Small molecule drug discovery: why we need a paradigm shift

An interview with Professor Graeme Robertson
Professor Robertson is currently Managing Director and co-founder of a small biotech company TES Pharma created and a research professor the University of Perugia, Italy. He has a detailed knowledge of the challenges of drug design gathered from over 24 years' experience in drug discovery.

He worked for several years at GlaxoSmithKline, where he was responsible for investigating ion channels as potential drug targets and leading chemistry discovery in this area. He then moved to Siena Biotech S.p.A. as Vice President of Therapeutic Research and later became Vice President Portfolio Management, providing support for a portfolio of drug discovery targets.

Professor Robertson recently moved to the academic environment and, together with other members of the Department of Medicinal Chemistry and Drug Technologies at the University of Perugia, co-founded TES Pharma. The company plans to find new ways to integrate in depth knowledge of drug design and chemistry with basic biology in order to better design and develop effective disease modifiers via a network of world class centres of excellence.

Graeme shared with us his cross-industry perspective on an environment which is fast moving and prone to change, with topics ranging from the current challenges facing the pharmaceutical industry and where it's heading, to the relationship between academia and pharma, and the ongoing interaction in research between biology and chemistry.
Highlighting problems with current approaches to drug development

The pharmaceutical industry, thought by many to be recession-proof and able to carry on producing sustainable and increasing profits, is suffering under the pressure of global economic decline. This is illustrated by the large numbers of recent mergers and site closures in Europe, and the increased use of facilities in Asia.

“Early in my career I, like many others, believed that the pharmaceutical industry would be going strong no matter what… but currently this isn’t the case and serious revision of the drug discovery process is needed.

“A significant problem has been the emphasis on a business model and profits for shareholders rather than exploring the science to see where it can take us. There are several core problems; a lack of productivity, a lack of innovation and a failure to get a sufficient number of drugs through the pipeline. Productivity, that is NCEs from pharmaceutical companies has been particularly low in recent decades.”

The strategy that has predominated in small molecule drug discovery during the last few years has been a stepwise and linear approach that has relied on reverse chemical genetics to generate a range of potential lead compounds.

“People within the industry have assumed that putting more compounds into clinical trials would produce a successful drug, but there is little evidence that this is the case. We should not be putting more compounds into clinical trials, we should be putting better compounds into clinical trials.”

Graeme believes that the process of developing drug candidates requires much better use of animal models and sharing of knowledge before moving into clinical trials.

“Clinical trials are something of a lottery now. If a candidate drug does not show the same effects in humans as it did in the animal model, then little is done to revisit the models to improve their predictivity using data from the clinical setting. We don’t spend enough time going backwards to try to work out how we can best use the data generated in the clinical setting. This information could be invaluable in learning more about the drug and the disease process it is trying to target. Unfortunately, however, pharmaceutical companies often move on to pursue the ‘next big thing’, without learning why they are failing.”

Graeme admits there is no magical answer, but the drug discovery process needs to be changed, and radically so, if we are to revitalise drug discovery.

“We need to get away from the mind set of ‘go faster or with lower costs’. If we go faster we’re just going to hit the brick wall with more of a bang and it’ll hurt even more than it has already done because the process we are using just does not work.”
In the current paradigm of drug development, individuals hard work is not adding up to corporate success.

“It is possible for an individual researcher within a drug company to be brilliant, hugely successful, highly motivated, and very productive but to add zero value to the company because they never work on a project that goes through to market. They are trying to add value, but they are failing and this is not their fault, or their company’s fault. It is really more of a reflection of how little we know about what we are doing in drug discovery.”

Another potential problem is that companies tend to link a target to a disease area far too early in the drug discovery process.

“We’re still way too reductionist in our approaches on selecting targets, and projects tend to be associated with a disease way too early. In our current pharmaceutical industry, compounds are developed for a predetermined product profile. What we should be doing is looking for good modulators of that target in a more disease-independent fashion and then finding out the effect of modulating that target with our compounds. Decisions need to be made on the basis of our findings, and we need to stop following rigid research protocols blindly like machines.”

Proposals for a paradigm shift

Graeme’s vision for drug development in the future would be for the pharmaceutical industry to share information and collaborate more closely in key areas.

“To achieve a more sustainable future, pharmaceutical companies should share a lot more if not all of their safety and toxicology data, such as cardiac liability data. If that happened, we could create a common understanding of how to avoid the same problems.”

Sharing and centralising data from animal models would be particularly effective and efficient.

“There are currently many problems with animal models because many are simply not good models of disease, particularly in certain areas of oncology. Our knowledge of oncology is very rudimentary and we often use an over-forced classification of tumour types, in my opinion. This results in testing of new drug compounds in animal models that are unrepresentative of human disease, and clinical trials that produce wildly different results.”

Graeme proposes that animal model screening for new drug compounds could be centralised in specialist laboratories who would develop expertise just in that area.

“I think there would be a lot of resistance to centralising all our animal model screening but I think that centres of excellence would develop models that would become more predictive of the translation to the clinic. If a system was also set up to bring in academic medical centres, which would do experimental studies in the clinical setting, this part of the drug discovery process would evolve into a much better system in the long term, if it could be done in a way that would not alienate specialist biotech companies.”
Graeme would also like to see drug development taking more account of what happens when a candidate drug ‘fails’.

“There are no right or wrong answers in science, you just get the results you wanted or the results you didn’t want. The problem is that pharmaceutical companies don’t spend enough time or money looking at why something didn’t work so they can understand the science better, the company just moves onto another project because the shareholders expect returns within a time-frame that we can’t match.”

