Developing methods of selective, location-specific drug delivery in the gastrointestinal tract

by

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Oral drug delivery remains the most commonly used method of drug administration, due to greater patient adherence to the treatment. However, drug efficacy when delivered orally remains suboptimal due to the presence of formidable barriers to drug diffusion in the gastrointestinal (GI) tract and subsequent absorption in the bloodstream. Current methods of overcoming these barriers involve encapsulating the drug in pH-responsive or mucoadhesive nanoparticle formulations, which protect the drug cargo from the harsh environment of the GI tract and allowing for controlled release at the optimal time and location. However, they generally provide minimal targeting capability (due to the wide spatial range of the pH environment or the presence of mucus), limiting their ability to release the drug in a specific location.

The GI tract is a very diverse organ system, and location-specific expression of certain targets can be used to improve the localization and retention of the drug carriers. One example of these differentially expressed targets are the mucin glycoproteins that compose the mucus layers, which cover the epithelial surfaces of the GI tract. These mucins are expressed differently in different regions of the GI tract. As such, the work in this thesis primarily aims to identify potential ligands (small molecule and peptide) that can selectively bind to the different mucins, thus allowing for improved targeting and localization within the associated regions of the GI tract.

For both small molecule and peptide ligands, the work in this thesis is presented similarly. First, the starting libraries of small molecules and peptides were chosen and prepared for initial *in vitro* screening. Next, *in vitro* screening was performed to select for the most promising "hits" which showed stronger binding and selectivity to the targets when compared to general mucoadhesives. These hits were then exposed to the mucin in a more physiologically relevant *ex vivo* model, which allowed for further selection of the top hits. These hits were then examined using bio-layer interferometry to measure the binding kinetics and calculate the kinetic affinity. Their performance was evaluated *in vivo* to demonstrate their ability to localize a bound cargo in a rodent model. Finally, computational methods were used to analyze the results and identify potential mechanisms of ligand-mucin binding. Overall, the work in this thesis will inform the development of further regioselective targeting approaches to improve oral drug delivery efficacy.

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