BIOBUSINESS BRIEFS

DEAL WATCH

Chiasma and Roche partner in oral peptide drug delivery

Roche and the specialist drug delivery company Chiasma have teamed up to develop an oral form of the somatostatin analogue octreotide. The drug is currently in Phase III clinical trials for acromegaly (a disorder that is characterized by excess production of growth hormone) and in Phase II clinical trials for neuroendocrine tumours.

Under the terms of the agreement, Chiasma will continue to develop oral octreotide until the Phase III clinical trial for acromegaly is completed (anticipated in the second quarter of this year) and Roche will receive an exclusive worldwide licence to commercialize oral octreotide. Chiasma will receive an upfront payment of US$65 million and milestone payments of up to $530 million, as well as sale-based royalties.

"This deal between Roche and Chiasma — as well as substantial investment in oral drug delivery technology by Novo Nordisk and Sanofi — confirms that major pharmaceutical companies continue to explore ways to convert injected peptides and proteins into oral versions," says David Brayden, Associate Professor of Drug Delivery and Director of the Irish Drug Delivery Network, University College Dublin, Ireland.

Octreotide, which inhibits the release of various hormones such as growth hormone, insulin and glucagon, is currently marketed for the treatment of acromegaly and neuroendocrine tumours. However, it needs to be injected (initially up to three times a day, but it can be given once every four weeks if a depot formulation of the drug is used).

"Two factors make oral delivery of peptide and protein drugs very challenging," says Robert Langer, the David H. Koch Institute Professor in the Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, USA. "First, the need to protect the peptide or protein against degradation by enzymes and dilution by intestinal contents in order to get them to the intestinal epithelium. Second, obtaining absorption through the intestinal epithelium into the bloodstream."

Langer also notes that the protein needs to be protected against degradation by stomach acid. "But this is relatively easy to achieve by surrounding the tablet or capsule with a surface coating (commonly known as an enteric coating) that is stable at the low pH of the stomach but dissolves in the higher pH of the upper and lower gastrointestinal tract," he explains.

Chiasma's technology ensures that the protein payload remains intact until it reaches its target region beyond the stomach, where it transiently increases the permeability of the small intestine. The peptide and a permeation enhancer (selected medium-chain fatty acids) make up a hydrophilic fraction that is then combined into a lipophilic medium (of oil and surfactants) to produce a suspension of solid hydrophilic particles in a hydrophobic medium. Once the formulated product reaches the small intestine, it is thought that the hydrophobic medium diffuses into the epithelium and then transiently opens paracellular tight junctions between adjacent epithelial cells to allow permeation of its payload peptide into the hepatic portal vein, from which it is transported to the liver and the bloodstream.

"Just like with small-molecule drugs, there will probably not be a single universal strategy that can be used for all peptides and proteins. However, technologies exist that enable delivery of broad classes of compounds that require minimal compound-specific optimization," says Langer.

"In addition to Chiasma's method, other technologies include the use of carrier molecules to transport the protein across the intestinal wall or small adhesive wafers containing the protein that provide direct contact with gastrointestinal membrane cells. This approach protects the drug from enzymes in the intestinal lumen and maximizes the contact between the drug and the intestinal surface. Nanoparticle-based approaches to target the protein to intestinal M cells or other cells in the intestine to enhance drug uptake might also be a solution," he continues.

Brayden notes that many of the techniques being tested in clinical trials — such as Chiasma's methods — are relatively simple compared to nanoparticle approaches. "Less complex approaches use mild non-ionic surfactant permeation enhancers to affect the transcellular pathway in addition to the tight junction route. Although many of these enhancers have a long history of use in humans (some are already in other products for different reasons), there is a concern that they might damage the intestine and allow transport of harmful molecules and pathogens from the intestine into the blood upon repeat administration when used for oral peptide and protein delivery. Nevertheless, these technologies have straightforward scalable manufacturing processes and appear to lead the way clinically," he says.

For example, Oramed — which has a platform based on the use of intestinal protease inhibitors and absorption enhancers — is about to begin a Phase II trial of an oral insulin pill for type 2 diabetes, and is also investigating an oral form of the glucagon-like peptide 1 (GLP1) analogue, exanatide, which is in early-stage clinical trials. However, such products face a further challenge compared to agents such as octreotide, for which achieving a formulation that has only single-digit oral bioavailability (estimated at around 5%) may be sufficient to achieve a therapeutic effect. "For antidiabetic polypeptides such as insulin and GLP1 analogues (where it can be argued that the oral route is the preferred physiological route to reach the liver target) an oral bioavailability of 15–20% is likely to be needed, so oral success for either of these molecules would make a really significant impact for the field," concludes Brayden.

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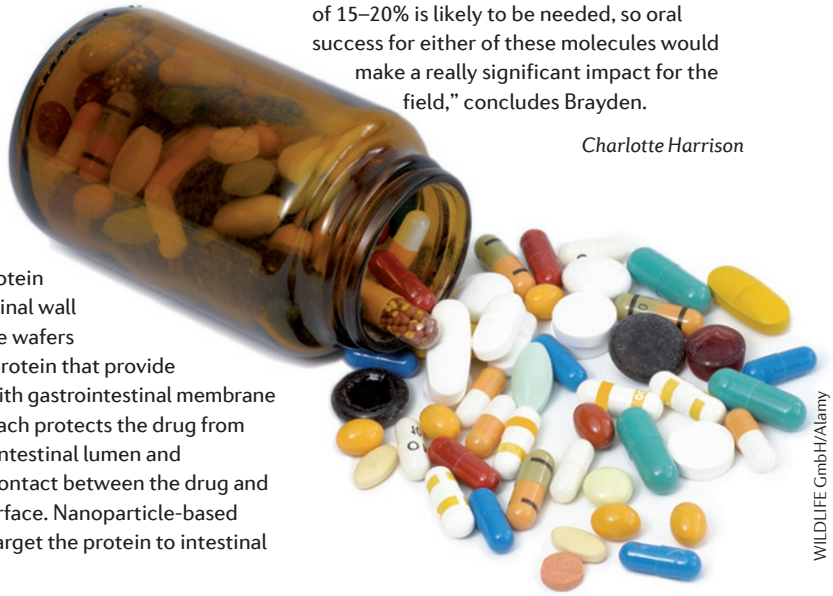

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