INTERVIEW: MIR IMRAN, RANI THERAPEUTICS

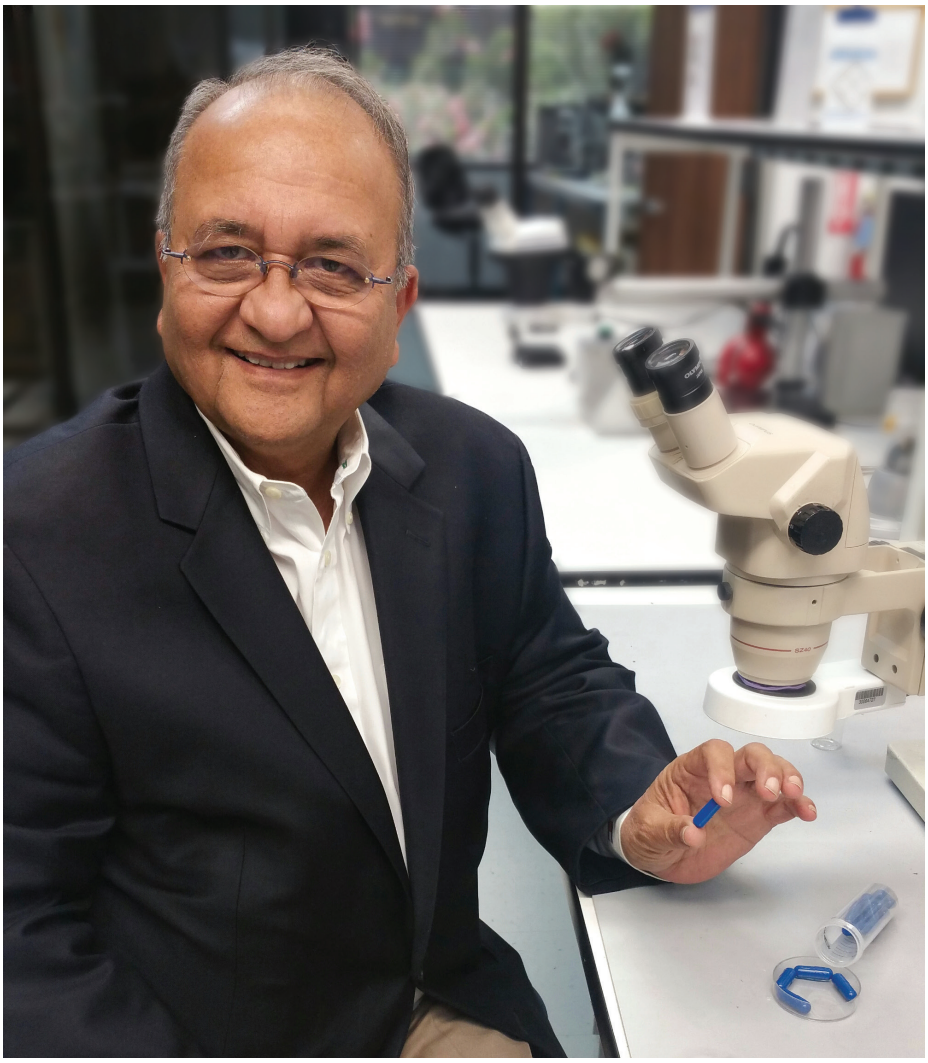
Mir Imran has spent the last 35 years focusing on his passion: creating breakthrough medical innovations that have saved or improved the lives of millions of patients. Mr Imran and his development company, InCube Labs, have a consistent track record of following that theme with many examples of successful companies and products.

Here, Mr Imran speaks with ONdrugDelivery Magazine in detail about one such example, concerned with the oral delivery of peptide therapeutics using a "Robotic Pill" technology, currently under development by Rani Therapeutics.

Q: Oral delivery of proteins and peptides is a notoriously tough market. Over the past decade or so many contenders have come and gone and there is – rightly or wrongly – real scepticism in the industry. What makes Rani Therapeutics' approach different? What are the key challenges any technology in this market will come up against, and how is Rani's Robotic Pill different from other oral delivery systems for biologics?

A: Not only over the past decade but over the past four or five decades people have been trying to deliver small peptides and proteins orally. Most notably insulin has been tried multiple times, and other smaller peptides like somatostatin, PTH and others have been attempted by various small, midsize and large companies. One executive at a large pharma recently told us they had counted at least 150 separate attempts over the last 40 years. There have been some minor successes in the sense that for smaller peptides you can achieve low single-digit bioavailability but it is not consistent and there is significant variability between patients and even within individual patients.

