Oral nanoparticles

By Lauren Martz, Staff Writer

Researchers from **Brigham and Women's Hospital** and the **Massachusetts Institute of Technology** have developed targeted nanoparticles that could enable the oral delivery of biologics such as insulin.[1] The clinical translation of the approach will require identifying a suitable therapeutic payload and fine-tuning the pharmacology of the system.

Poor intestinal absorption prevents the oral delivery of many compounds and virtually all biologics. Factors that affect oral bioavailability include stability and size, as peptide therapeutics generally are degraded in the GI tract and large molecules cannot be passively absorbed through the intestinal epithelium.

Several companies have tried to develop oral delivery methods for biologics. In 2006, an oral insulin tablet from **Emisphere Technologies Inc.** failed in a Phase II trial in type 2 diabetes. In 2011, Emisphere and partners **Nordic Bioscience A/S** and **Novartis AG** discontinued development of the oral salmon calcitonin biologic SMC021 after it failed several Phase III trials in osteoarthritis and osteoporosis.

Emisphere is now using its Eligen oral drug delivery platform, which consists of binding small molecules to the therapeutic of interest to facilitate its passive transport into the cells, to develop oral formulations of **Novo Nordisk A/S**' glucagon-like peptide-1 (GLP-1) analogs for diabetes.

Altus Biologics Inc. discontinued development of the oral cross-linked pancreatic enzyme crystal biologic Trizytek liprotamase, which was in development to treat malabsorption caused by exocrine pancreatic insufficiency in patients with cystic fibrosis (CF). The company, which was creating oral biologics using the cross-linked enzyme crystal protein technology platform, filed for bankruptcy in 2009 and was acquired by **Althea Technologies Inc.** in 2010.

Omid Farokhzad and colleagues at Brigham and Women's Hospital decided to tackle oral biologics by marrying a drug-stabilizing approach with a method for improving the uptake of biologics. Farokhzad is an associate professor of anesthesia at Brigham and Women's Hospital.

For stability, the team opted for nanoparticles that encapsulate compounds or peptides. For uptake, the group chose to target neonatal Fc fragment of IgG receptor transporter-α (FCGRT; FCRN).[2,3] FCRN normally functions to transport maternal IgG from breast milk to offspring; however, receptor expression persists in the adult intestines and is also present in tissues including the blood brain barrier, liver, lungs, vascular endothelium and kidneys.[4,5]

A team from **The University of Nottingham** had previously shown that peptides bound to FCRN could be transported across the airway epithelium.[6]

Next, the Brigham and Women's Hospital team conjugated the Fc portion of IgG, which binds FCRN, to the surface of standard polylactic acid (PLA)-polyethylene glycol (PEG) nanoparticles using maleimide linkers. PEG-PLA nanoparticles have a hydrophilic PEG shell and a hydrophobic PLA core to carry drug payloads.

In vitro, the FCRN-targeting nanoparticles had twofold higher transport across a human epithelial colorectal adenocarcinoma cell monolayer, a common model used for drug permeability testing, than nontargeted nanoparticles.

Next, the group fed fluorescently labeled, FCRN-targeting nanoparticles to fasted mice. Transport of the targeted nanoparticles to the villi could be seen by microscopy, whereas no signal was seen for nontargeted nanoparticles.

Detailed biodistribution studies showed that the targeted nanoparticles accumulated in multiple organs in the mouse including the spleen, lungs, liver and heart. The targeted nanoparticles had an oral absorption efficiency of 13.7%; the efficiency for nontargeted nanoparticles was 1.2%.

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The nanoparticles also were able to deliver a therapeutically relevant payload. In fasted mice, oral administration of targeted, insulin-loaded nanoparticles caused a hypoglycemic response that was greater than that caused by oral delivery of free insulin or insulin-loaded, nontargeted nanoparticles.

The hypoglycemic effect of the targeted nanoparticles lasted for 15 hours, whereas it lasted only 1.5 hours for injection of free insulin.

Results were published in *Science Translational Medicine*.

The paper also included researchers from MIT, **The David H. Koch Institute for Integrative Cancer Research at MIT** and the **MIT-Harvard Center of Cancer Nanotechnology Excellence**.

Going bigger

Farokhzad's team is planning to test the platform in larger animal models that more accurately replicate how the nanoparticles will behave in humans.

Edith Mathiowitz, a professor of medical science and engineering, director of the Biotechnology Graduate Program and a member of the Center for Biomedical Engineering at **Brown University**, said that manipulating the FCRN system to enable oral drug delivery is a major step forward.

