Translating academic discoveries

This is a short piece about a large issue: translating academic discoveries. It is a story quickly told, and is summed up in the following quote:

> 'A couple of years ago, we *knew* that our team of [academic] scientists had produced some dramatic breakthroughs. And so we started going to pharmaceutical companies, and saying 'This is what we've discovered. Aren't you interested?' We kinda got blank stares back. And we couldn't quite figure out why they weren't interested. And so, … we had two workshops … and we invited senior people from the biotech industry, the pharmaceutical industry, and we said to them … "*Why* aren't you interested in the science we're producing? We're doing great science." …. They said "You know, we would view any in-licensing decision as a several 100 million dollar decision. We wouldn't license something unless we thought it would be a successful development programme. And we don't have that kinda money just sitting around. So we would really have to be thinking about dropping an internal programme. So what we would really want to see from *you* non-profit, we would like to see a data package that is similar to what we have for our internal programmes." As soon as they said that, it was common sense, it was "Of course, they need to see an apples to apples comparison". So what we realized we needed to do was to take those discoveries that were being made by our academics and do the kind of work in terms of target validation, and replicating the experiments and doing them across many different models to develop a data package that the industry could look at and say "ok, I now *believe* that science and can take it forward." And to me that's the disconnect. All these papers that come out – there are several really important questions that aren't asked. Academic scientists don't think in terms of "Can these findings be reproduced consistently?" "Are they therapeutically relevant?" "Is this a drugable type of discovery?" "… the discovery that I made – is it translatable from animals to humans?" Those are four basic questions that don't typically get asked by academics in the academic setting, which are *essential* to pharma. Because without those questions being answered, pharma's not going to take the risk and move forward and take that discovery and take it to where it needs to go to turn it into a treatment. And I think that's one of the fundamental things that's not working and I think that as a non-profit we have a kind of unique role in the value chain to be able to take on some roles that academics can't really and that pharma can't and that the government can't.… Non profits should use the power of their non-profit status to be this kind of systems' integrator across the entire value chain.'

Scott Johnson, President and Founder, Myelin Repair Foundation (http://www.milkeninstitute.org/events/gcprogram.taf?function=detail&EvID=2121&eventid=GC10).

This is a two-minute clip taken from a 75 min panel discussion entitled 'Designing Innovative Medical Research Systems', hosted by the Milken Institute in Los Angeles in April 2010. Although in India we are aware that we do not know much about translational research, it is somewhat surprising that even in California those trying to find cures are not aware of what is involved in taking science closer to the market.

The science of translation

First, we discuss some examples of translation. When drug discovery is done in a biotech company, for instance, it is called 'discovery work', not 'translation'. Even in this situation, the ultimate goal is often to license the science to a larger company. Thus, as in academia, a biotech company also needs to be concerned with what pharma is interested in.

The first issue that Johnson raises: can the finding be reproduced consistently? All experiments do need to be reproducible before they can be considered for publication. In this context, however, this is not enough: another person, preferably in another laboratory or institution should be able to reproduce the results. Thus, the reproducibility needs to be more rigorously demonstrated. We give here an account from a start-up drug discovery company in the US (Nandini Arunkumar, pers. commun.). 'We were working on a protein that is expressed on the surface of a B cell. It has the capacity to modulate the response of the T cell. Let's call the protein "X". From the very beginning, even before the phase 1 trial, there was a very clear idea that X was going to go into patients. So, even though we didn't have a GMP facility, every possible precaution was taken to ensure reproducibility of procedures. We would hand out X to any number of scientists, to ensure that it could be handled reliably. All we wanted was feedback on how it was behaving. I don't think any academic lab would have this kind of rigour. In fact, one of my colleagues who leads this effort and who has much industry experience, won't even discuss academic scientists' efforts – they fall way short of what he knows is required in industry.' Thus, 'reproducibility' in drug development is a different kind of effort from that seen in academia.