So, when we started work on our technology, we decided not to go down the same path that everyone else had gone down and failed. We felt that a better approach would be to take advantage of the biological fact that, unlike the skin, the intestines don't have sharp-pain receptors. You can poke needles all over the intestine without the patient even being aware of what is going on. The intestines do have stretch receptors so when you have gas you can feel the bloated feeling, even pain, but if a fish bone lodges in your intestine you wouldn't even feel it.



We took advantage of this physiological fact and decided to create a pill that actually injects the drug in the intestine. As far as the patient is concerned they are taking a pill, but when it reaches the intestine it delivers the drug by injection and the patient is of course oblivious to it. This approach allows us to deliver any biologic of any molecular weight regardless of chemistry and whether it is soluble or not. So not only small peptides and proteins but therapeutic antibodies, for example, and RNAi therapies can easily be delivered by our platform.

In a nutshell, it's an intestinal injection. It's taken as a pill and the rest happens automatically. It's so unique that when we started filing patents there was nothing similar in the existing patent or scientific literature. As a result we have very, very strong patent protection around the technology.

My background is in both engineering and medicine and I've been developing engineering-based therapies and medical devices for the last 36 years or so. In the development of Rani Therapeutics' technology we had to bring together a number of technologies that I've been exposed to over the years and a lot of materials science expertise as well.

Q: Are you able to go into more detail about some of the engineering and materials science challenges that you faced during the development of the Robotic Pill?

A: The first hypothesis was to inject the drug into the intestine because there are no pain receptors there. The next question was then about what kind of needle do you use to inject. Immediately I knew we could not have any metal needles, so what do you use? That was a unique challenge. Another challenge: how do you create the force to push the needle into the intestinal wall and how do you inject the drug? Do you have a liquid drug reservoir, for example?

We decided that we didn't want to have liquid drug, and instead we opted to make the needle out of sugar. It's an injectable-

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grade molecule that's used as an excipient in injections. We had to do a lot of process development to come up with a sharp needle. Then we had to deliver the drug. A liquid drug would dissolve the needle very quickly, so we decided to put the drug in solid form inside the needle, and that is what we do now.

Rather than delivering and retracting the needle, we made the needle short enough so that it could be delivered and left inside the intestinal wall to dissolve, releasing the drug to be absorbed into the highly vascularised intestinal wall.

The challenge that took us the longest to figure out was developing enough force to deliver the needle into the intestinal wall. Initially I was thinking about using levers and springs but it didn't make sense that anybody would want to swallow springs every day. It took us almost a year and a half and finally we came up with the idea of a self-inflating balloon. The self-inflation happens when carbon dioxide is produced from a chemical reaction that takes place inside the balloon, and this creates the pressure. It does it in a way that does not stretch the intestines. Once the needles are delivered, all you are left with is a deflated polymer balloon which has the consistency of a bell pepper skin or tomato skin, which the patient can pass out safely.

So while addressing the challenge of creating the force to deliver the needles, we addressed the safety concern that you don't want to have any solid material remaining that has the potential for causing blockage. We had to stay within the confines of FDA-approved ingestible materials.

We put it all in a capsule and had to develop very robust pH-sensitive coatings so the capsule would not disintegrate in the stomach but would actually go all the way into the intestines, past the duodenum. Once the pH reaches to 6.5 the outer shell dissolves, triggering the chemical reaction inside the balloon which inflates and delivers the needle (see Figure 1).

In addition to safety, we have to achieve high reproducibility – consistent, successful delivery of the needles. In our animal studies we have demonstrated reproducibility of more than 95%. The failures we have noticed are mostly manufacturing process defects that can be overcome with process refinements, better tooling, better machinery and so on. We think that with these refinements we will be able to achieve >99% reproducibility.

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Each one of these challenges and solutions I've described in a few short sentences took months or even years to figure out and therefore each one of these aspects itself led to a series of patents and IP.

Q: A lot of technology, e.g. electronic tech, is prototyped at a larger size for proof-of-concept and then another challenge is reducing its size down to a viable scale. Was it the case with Rani's technology that it was initially developed larger and then reduced to the size it is at now?

A: It was developed at the size it currently is, which is about the size of a calcium pill or fish oil capsule that people take every day. We do have plans to downsize it a little bit, but at present it is of a size that most people can take it relatively easily.

Q: In short, it appears that this technology completely subverts the problems that excipient-based and other oral protein delivery systems have to face, by taking such a completely different approach…

A: Previous attempts tried to block the proteases and other enzymes which break down proteins but you cannot win the battle with nature. The digestive system is really designed to break down proteins in order to absorb them but if protein drugs are broken down they cease to be drugs and they're just amino acids. In order to keep the drug in tact you have to prevent exposure to intestinal fluid and so the best option is to quickly inject it without exposing the drug. We've done numerous animal studies to demonstrate that this works – insulin and therapeutic antibodies, for example. Because it works without regard to molecular weight, it becomes a ubiquitous delivery platform in that almost any drug can be delivered.

