Putting drug discovery back on target

October 23 2013, by Jonathan Wood

'The world urgently needs new medicines for many diseases such as Alzheimer's, depression, diabetes and obesity,' says Professor Chas Bountra. 'Yet the pharmaceutical industry's success rate for generating truly novel medicines remains low, despite investing tens of billions of dollars.'

What's going wrong? Why can't we depend on the vast commercial pharma industry to deliver the new treatments we need? Professor Bountra is in the ideal position to ask. He came from the drug firm GSK

to lead the Structural Genomics Consortium at Oxford University, a public-private partnership that bridges academia and industry and produces data that is directly relevant for coming up with new drugs.

'What the pharma industry has done is recruit some of the smartest people on the planet, invested tens of billions in technology and infrastructure, and acquired promising companies,' he says. 'It's not that industry is doing anything wrong. The problem is that it's so difficult. The fundamental bottleneck is our ability to identify new targets for drug discovery.'

Those working in this area talk about 'targets'. If you have a biological molecule, most often a protein, that you find is critical in a disease process in the body, this is a target.

It is a target because you can throw tens and hundreds of thousands of small chemical compounds at it and see which of these would-be drugs stick. You might come away with a handful of compounds that bind your target protein and block the disease process. Now you have somewhere to start, you have some candidate drugs against this disease.

You'll want to optimise the chemical compound, do toxicology checks, and there would be years of clinical trials to determine it was safe and beneficial. But the starting point turns out to be crucial. If you don't know enough about the target and the disease process it affects, you may waste billions of pounds, years of effort and expose patients to something that may have no medical benefit – or worse, find side effects you didn't know about.

Professor Bountra explains: 'There are around 22,000 different proteins in humans, any of which could be a target for a drug. There are hundreds of diseases and hundreds of subsets of diseases. What we can't do right now is say this protein will work in this subset of Alzheimer's patients.

'Pharma is extremely good at taking a candidate drug molecule through to market. None of us – and I include the whole global biomedical community in this – is good at selecting the right target for drug discovery.'

Peter Ratcliffe, Nuffield Professor of Medicine at Oxford University, is of exactly the same mind: 'It's almost self-evident that in starting drug development you need to start in the right place. We need to have the right molecular target.'

He is the director of the new Target Discovery Institute at Oxford University, an institute whose whole purpose is validating targets for

drug discovery.

Researchers have just started moving into the TDI's impressive new building on the Old Road Campus. All clean lines, sharp angles and a glass frontage to guide you in, it brings the best biologists and chemists together with the latest genetic and cell biology technologies.

Modern biology research is delivering thousands of potential targets, Professor Ratcliffe says, but it is currently hard or impossible for scientists in pharma to know which are the most promising to pursue for new drugs. He believes that at least a portion of academic research should be more aligned to what industry needs to take things forward.

One of the examples Professor Ratcliffe gives is a set of enzymes called histone demethylases. These are involved in switching genes on and off in cells, and drugs targeting these proteins may be useful in cancer and inflammatory disease. But this work is still at a relatively early stage and there is a lot to be done to determine the range of effects that blocking these enzymes can have, and whether discrete medical benefits can be achieved. That's where the interest of the TDI comes in.

Forging successful partnerships between academia and industry is exactly what Professor Bountra has done at the SGC. This not-for-profit group, which with academic and industry partners worldwide determines the three-dimensional structures of proteins of importance to human health, places the data in the public domain, open and free to all. Knowing the structure of a protein is important in finding candidate drugs that bind this target.

More recently, the SGC began working further along the drug discovery chain in coming up with novel chemical compounds that block target proteins. Again the data and reagents are openly available to allow anyone to investigate them. Some novel drug compounds are already

being taken forward by new biotech companies.

'We need to pool the strengths of academia and industry,' Professor Bountra believes, 'to create a more efficient, more flexible way of discovering new drugs. It is only by pooling resources and by working with the best people that we can hope to reduce costs and reduce risks in this very difficult task of discovering new drugs.'

Professor Ratcliffe adds: 'The failure of drug candidates at a late stage in large-scale trials is reasonably held to be the thing killing the pharma industry. We have to secure the rationale for developing a drug in the first place, and we have to make sure we don't find untoward aspects at a late stage.'

Both professors believe that there is wider importance to the British economy, following many drug companies downsizing their research capacity in the UK. By making these projects in Oxford a success, it can bring in drug company investment, it can see new biotechnology companies spun off and help in retaining highly skilled people in this country, they say.

'I honestly think what is happening in Oxford is phenomenal,' says Professor Bountra. 'In the next one to two years, Oxford will be the academic drug discovery centre in the UK. What distinguishes Oxford is a culture that makes all of this work. We are all pulling in the same direction to help industry develop new medicines because society desperately needs new medicines.'

Provided by Oxford University