Pills of the future: Scientists develop way to successfully give nanoparticle therapeutics orally

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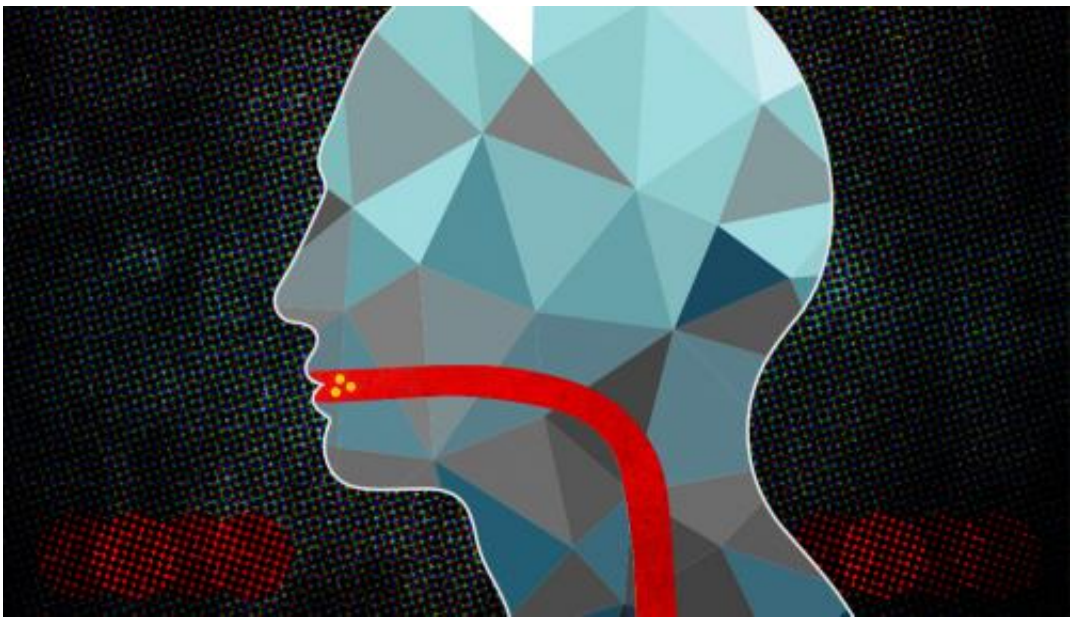

Credit: CHRISTINE DANILOFF

Drugs delivered by nanoparticles hold promise for targeted treatment of many diseases, including cancer. However, the particles have to be injected into patients, which has limited their usefulness so far.

Now, researchers from MIT and Brigham and Women's Hospital (BWH) have developed a new type of nanoparticle that can be delivered orally and absorbed through the digestive tract, allowing patients to simply take

a pill instead of receiving injections.

In a paper appearing in the Nov. 27 online edition of *Science Translational Medicine*, the researchers used the particles to demonstrate oral delivery of insulin in mice, but they say the particles could be used to carry any kind of drug that can be encapsulated in a nanoparticle. The new nanoparticles are coated with antibodies that act as a key to unlock receptors found on the surfaces of cells that line the intestine, allowing the nanoparticles to break through the intestinal walls and enter the bloodstream.

This type of drug delivery could be especially useful in developing new treatments for conditions such as high cholesterol or arthritis. Patients with those diseases would be much more likely to take pills regularly than to make frequent visits to a doctor's office to receive nanoparticle injections, say the researchers.

"If you were a patient and you had a choice, there's just no question: Patients would always prefer drugs they can take orally," says Robert Langer, the David H. Koch Institute Professor at MIT, a member of MIT's Koch Institute for Integrative Cancer Research, and an author of the *Science Translational Medicine* paper.

Lead authors of the paper are former MIT grad student Eric Pridgen and former BWH postdoc Frank Alexis, and the senior author is Omid Farokhzad, director of the Laboratory of Nanomedicine and Biomaterials at BWH. Other authors are Timothy Kuo, a gastroenterologist at BWH; Etgar Levy-Nissenbaum, a former BWH postdoc; Rohit Karnik, an MIT associate professor of mechanical engineering; and Richard Blumberg, co-director of BWH's Biomedical Research Institute.

No more injections

Several types of nanoparticles carrying chemotherapy drugs or short interfering RNA, which can turn off selected genes, are now in clinical trials to treat cancer and other diseases. These particles exploit the fact that tumors and other diseased tissues are surrounded by leaky blood vessels. After the particles are intravenously injected into patients, they seep through those leaky vessels and release their payload at the tumor site.

For nanoparticles to be taken orally, they need to be able to get through the intestinal lining, which is made of a layer of epithelial cells that join together to form impenetrable barriers called tight junctions.

"The key challenge is how to make a nanoparticle get through this barrier of cells. Whenever cells want to form a barrier, they make these attachments from cell to cell, analogous to a brick wall where the bricks are the cells and the mortar is the attachments, and nothing can penetrate that wall," Farokhzad says.

Researchers have previously tried to break through this wall by temporarily disrupting the tight junctions, allowing drugs through. However, this approach can have unwanted side effects because when the barriers are broken, harmful bacteria can also get through.

To build nanoparticles that can selectively break through the barrier, the researchers took advantage of previous work that revealed how babies absorb antibodies from their mothers' milk, boosting their own immune defenses. Those antibodies grab onto a cell surface receptor called the FcRN, granting them access through the cells of the intestinal lining into adjacent blood vessels.

The researchers coated their nanoparticles with Fc proteins—the part of the antibody that binds to the FcRN receptor, which is also found in adult intestinal cells. The nanoparticles, made of a biocompatible

polymer called PLA-PEG, can carry a large drug payload, such as insulin, in their core.

After the particles are ingested, the Fc proteins grab on to the FcRN in the intestinal lining and gain entry, bringing the entire nanoparticle along with them.

"It illustrates a very general concept where we can use these receptors to traffic nanoparticles that could contain pretty much anything. Any molecule that has difficulty crossing the barrier could be loaded in the nanoparticle and trafficked across," Karnik says.

Breaking through barriers

In this study, the researchers demonstrated oral delivery of insulin in mice. Nanoparticles coated with Fc proteins reached the bloodstream 11-fold more efficiently than equivalent nanoparticles without the coating. Furthermore, the amount of insulin delivered was large enough to lower the mice's blood sugar levels.

The researchers now hope to apply the same principles to designing nanoparticles that can cross other barriers, such as the blood-brain barrier, which prevents many drugs from reaching the brain.

"If you can penetrate the mucosa in the intestine, maybe next you can penetrate the mucosa in the lungs, maybe the blood-brain barrier, maybe the placental barrier," Farokhzad says.

They are also working on optimizing drug release from the nanoparticles in preparation for further animal tests, either with insulin or other drugs.

More information: "Transepithelial Transport of Fc-Targeted Nanoparticles by the Neonatal Fc Receptor for Oral Delivery," by E.M.

Pridgen et al. *Science Translational Medicine*, 2013.