A NOVEL APPROACH TO THE ORAL DELIVERY OF BIOLOGICS, PEPTIDES AND ANTIBODIES

Mir Imran, from Rani Therapeutics™, provides an exclusive update on his company's groundbreaking robotic Auto-Pill™, which delivers a pain-free intestinal injection using a dissolvable needle made from materials that can be absorbed or easily passed out of the body. This approach allows the delivery of biologics of any molecular weight.

Over the past several decades, biologic therapeutics have proven to be highly effective treatments for a number of chronic diseases such as arthritis, diabetes, multiple sclerosis, plaque psoriasis, Crohn's disease and ulcerative colitis, among others. Collectively, these agents represent a market with annual sales exceeding US$200 billion (£150 billion), and sales growth in this area has steadily increased. In fact, between 2009 and 2012, the industry saw a 33% increase, with therapeutic proteins and monoclonal antibodies showing the greatest upwards trend.

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Despite their blockbuster success, the delivery of biologics is far from ideal as the majority of these drugs can only be delivered by injection. As a result, patients must endure painful and frequent injections, some as often as daily, which can have a dramatic impact on a patient's quality of life and compliance.

There is no doubt that the oral delivery of biologics, peptides and antibodies would be a breakthrough for patients and a bonanza for pharmaceutical companies. With as many as 150 failed attempts over the past 40 years, oral delivery of biologics remains the "holy grail" of drug delivery. Most notably, oral delivery of insulin, as well as other peptides like somatostatin and PTH, have been attempted multiple times, with low-single-digit bioavailability, which makes them clinically and commercially impractical. These prior attempts failed primarily because pharmaceutical approaches designed to protect the proteins from degradation and digestion in the GI tract were unsuccessful.

When we founded Rani Therapeutics in 2012, we decided to take a completely new approach to the problem of oral delivery of biologics. The result is the Rani Auto-Pill™ – a robotic pill that delivers an intestinal injection without exposing the drug to the digestive enzymes. The patient takes what appears as an ordinary capsule, but the Rani Auto-Pill™ is a sophisticated device which incorporates a number of innovations, enabling it to navigate through the stomach and enter the small intestine where it goes through a transformation and positions itself to inject the drug into the intestinal wall.

HISTORY OF THE RANI AUTO-PILL™

We started with the premise that injecting the drug into the intestinal wall would be ideal because there are no sharp-pain receptors in the intestine, rendering the injection painless. In addition, the intestinal wall is highly vascularised which means that the drug once delivered will be quickly absorbed. With deep experience in engineering and materials science, we designed the Rani Auto-Pill™ to ensure that the drug would stay protected within the pill until injected. To ensure safety of the Rani Auto-Pill™, we selected US FDA-approved injectable and ingestible materials that are either safely absorbed or easily passed out of the body (see Figure 1).

One decision we made early on was to formulate the biologic drug with appropriate excipients, in solid form. This has two distinct advantages; first, we can maximise the amount of drug in a small volume and second, the drug in solid dry form has longer shelf-life than in liquid form. The next question was what kind of needle to

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use for the injection? Metal needles were not an option for obvious reasons…no one wants to swallow metal needles! We decided to create tiny dissolvable needles which would contain the biologic drug. The idea was to deliver the dissolvable needle containing the solid drug into the intestinal wall. The drug would be released after the needle is injected and the needle is dissolved.

The next challenge was to figure out a way to develop enough force to deliver the needle into the intestinal wall. Initially, we considered levers and springs, but quickly ruled that out as no patient will want to swallow springs. We settled on the use of an inflatable balloon-like structure that would supply the force to deliver the needle. Balloon inflation happens when carbon dioxide is produced from a chemical reaction between citric acid and sodium bicarbonate that takes place inside the balloon, and this creates the pressure needed to inject the needle.

The balloon, including the needle and drug, are assembled in a cellulose capsule shell which is then coated with a pH-sensitive polymer that is designed to dissolve at a pH >6.5. This ensures that the capsule does not dissolve in the stomach where the pH is generally <5. Once the capsule goes past the duodenum, and the pH rises above 6.5, the outer shell dissolves, triggering the chemical reaction inside the balloon. The balloon then inflates and delivers the needle with the drug. Once the needle is delivered, all that is left is a deflated polymer, having the consistency of a bell pepper skin or tomato skin, which the patient passes out.

We believe this approach will allow us to deliver biologics of any molecular weight regardless of its structure or properties. So not only small peptides and proteins but even therapeutic antibodies, and RNAi therapies can easily be delivered by Rani's technology. The Rani route of administration presents additional advantages for certain biologics, such as those targeting the liver. Unlike subcutaneous delivery, where the drug first targets the systemic circulation and ultimately makes its way to the liver, with our approach the first organ the drug goes into is the liver. Thus, Rani Auto-Pill™ could potentially be very useful for drugs such as PCSK9 antibodies and insulin which target the liver.

