

Crossing of the Intestinal Barrier Thanks to Targeted Biologics: Nanofitins

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Abstract : The limited stability of clinically proven therapeutic antibodies limits their administration by the parenteral route. However, oral administration remains the best alternative as it is the most convenient and less invasive one. Obtaining a targeted treatment based on biologics, which can be orally administered, would, therefore, be an ideal situation to improve patient adherence and compliance. Nevertheless, the delivery of macromolecules through the intestine remains challenging because of their sensitivity to the harsh conditions of the gastrointestinal tract and their low permeability across the intestinal mucosa. To address this challenge, this project aims to demonstrate that targeting receptor-mediated endocytosis followed by transcytosis could maximize the intestinal uptake and transport of large molecules, such as Nanofitins. These affinity proteins of 7 kDa with binding properties similar to antibodies have already demonstrated retained stability in the digestive tract and local efficiency. However, their size does not allow passive diffusion through the intestinal barrier. Nanofitins having a controlled affinity for membrane receptors involved in the transcytosis mechanism used naturally for the transport of large molecules in humans were generated. Proteins were expressed using ribosome display and selected based on affinity to the targeted receptor and other characteristics. Their uptake and transport ex vivo across viable porcine intestines were investigated using an Ussing chambers system. In this paper, we will report the results achieved while addressing the different challenges linked to this study. To validate the ex vivo model, first, we proved the presence of the receptors targeted in humans on the porcine intestine. Then, after the identification of an optimal way of detection of Nanofitins, transport experiments were performed on porcine intestines with viability followed during the time of the experiment. The results, showing that the physiological process of transcytosis is capable of being triggered by the binding of Nanofitins on their target, will be reported here. In conclusion, the results show that Nanofitins can be transported across the intestinal barrier by triggering the receptor-mediated transcytosis and that the ex vivo model is an interesting technique to assess biologics absorption through the intestine.

Keywords : ex-vivo, Nanofitins, oral administration, transcytosis

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