The only limitation of course is how much drug we can put inside the needles. We have a limit of about 3-5 mg per pill and so if you look at the range of therapeutic peptides, proteins and antibodies I think we cover about 70-80% of all biologics out there. Clearly there will be some drugs that are given in the hundreds of milligrams at

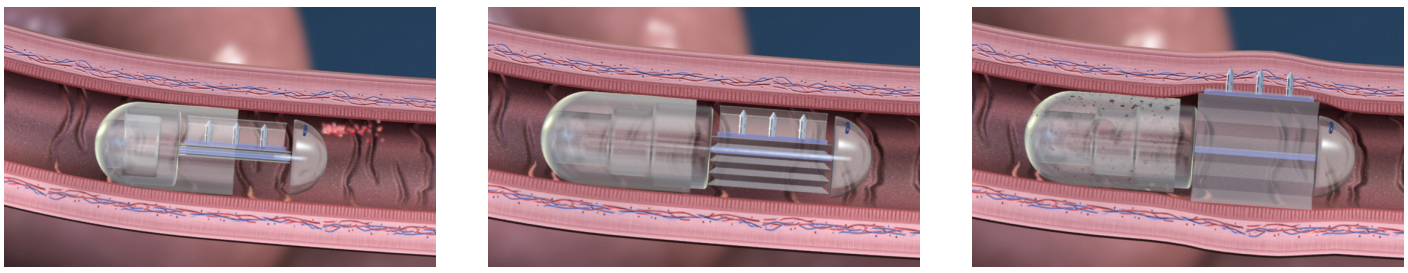

Figure 1: As it travels through the GI tract, the capsule remains intact (left), until the pH increases to 6.5/7.0, at which point the capsule dissolves, activating the chemicals within the capsule which react to release CO_2 and begin to inflate the balloon (middle). As the balloon becomes fully inflated, the drug-loaded needles are delivered into the intestinal wall (right).

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a time, and those will not fit into our platform. Every delivery technology has its own limitations. Ours is basically the payload. However many biologics are so potent – in the microgram range in fact, as with PTH, somatostatin, GLP1 analogues, for example – so really it is not a major limitation.

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Q: Non-invasive, non-oral delivery routes such as systemic delivery via the lung are advancing and an inhaled insulin product is once again on the market. And advances in the self-injection sector – auto-injectors and wearable injection devices for example – make them more viable products and more tolerable to patients than traditional needles and syringes. How does Rani's system stack up against delivery technologies that use these other routes of administration?

A: Yes, the auto-injectors have become more user-friendly, the patient doesn't see the needle and it is a shorter needle. However, you talk to the people who are using these auto-injectors and they hate them. They do it because they have to. Patch based injectors are still injections. As far as inhaled products are concerned, if you are treating a respiratory condition and you can deliver to the lungs then this makes sense and there are many products out there for COPD, asthma and pneumonia. Delivering, for example, insulin via the inhaled route is inherently risky and this is why the FDA has black box warnings on these products; dose variability is an issue and the potential for local interaction with lung tissue. With transdermal delivery, variability can be high depending on where the patient is pressing the patch on their body – a soft area or a bony area. And with microneedles, another big limitation is payload, which is only at microgram level. That is probably an order of magnitude smaller than Rani's oral technology.

If you have all options available – injection, transdermal inhalation or oral – guess what the patients and the physicians will opt for? And if you talk to physicians who are really interested in patient compliance, they know that efficacy of medications is so dependent on patient compliance – you might have the best drug, but if the patient doesn't take it, it's useless.

The Rani route of administration presents specific additional advantages for certain drug molecules, 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 the intestinal route the first organ the drug goes into is the liver. So a drug like the PCSK9 antibody [proprotein convertase subtilisin/kexin type 9 antibody, for reducing low-density lipoprotein (LDL) cholesterol] which Regeneron and Sanofi have, and which Amgen and a few others are developing, is very exciting. We don't have data yet but it is our belief that because the liver is the first organ the drug goes into after Rani delivery, and because the drug itself is targeting the liver, this could lead to a lower dosage requirement with fewer side-effects because you don't get drugs stuck in other compartments of the body. For patients not responding to standard statin therapy, PCSK9 can dramatically lower LDL.

One other advantage of the Rani technology, because we have such a unique formulation approach and unique delivery platform, is that we have taken off-patent drugs and put them back to a 20 or 30-year patent life in combination with our platform. For example, we have patents filed on every biologic that's out there – off-patent, about to go off-patent and patented. We think that this is a distinct advantage for companies who might be partnering with us.

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Q: Please could you tell me a little about the company, its founding and key events in its history that have got it to the stage it is at now?