The one limitation of the Rani Auto-Pill™ is how much drug can be put inside the needle. Currently, the limit is about 3-5 mg per capsule that should allow for the delivery of ~70-80% of all biologics (therapeutic peptides, proteins and antibodies). Drugs that are given in high doses, such as hundreds of milligrams at one time, may not be suitable for the Rani platform. However, the small payload is not a limitation for most peptides, proteins and therapeutic antibodies.

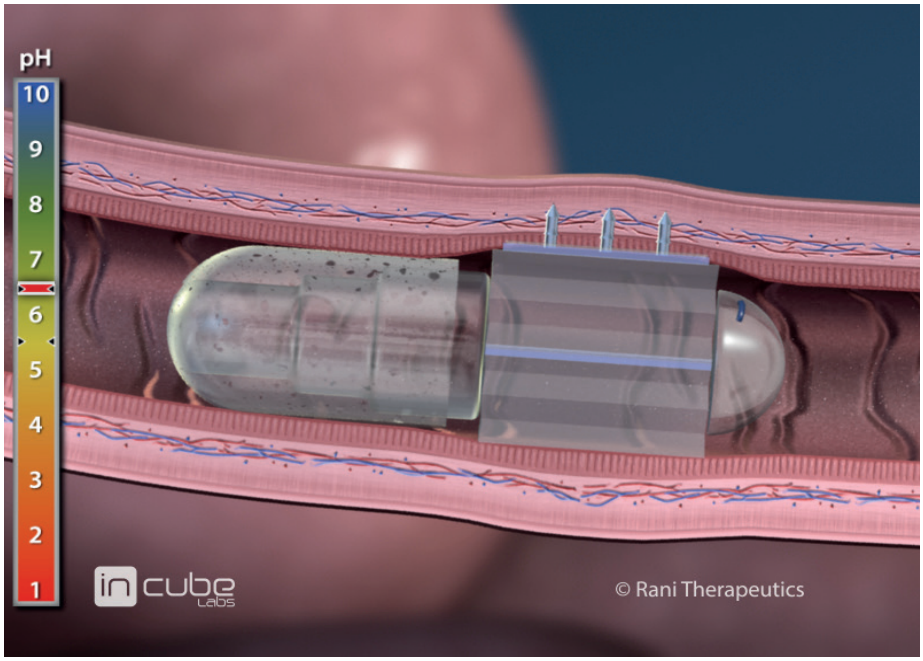

Figure 1: A diagrammatic depiction of the Rani Auto-Pill™. The current Auto-Pill is a 000 size, or the equivalent of a calcium or fish oil pill, and currently includes one needle for drug delivery. Over time, we envision multiple needles will be possible to increase payload.

RANI'S PATH FORWARD

This is a very exciting time for our company. We have brought together a diverse group of experts across disciplines including biology, material science, engineering, pharmacology and manufacturing. We are currently conducting a variety of studies in relevant pre-clinical models. The goal is to achieve safe and reliable delivery of the needles. Initial studies have shown that the Rani route of administration is as effective as subcutaneous injections. We have a strong patent position with more than 25 approved patents and 50 pending applications. We are now collaborating with two large pharma companies – Novartis and AstraZeneca – to test different molecules on the Rani platform.

CONCLUSION

We recognise that we are working on one of the biggest challenges in drug delivery, something we do not take lightly. We know there are many challenges ahead of us, but we stay focused on our mission. Rani has the potential to transform how biologics are delivered and most importantly, the potential to radically improve the quality of life for millions of patients suffering from chronic diseases.

ABOUT RANI THERAPEUTICS

Rani Therapeutics was developed at InCube Labs, a multi-disciplinary life sciences R&D lab focused on developing breakthrough medical innovations. The company has raised more than $70 million. Investors include Novartis, AstraZeneca, Google Ventures, Buttonwood, GF Ventures, KPC Pharmaceuticals, Virtus Inspire Ventures, Ping An Ventures, InCube Ventures and VentureHealth.

ABOUT THE AUTHOR

Mir Imran is a prolific medical inventor, entrepreneur and investor, who has founded more than 20 life sciences companies and holds more than 400 issued and pending US patents. Many of Imran's innovations have resulted in new standards of care, including the first FDA-approved Automatic Implantable Cardioverter Defibrillator. For more information, please visit: www.ranitherapeutics.com and www.incubelabs.com.