Next we consider Johnson's three other questions. A few years ago, we wrote about developing conotoxins into drugs[1]. Let us revisit this example with the assistance of a senior scientist who was closely involved in the process (J. Ramachandran, pers. commun.). At the time it was known that there are three types of voltage-gated calcium channels. T-type, that are open transiently, L-type that are open for longer and N-type, which are neither T nor R. It was also known that the conotoxins block the N-type channels. However, there were many assays that needed to be done to confirm this. When isolated from the snail, the toxin is available only in microgram quantities. So it had to be synthesized in laboratory. As it has three disulphide bonds, this was not trivial. This challenge was overcome and in due course gram and kilogram amounts could be reliably synthesized. Next it had to be shown that the conotoxin binds to the N-type channels. As the toxin has a tyrosine in its sequence it could be iodinated, and radioactive iodine was used to show that the toxin indeed binds to synapses. It also had to be shown to bind to the hippocampus, and not the cerebellum, as expected from the distribution of the N-channels and this was done. At the time, the toxin was being developed as a drug

for stroke. However it was also found to bind to the dorsal horn of the spinal cord, an area through which signals for pain travel. In due course this led to a change in goal from treating stroke to treating pain. In the meantime toxicity studies were done and once the results were satisfactory in animals, the company (Neurex) tried to license the molecule to Sandoz in Europe. A Sandoz team travelled to the US to look at the data and found them interesting. Having obtained the molecule for evaluation in monkeys, however, they did not follow instructions on drug delivery (one of the pitfalls of translation) and when things did not work out, they turned it down. One of their objections was that the toxin caused a sudden drop in blood pressure. With the molecule back in their hands, Neurex scientists looked into this effect and found that the many basic residues caused the non-specific release of histamine. If the molecule was co-administered with anti-histamines, there was no drop in blood pressure. Furthermore, a slower and longer infusion process demonstrated that it was effective at much lower concentrations. This made the molecule much more attractive as a drug. Thus, many problems had to be solved along the way to convert the conotoxin into a drug. En route, various experts – from chemists to clinical pharmacologists – had to be consulted. Needless to say, these problem-solving exercises were later published in over a dozen research articles in journals such as *Biochemistry*, *Journal of Molecular Biology*, *Neuron* and *The Proceedings of the National Academy of Sciences, USA*.

Another, more recent example of translational research, is from Bangalore and is closer to the clinic (Suri Venkatachalam and T. S. Sridhar, pers. commun.). The company Connexios Life Sciences collaborated with St John's Research Institute, that is linked to St John's Hospital, to do a clinical study based on their ongoing work related to diabetes. The study was as follows. During the conventional glucose load test, when one receives a dose of 75 g of glucose, a healthy person's system responds with a sharp spike in insulin very soon. As this tapers off, there is a lower and longer-lasting spike. The underlying mechanisms for these two insulin spikes are different. The question was posed: how does a healthy person respond to additional 'glucose stress', that is when the system receives a dose of glucose that is double that mentioned above. Are there differences in how people respond, making it easy to screen for people who are likely to become diabetic versus those who are not? To answer this, a small clinical study was conducted involving 11 healthy subjects. It turned out that the 11 subjects fell into two very distinct groups: those who can handle the additional glucose readily, and those who cannot. In the latter individuals, the first insulin spike was blunted leading to a decreased glucose handling capacity, followed by the second insulin spike that was more prolonged than usual. This blunted response to excessive glucose stress uncovers an underlying defect in the pancreatic beta-cell response mechanism, which is a potential indicator of future full-fledged type-II diabetes in such individuals.

In the examples above, the scientists or clinicians would have had the same sense of satisfaction of solving a technical problem, or of a 'result' that one gets with any successful experiment.

Institutions concerned with translation

Keeping in mind what Johnson has to say, one looks around to know which organizations in India, especially in the non-profit or public sector, are dedicated to this kind of work. Not many. The Centre for Cellular and Molecular Platforms (C-CAMP) in Bangalore is one such effort in 'translational space'. C-CAMP started its activities in 2010, and has so far concentrated on developing various technology facilities such as for flow cytometry, imaging, next-generation sequencing, proteomics and transgenic flies that serve academic and corporate scientists. It also conducts training in these areas. Whereas there is a requirement for such facilities and such training, these activities do not directly address any of the four questions that Johnson raises.