A: I started working on the technology about five years ago. There have been many tough challenges along the way, and it's the combination of the variety of problems I have solved over the years that really gave me the background to address such a unique set of challenges that we faced in Rani. My background is in electrical and mechanical engineering and materials science, and I went to medical school though never practised medicine. I then started developing companies such as the one which developed an implantable defibrillator which has become the standard of care in cardiology and was acquired by Eli Lilly. I started a number of subsequent companies, mostly focusing on specific therapy areas such as cardiology, CNS and chronic pain etc, and developing devices to treat chronic diseases where we can have a profound impact on patient outcomes. There are some things that can only be treated with – or are better treated with – devices, not drugs.

So this long history of dealing with a number of conditions gave me the back-

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ground and familiarity to solve the unique problems Rani is addressing: how do you auto-inject drug into the intestine very cheaply, very reliably and very safely. It's really a culmination of those decades of experience, making mistakes and learning from them, that has allowed us to do this.

I don't work alone now. We have a very smart scientific and engineering team, working on the biology, designing the preclinical experiments, and really systematically testing our platform and the drug. This has been led by Dr Mir Hashim [Rani's Vice-President of Research & Development] who has a PhD in pharmacology and came to us from GSK and is an absolutely brilliant scientist. He's leading all the preclinical and clinical work. Our engineering team is a very talented group of engineers and materials scientists who are focused on making this platform scalable and manufacturable and reducing the cost. And of course I have a great senior team helping me take Rani and a number of other companies forward.

Rani Therapeutics itself was founded in 2012 and up until then InCube Labs funded its initial development, which took place within InCube. We also manage a venture capital find called InCube Ventures, which was the first investor. The second round of funding in summer 2013 was led by Google and our venture fund also participated. And then recently we announced a third round of funding where Novartis participated, together with a number of financial investors, and this will raise well over $40 million by the time we're done.

The Novartis partnership happened at the same time, and it's a deal we're very excited about.

We're in discussions with around a dozen other large pharma companies. You know, they always start off very sceptical because of the long history of failure but I'm quite happy with their scepticism because if they thought it was easy, the technology wouldn't have as much value. So by the time they go through our technology and examine the data in detail, they realise this might actually work and then they really get very excited about it.

Just imagine three of four players in the market for one particular molecule – basal insulin, for example, or TNF-alpha. Whoever has our platform is going to corner that market – there's no question in my mind about that, so this could shift market share in key areas dramatically.

> "We'll take our potential partner's molecule, formulate it into our platform, run animal studies and give them the data. They can then decide whether to sit down and negotiate a licensing deal with us or not. We don't get into a licensing situation at the outset, without first undertaking the feasibility"

Q: What is the current development and partnership status of the Robotic Pill platform? What are the most interesting applications/product programmes currently being explored?

A: We're in discussions with numerous companies about delivering their specific molecules. Some of these molecules are already approved, some are in the development pipelines of these companies.

Our approach is that we'll do an exclusive feasibility study because after they've looked at our internal data the next question they will ask is, "Can you actually deliver our molecule?" So we've come up with a standardised feasibility test, and during the feasibility period we don't talk to anybody else and we give an exclusive option to negotiate a licence at the end of the study. During the study, we'll take our potential partner's molecule, formulate it into our platform, run preclinical studies and give them the data. They can then decide whether to sit down and negotiate a licencing deal with us or not.

We will likely be announcing a second partnership in the coming months.

Q: The Robotic Pill is showing real promise, has attracted healthy funding and at least one major pharmaceutical partner, and the magnitudes of therapeutic markets that the Robotic Pill has the potential to access are staggering. What is Rani's strategy for the coming years?

A: We're very mindful of the regulatory process. The Rani technology is going to be treated by the regulatory agencies as a combination product. The most straightforward and fastest route is to make the first drug we would want to take into humans one that is already approved and has a long history of safety and efficacy. Getting first-in-man experience is a key milestone for us and one which we're looking forward to. We will also be continuing to focus on forming exclusive licensing partnerships on specific molecules with large pharma companies. And the ultimate for the company if we're successful could be a public offering at some time in the future.

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After attending medical school, Mir Imran began his career as a healthcare entrepreneur and has since founded more than 20 life sciences companies, more than half of which have been acquired. Mir has been running his R&D lab, InCube Labs, since 1995 and is recognised as one of the leading inventors and entrepreneurs in the field. He now holds more than 300 issued patents and is perhaps most well-known for his pioneering contributions to the first US FDA-approved automatic implantable cardioverter defibrillator (ICD). In addition to leading InCube Labs, Mir also runs a life sciences venture fund, InCube Ventures; VentureHealth, a healthcare crowd funding portal; and Modulus, a medical manufacturing company.

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