Swallowing A Biologic Drug?

biotech Primer
Industry Knowledge Delivered

SURVIVING THE STOMACH IS KEY

Over the past two decades, biologic drugs — drugs composed of proteins produced by living cells — have become the safest, most effective top sellers within the pharmaceutical industry.

Approved to treat a variety of diseases including rheumatoid arthritis, diabetes, multiple sclerosis, Crohn's disease, and a whole range of cancers, these drugs include monoclonal antibody therapeutics, hormones, and immune system signaling molecules. Their safety and efficacy depend largely on the complex, three-dimensional structure of the protein product itself — which is incredibly delicate and time-consuming to develop on a large scale. The majority of these are administered via injection directly into the bloodstream for maximum potency.

So, why can't we just swallow a biologic pill? The simple answer: biologics would not survive the acidic pH and digestive enzymes of the gut. Even if survival were possible, the next issue to contend with is absorption; if the protein is not broken down properly, it will not be absorbed into the bloodstream. Companies seeking to develop oral delivery of biologics must overcome both hurdles.

Injectable delivery is cumbersome at best. It has a significant impact on a patient's quality of life, which in turn affects compliance to drug therapy regimes. In many cases, patients must make regular trips to an infusion center to receive required treatments. Thus oral administration is the holy grail in terms of delivering biologics. In this WEEKLY, we'll take a look at the different paths being pursued to make this ambition a reality.

THE ROBOTS OF RANI THERAPEUTICS

One of the hottest companies in the oral delivery of biologics space is **Rani Therapeutics** (San Jose, CA). Their product is a "robotic pill" — a small device capable of traversing the intestinal tract and injecting a biologic drug directly into the body. It works in the following way:

- After the pill is swallowed, it makes its way through the digestive process, keeping its fragile biologic drug cargo tucked safely inside. Its capsule is pH-sensitive and stays intact at the low pH of the stomach.
- When it enters the intestine, its outer coating dissolves at the slightly higher pH of the intestine.
- This pH change also triggers a chemical reaction to occur, which releases carbon dioxide which blows up a tiny "balloon" found within the pill.
- This supplies the force needed to drive the drug-containing needle into the intestinal wall — delivering the biologic to the bloodstream.
- The needle itself then dissolves, and the balloon is excreted.

This may sound like the stuff of science fiction — and indeed, the device is still in preclinical trials — but the robotic pill has attracted big name pharma partners, including **AstraZeneca** (London, UK) and **Novartis** (Basel, Switzerland), as well as investment from **Google Ventures** (Mountain View, CA) among other venture funds. If the device ultimately succeeds, it will revolutionize the delivery of biologic drugs.

ENGENE'S GUT CELL FACTORIES

enGene (Vancouver, Canada) is bypassing the delivery obstacle by attempting to turn the cells of the gut into drug-producing factories. The trick is to deliver a gene — the instructions for a specific therapeutic protein — to those cells. enGene is using tiny carbohydrate-based nanoparticles to encase the gene. The carbohydrate coating protects the gene as it passes through the stomach, yet allows it to be absorbed into the intestines. The protein is then made in the intestines.

This approach is especially appealing for diseases affecting the colon and small intestine, such as inflammatory bowel syndrome or Crohn's disease. enGene is currently using this platform in the preclinical development of the anti-inflammatory protein IL-10, for the treatment of inflammatory bowel disease.

APPLIED MOLECULAR TRANSPORT

Applied Molecular Transport South San Francisco, CA) is using a protein scaffold adapted from pathogenic microbes such as salmonella, which colonize the gut by secreting immune-crippling proteins into our body.

Proteins from these "gut bugs" work by tricking the intestines into absorbing toxic proteins in the same way that they absorb nutrients from food. Applied Molecular Transport scientists have tweaked these microbial proteins to carry a therapeutic payload, rather than the toxins. Development efforts are currently aimed at delivering anti-inflammatory proteins to the intestines.

Swallowing biologic drugs is no longer a pipe dream. Sensing the opportunity to make a significant impact on the biopharma industry, innovative companies are approaching the drug delivery problem with a range of strategies. It is likely that no single strategy will work for all types of biologics, but any success with a handful of products would represent a major breakthrough for the industry.