAPE pathogens ABG 24 that neutralises all the pathogens effectively developing a broad spectrum antibiotic for critical care applications. With funding from Bill and Melinda Gates foundation , we are developing a diagnostic kit for the detection of these pathogens in sepsis patients using the same camelid antibody fragments that can be used as companion diagnostics prior to the deployment of AbTids to definitively control recalcitrant drug resistant pathogens in critical care or community settings.

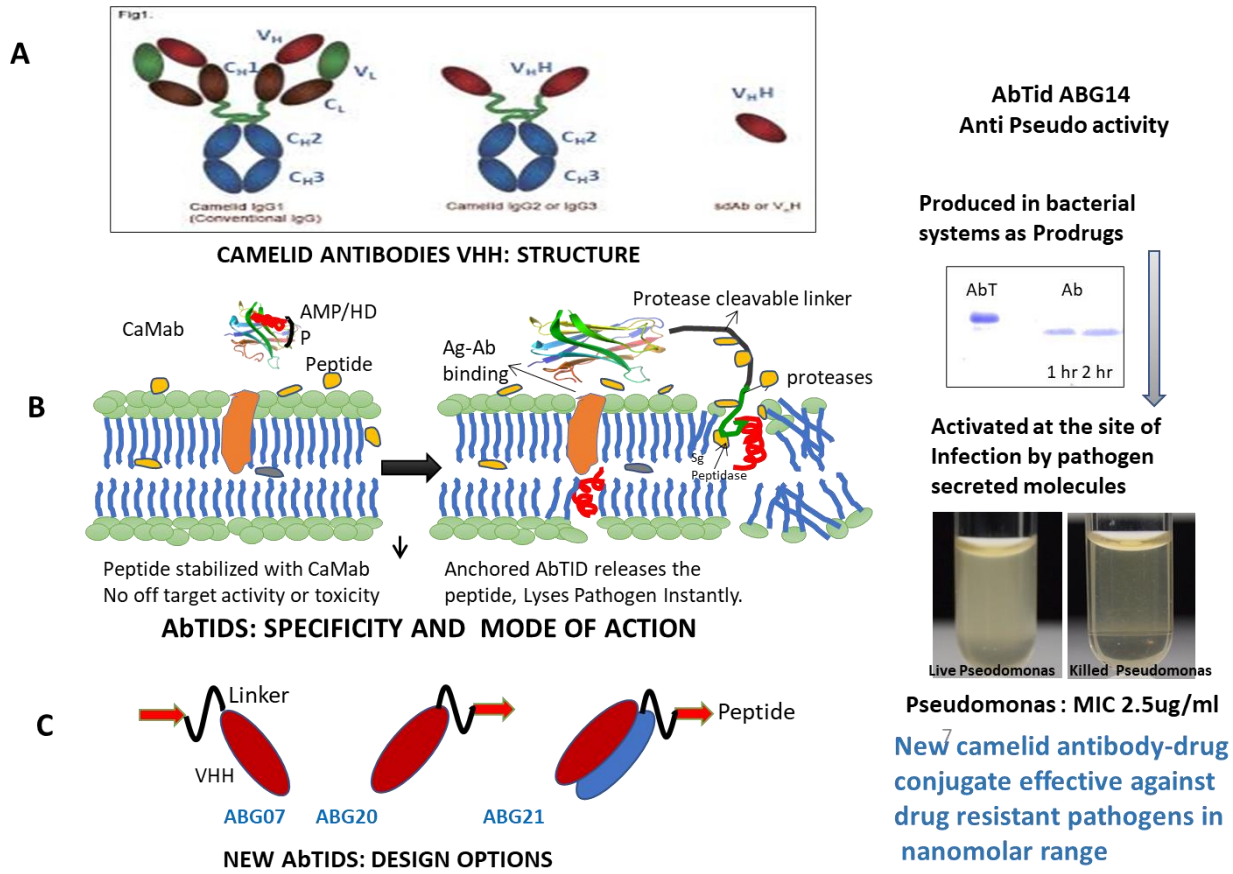

Fig: Design and mechanism of action of AbTids. A: Comparative structure of a conventional antibody and camelid antibody fragment VHH. B Design of AbTid: VHH (CaMab) is attached to an AMP by a protease cleavable linker. The VHH binds to the target and the peptide is released by the surface proteases of the pathogen. RHS: Activation of the anti-Pseudomonas AbTid ABG14 and its bacteriolytic activity. C: Design options of AbTids: The AMP can be attached to the N terminal, C terminal or to a bivalent/bispecific VHH to improve its druggable properties.