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## Innovative methods for non-invasive delivery of vaccines/therapuertics to combat infant and childhood diarrheal diseases

**Saul Tzipori**
Tufts University Cummings School of Veterinary medicine, USA

Oral or mucosal delivery of vaccines and therapeutics to the gastrointestinal track remains a serious challange despite much effort over many years. Below are two of new approaches to generate and deliver broad spectrum immune-based therapeutics and immunogens to the gastrointestinal track. 1) Theraputics using VHH-based neutralizing agents (VNAs): VNA that target and neutralize specific essential functions unique to each pathogen and thereby prevent/treat/alleviate disease. Camelids produce antibodies (Abs) with single-chain VH domains (VHHs) that can be expressed as recombinant proteins that can bind and neutralize antigens. VNAs are heteromultimers of linked, pathogen-neutralizing VHHs targeting non-overlapping epitopes that possess dramatically enhanced in vivo potency and can target multiple toxins/pathogens as a single biomolecule. The VHH components are highly stable to destruction by GI track enzymes and we have developed linkers that also resist degradation. Linked VHHs are known to neutralize and protect animals from virus infections. We have so far developed VNAs that potently neutralize several bacterial toxins, including botulinum toxins (A and B), ricin, anthrax (submitted), both *Clostridium difficile* toxins (TcdA & TcdB), both Shiga toxins (Stx1 & Stx2) liberated by Stx-producing E. coli (STEC). Our preliminary data demonstrate that VHHs against the *Shigella* type III secretion proteins, IpaB and IpaD, can block cell invasion. We have shown VNAs to be highly effective when delivered by gene therapy. They will be generated and characterized against all 4 targeted diarrheal disease agents. 2) New methods of non-invasive oral delivery of immunogens and therapuetics: a) Adenoviral vectors (Ad) for effective delivery. Vector-mediated in vivo transduction is an effective means to deliver immunogens or therapeutic antibody. We have developed genetic Ad delivery vectors which promote prolonged, high-level secretions of VNAs or immunogens to the bloodstream providing long-term protection of mice from Botulinum toxin exposure and protection of pigs from the fatal consequences of enterohemorrhagic E. coli (ETEC) and *Clostridium difficile* infections. Tropism modification of Ad allow targeted cell-specific in vivo transduction, leading to a localized expression of key effector molecules from enterocyte target cells. GI luminal delivery of either VNAs or immunogen is accomplished using the tropic human serotype 41, which has an enhanced capacity to transduce GI epithelial targets; a capacity exploited for the development of mucosal immunity in the GI track. *b) Bacillus subtilis* oral delivery platform: has been used to safely produce and deliver therapeutic VNAs to the gut so as to treat/prevent diarrhea. *B. subtilis* (BS) are spore-forming probiotic bacteria that proliferate in the GI track of all mammals including humans, and in piglets for >25 days. BS can be economically produced at high levels, are thermostable, and are common dietary ingredients in Asia. We have used BS to successfully deliver vaccine immunogens such as tetanus, and developed vectors which permit the secretion of functional VNAs or immunogens such as tetanus by BS in the gut lumen.

Saul.Tzipori@tufts.edu

## Novel synthetic strategies for the construction of lipopeptide vaccines using carbohydrate scaffolds

**Pavla Simerska**
The University of Queensland (UQ), Australia

The goal of this project was to develop methodologies for the construction of self-aduvanting carbohydrate-core lipopeptide vaccines containing multiple copies of immunogenic peptide antigens. The lipidic sequence imparted self-aduvanting properties and the carbohydrate core was varied to determine the optimum orientation of the antigens. The group A streptococcal (GAS) infection was chosen as a model disease, and therefore different GAS B-cell peptide antigens were incorporated into our vaccine system. In order to be able to quickly and efficiently construct libraries of vaccine candidates, a convergent strategy was developed where-by building blocks could be synthesised and purified prior to final assembly. An efficient and convenient synthesis of a highly versatile alkyne functionalised carbohydrate building block and lipidated Fmoc-lysine were devised. The carbohydrate building block was coupled to the lipidic moiety (three lipidated Fmoc-lysines) on solid support, and allowed for the conjugation of four copies of purified GAS peptide antigens using the alkyne-azide Huisgen cycloaddition click reaction. Since each component was synthesised and purified before final assembly, the purity of the final vaccine constructs was significantly improved, hence final purification was less demanding. The strategy was elaborated by the preparation of a vaccine candidate which incorporated an additional promiscuous T-helper epitope. Although B cells may be activated via a number of T cell-independent routes, the T cell-dependent activation of B cells can lead to stronger and more long-term immune responses. In vitro and in vivo methods were used to evaluate structure activity relationship of the carbohydrate-core lipopeptide GAS vaccines.

p.simerska@uq.edu.au