"I am a believer that this is one of the technologies that can be used to deliver more therapeutic molecules orally, and specifically peptide therapeutics," she said. "Peptides need the protection of nanoparticles for stability through the GI tract, but until now the issue of poor uptake in the intestines has been unresolved. This system may allow us to overcome this major barrier."

Jeff Hrkach, SVP of technology and R&D at **Bind Therapeutics Inc.**, added that many small molecules with poor bioavailability could benefit from the approach. "This nanoparticle system has the potential to expand broadly for oral small molecule drugs by overcoming barriers like first-pass metabolism and liver toxicity. If you're getting optimal systemic exposure via this pathway, it opens up the opportunity for more drugs with poor oral bioavailability," he said.

The maleimide linker used to attach the IgG Fc fragment to the nanoparticles might need to be rethought, according to Jörg Kreuter, a professor of pharmaceutical chemistry at **Goethe University Frankfurt**. He was concerned that the linker will complicate preparation and increase the risk of GI toxicity.

"Such linkers could lead to interaction with the GI tract contents and could lead to an immunological reaction. For this reason, I would always try to avoid such linkers if you can," he said.

Mathiowitz agreed that GI toxicity is a risk. "They also need to study the general toxicity of the method. The GI tract is designed to reject molecules like these from being absorbed into circulation, so we need to be sure that this does not cause any toxic effects."

Farokhzad said that although maleimide linkers are used to induce immunogenicity for vaccines, he does not expect that immunogenicity should be a problem. "The relative ligand density on the nanoparticle surface is low, and there should not be any unconjugated linkers on the surface that could cause an immune response," he said.

Thomas Rademacher, founder and CSO of **Midatech Ltd.**, added that broad tissue uptake by FCRN could also be a liability, particularly for insulin. "The clinical consequences of insulin release from organs such as the lungs, heart and spleen or other FCRN-rich tissues will take a long time to assess," he said.

Midatech's Midaform Insulin PharmFilm, an oral film formulation of insulin-coated gold nanoparticles for delivery through the cheek, has completed Phase I testing to treat diabetes.

Farokhzad said, "We should be able to design the nanoparticles to go where they need to go. In this proof of concept, the nanoparticles were not designed for localization but rather to enhance bioavailability, so we considered the fact that the particles were able to get to those organs to be a very good thing. In addition to IgG Fc, additional ligands could be added to the surface to fine-tune nanoparticle localization."

Kreuter said that insulin may not have been the best choice for a proof-of-concept molecule because of its unique pharmacology issues.

"The biggest problem with the oral delivery of insulin bound to nanoparticles is the fact that it leads to a retarded and rather uncontrolled prolonged action, which may not be the optimal solution for a diabetic patient," he said.

Farokhzad told *SciBX* that whether or not the oral insulin application will be pursued will be decided by the commercial entity that develops the technology.

"We do plan to test the insulin-loaded nanoparticles in larger animal models, which could serve to validate both the general approach and the insulin platform, but there may be lower-hanging fruit. There is a high safety hurdle for diabetes, and there may be other indications with greater unmet need for our first platform-validation product," he added.

Farokhzad noted that the approach has potential beyond insulin delivery. "We also plan to expand the platform within the oral application to test nanoparticles carrying other drugs," he said.

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Nano-tuning

Farokhzad is planning a number of steps to enhance the platform, including more specific tissue targeting that could open potential ocular or pulmonary indications to nanoparticles.

"The lung and the placenta express FCRN, and it transports molecules in the correct direction needed for drug delivery. We may be able to tweak the current nanoparticle structure to target transport across those systems," he said.

Farokhzad has cofounded three companies based on his earlier work with nanoparticles, including FCRN-targeting nanoparticles: **Selecta Biosciences Inc.**, **Blend Therapeutics Inc.** and Bind Therapeutics. He said that the IP covering this extension of the technology that more broadly demonstrates proof of concept for the FCRN-binding technology is not yet licensed to any company.

Selecta licensed rights to the earlier targeted nanoparticle technology for vaccine and immunological applications, and Bind licensed the technology for all other indications. Bind is developing Accurins, which are targeted polymeric nanoparticles with prolonged circulation and controlled payload release, for oncology.

Farokhzad said that both companies may be interested in licensing the new IP.

Hrkach said that although Bind Therapeutics is focused on nanoparticles for cancer, which can be delivered intravenously, the company is interested in broadening its scope, and a technological advance such as this is very exciting.

"For Bind, this is a prototype for our technology platform and represents an interesting opportunity as we continue to expand our pipeline," he said.

Farokhzad said that MIT and Brigham and Women's Hospital have filed for a patent covering the extension of the FCRN technology. The IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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