

## Crossing the barrier: targeting epithelial receptors for antigen delivery to the mucosal immune system

Bert Devriendt, Vesna Melkebeek, Bruno Goddeeris, Eric Cox

Laboratory of Immunology, Faculty of Veterinary Medicine, UGent, Merelbeke, Belgium  
b.devriendt@ugent.be

The gastro-intestinal immune system daily encounters a vast array of foreign antigens derived from food, gut-residing commensal micro-organisms and pathogens. To keep these innocuous and hazardous antigens at bay a single layer of epithelial cells, mostly enterocytes, lines the intestinal tissues. These enterocytes not only function as a barrier to prevent uncontrolled access of macromolecules to the subepithelial tissues, they also convey information on the gut luminal content to the underlying immune cells and as such enterocytes create and sustain a tolerogenic environment under steady state conditions. During infection however they are still able to sense pathogens and relay this information to induce an immunogenic environment, enabling antigen-presenting cells (APCs) to mount an adequate pathogen-specific immune response. This crosstalk between the intestinal epithelium and underlying APCs plays a key role in shaping the local micro-environment towards tolerance or immunity. The immune response in the alimentary tract to soluble antigens is by default tolerance. As such oral vaccination with soluble antigens is quite ineffective to induce protective immunity, although a few exceptions exist such as cholera toxin (CT), the LT enterotoxin and colonisation factors (F4 fimbriae) purified from the porcine-specific pathogen enterotoxigenic *E. coli* (ETEC). Indeed, oral delivery of purified F4 fimbriae induces intestinal immune responses, protecting piglets from a challenge ETEC infection. The polymeric nature of the fimbriae is pivotal for this protective mucosal immunity. Intriguingly, the oral immunogenicity of these antigens relies on their binding to receptors at the apical surface of enterocytes. We recently identified aminopeptidase N (APN, CD13) as the epithelial receptor involved in transcytosis of F4 fimbriae. Antibody-mediated targeting to APN resulted in enhanced epithelial transcytosis and promoted mucosal immune responses in a pig model. This ligand-induced receptor activation seems necessary to switch the local micro-environment from a tolerogenic to an immune-inductive state. Thus, selective targeting of antigens to epithelial APN could enhance the efficacy of oral vaccines and accelerate their design.