C-CAMP has also tried technology transfer, and has found it to be a non-trivial exercise. Although scientists sometimes think that anything patented can be licensed, this is not the case. No matter how good the science, industry is simply not lining up to license it. In fact, very often it wants further work to be done – with different companies wanting different things to be done with the same science – before they seriously consider it. Thus, a key aspect of technology transfer is to understand what a potential licensee is looking for, and do the required 'bridge work'. Closer to the stated need, the Centre intends to create laboratories where scientific staff will work under the direction of Principal Investigators (PIs) who have science that they seek to translate. The PI knows his or her science very closely, but may not have the time or motivation to work on its practical applications. A team of scientists at C-CAMP will focus on translation and, by working with the PI, will benefit from an expert's knowledge while having the mandate to attend to the questions that Johnson poses.

Another institute with a similar mandate is the Translational Health Science and Technology Institute (THSTI), set up by the Department of Biotechnology, Government of India. THSTI has adopted a different strategy from C-CAMP. Divided into four divisions, with experienced scientists or clinicians heading each one, it focuses on vaccines and infectious diseases, paediatric biology, clinical research, and bio-design and diagnostics. Also a young initiative, THSTI's activities are yet to take off in a big way.

Yet another young effort in the country is a programme called CSIR800, that is meant to translate science from the laboratories of the Council of Scientific and Industrial Research (CSIR) to the left-behind 800 million people of this country. CSIR's laboratories span a wide range of activities, and therefore the engineering-type projects, for instance, may not require the same kinds of funds as a drug-discovery project. In all cases, however, there will be need for a much more 'applied' effort that the average scientist is used to.

Thus, there are very few 'translational' centres in the country. Possibly such centres are rare even in the US, as it is been reported that there is disappointment in American academia that only 0.56% of its funds comes from technology transfer[2]. Until the above-mentioned translational institutions mature, Indian organizations looking to out-license their technologies may wish to use the US-based iBridge Network that helps disseminate innovations. The Network has approximately 17,000 innovations and 8,000 members from 150 organizations, including some from abroad.

The concept of 'value' in business

Technology is usually transferred to industry which then brings a product to the market. One must therefore think about R&D taking place in industry, and naturally one then has to be alert to corporate concerns. In the business community, it is common-place to hear discussion of 'value' and its importance to a business transaction. The author has interviewed a variety of people connected to the drug industry, and the following extracts illustrate their concerns.

An Indian investor commenting on the Indian regulatory authorities' slow permissions for Phase 1 trials of drugs being discovered locally, forcing companies to out-license to foreign companies very early in the game:

'Yes, there is corruption, yes they have inexperience. But how can one license out early? Where is the value?'

An Indian in the United States, who facilitates outsourcing deals to Indian companies:

'Target discovery usually happens in the universities .... Then one interrogates the target with small chemicals. These small chemicals are being synthesized in India .... The compound at this stage doesn't have much value.'

The discussion here, of course, is of financial 'value'. Let us imagine intellectual property (IP) from an Indian academic laboratory that ultimately could end up as a drug on the market. How much would it be out-licensed for? A few tens of lakhs of rupees? A crore or two? Its ultimate fate is to be a new (original) drug on the Western market and within a year it quite likely has earned a few hundred million dollars. In fact, if a drug is unlikely to bring in such revenues, it would probably be scrapped early in the development process[3]. Thus there is a huge gap in the value that is created in academia at present with what could be created with some more work on the same discovery science. There is no point complaining about it: We need to have a systematic way to take our science to higher levels of value so that we derive greater monetary benefit by licensing it to a company that can take it to the market. Along the way, we will also gain much needed expertise. Perhaps we cannot do the entire process within the country yet, but in due course we should be able to, and may even choose to do it in non-profit mode[4]. However, for the moment it is probably necessary to engage with the current paradigm. Drug development will not go far without investors, and investors will not be attracted unless they can make good money.

Summary

We have seen that in India, and elsewhere, an academic project usually stops with a publication. There are various things that need to be done after this so that the work has practical applications, or even to make the work suitably attractive to industry so that it will complete the job. At the moment the country has a large structural problem, a distinct 'valley of death' after the basic science. Although there are now a handful of institutions whose mandate it is to bridge this valley, they are all very young. It will be a while before society benefits significantly from biomedical translational research done in India.

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4. Venkatachalam, S. and Saberwal, G., *Curr. Sci.*, 2012, **102**, 1375–1381.

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