Understanding the interaction of gastrointestinal biomolecules with cell penetrating peptide-functionalised PLGA-nanoparticles

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Surface modification of nanoparticles with cell-penetrating peptides (CPP) is a promising tool in nanomedicine research to enhance the cellular uptake of drug-loaded nanoparticles. To achieve the greatest benefit from those nano-drug delivery systems, it is important to understand the interplay between nanoparticles and the bio-interface. While cell culture studies are used ubiquitously to study nanoparticle-cell interactions, the interaction of nanoparticles with the complex biological fluids encountered before reaching the cell surface is less well understood. While interactions between nanoparticles and blood components have been intensely investigated, almost unknown is the interaction of nano-systems with contents in the gastrointestinal tract (GIT). Oral intake is one of the most common routes of administration for medicines and so a deeper understanding of nanoparticle behavior in the gut is necessary. Previous studies[1] have found that digestive enzymes form a corona around nanoparticles in the GIT, as has been observed for protein adsorption in the blood. The charge of nanoparticles is known to play a crucial role in cellular uptake [2]. Therefore, as a first step towards studying more complex GIT fluids, our initial aim in this project was to investigate how bile salts influence the surface charge of nanoparticles with different CPP modifications.

We synthesized poly(lactic-*co*-glycolic) acid (PLGA) nanoparticles with an average size of 213 ± 21 nm using the technique of microfluidics[3]. Dynamic light scattering (DLS) was used to measure the zeta potential of nanoparticles with increasing concentrations of a model bile salt, sodium taurocholate. Adsorption of this bile salt to the PLGA nanoparticle surface followed a Langmuir isotherm model, suggesting the formation of a single layer of sodium taurocholate around the negatively charged PLGA-nanoparticle, reaching an equilibrium concentration of approximately 2.0 mM. We then modified the particle surface with positively charged cell-penetrating peptides and exposed them to the same experimental conditions. We focused on the novel branched TAT CPP, which facilitates the electrostatic interaction with the negatively charged phospholipid membrane because of its unique architecture[4].

Future work will investigate the adsorption phenomena with nanoparticles in more physiologically-relevant media (e.g. simulated gastrointestinal fluids containing e.g. phospholipids and proteins/enzymes). This data will provide key information about the *in vivo* behavior of CPP-conjugated PLGA-nanoparticles in the gastrointestinal tract and guide the design of nanomedicines for application in oral delivery.

References:

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