The hurdles that prevent analysis of ‘failed’ clinical trials are regulatory as well as business-oriented.

“We are working in a climate of increased regulatory expectations, we have a poor understanding of the basic biology underpinning disease pathology and we do not build the most productive collaborative networks. Many companies end up working on the same or very similar compounds, to target the same diseases. They are only different because of the cultural differences between the companies. The result is a group of candidate drugs that are all potent inhibitors of target X, but no-one in any of the companies concerned knows very much about them at a synotypic or biological level. Sharing information could reveal detailed differences in drug candidates directed towards the same target, and this information could be used to leverage a business position. This would go some way to overcoming the hurdle of proprietary culture that exists today.”

In the present system, this is not done.

“Instead, each company tries to beat the competition with something that’s very similar. In many instances the top ten pharma in the world all fail on the same target because they didn’t share the information. They might have failed anyway but if they’d shared a certain level of information they may have stopped research on some compounds earlier, and saved a great deal of investment.”

As Graeme points out, industry works along very different lines from academia, and pharma companies could benefit from taking on board some academic working methods.

“Much of academic science is about building on somebody else’s data. Information and discoveries, even unexpected ones, are often shared more openly and discussed. From that openness, new hypotheses emerge and scientific knowledge expands. The pharmaceutical industry must break with the tradition of working in silos and behind firewalls.”

The challenges ahead

Any paradigm shift generates suspicion, if not downright hostility, and a sea-change in the approach to drug development would be no exception.

“There is huge resistance to this within the industry because of pressure from shareholders. At the moment, because of the problems we have had in the last 15 years, shareholders are not getting the returns they want, which is making them even more resistant to change. There are no easy answers and the instability in the industry is not providing confidence either externally or,
perhaps more importantly, internally. It is unfortunate for researchers in the industry who lose jobs, but those who are left are all much more nervous than they were.”

The importance of understanding the science
Currently, the drug discovery regulatory bodies do not require researchers to understand why a drug works, rather that they show that it does work.

“We have a relatively poor understanding of how drugs work, even ones that have been approved and are being used in the clinic. Once a compound is on the market, post-marketing observational studies can still come up with adverse effects that will kill the compound after four years. We don’t know how to visualise or understand the complexity of the biology, so using chemistry to try to manipulate it is always going to be educated guesswork.

“I got into trouble when I worked in industry for calling chemical structures a non-verbal language rather than “structures”. They convey a lot of useful information but in terms of understanding a biological target, and how the target interacts with a receptor, they are just not enough.”

The need for collaboration
Pharmaceutical companies do make use of outsourcing and do collaborate to some extent, but Graeme stresses that companies need to rethink their approach.

“Outsourcing is OK if you want to make 5 kilos of your compound. Once the objective is clearly defined and an outsourcing facility has scaled up the process and has a good manufacturing capability, outsourcing works well and this is a successful part of today’s industry. Some companies operate a ‘hybrid’ business model, which involves part discovery and part fee-for-service work.”

Collaboration is a different matter. This is a necessity within the new paradigm of drug discovery.

“We need to focus on the expertise of individual research groups. It is better to have five expert groups working together than the same group trying to do all five aspects, and failing.

“Collaboration is a necessity and the driver behind that is the need to understand more about what we are doing. How this type of collaborative research would be funded however is an issue that needs to be addressed. The current business model is flawed, but without it there is no funding for drug discovery research.”

Academia does do in depth research and is funded in a different way from industry. Would governments or foundations provide the money for drug development? Graeme cites some limited examples where this does already happen.

“Vertex have compounds for cystic fibrosis in clinical trials that have been funded by the Cystic Fibrosis Foundation. This is one way of working towards bringing benefit to patients, rather than concentrating on profits for shareholders.”
Graeme’s interest in chemistry began back at school with a particularly inspirational teacher. After completing a first degree in Chemistry, a PhD in Organic Chemistry, and a post-doc in Synthetic Chemistry, he still supports the necessity that drug developments needs a sound knowledge of organic chemistry, but if he was ever given a second chance at life, he would come back as a biologist…

“When I first became interested in chemistry I wanted to make things, to synthesise new structures and compounds. Now I am much more interested in what the compounds do. It is still very important that scientists involved in drug discovery are specialised but if we are to get the most out of basic science, we need to integrate biology and chemistry at the academic level. Rather than taking organic chemists and then giving them experience of medicinal chemistry in industry, the young scientists who will be working on drug development in the future would benefit from this integration much earlier in their training. Italy is one of the few countries that has a long tradition of doing this and

I think it is one of the ways forward. Indeed several UK universities are also now offering medicinal chemistry degrees.”

Graeme also thinks that we need to take a step back and re-evaluate what we mean by medicinal chemistry.

“The label means something very different now to a few years ago, and medicinal chemistry will continue to evolve. I am the Chairman of the Industrial Liaison Committee of the European Federation of Medicinal Chemistry and we’re organising a session at a conference next year to discuss how the definition of medicinal chemistry will change as we move towards 2020.

“The roles of the scientists within medicinal chemistry are changing fast and if industry is not able to provide a rejuvenated definition of what medicinal chemistry is and what pharmaceutical development is going to require in the next few years, you cannot really expect academia to understand how to provide the next generation of chemists.”

Medicinal chemistry and drug discovery

Who is leading the way?

Several small companies like TES Pharma are working within the new paradigm that Graeme envisions but they are too small to lead the way. There are signs that larger organisations such as The Structural Genomics Consortium are moving towards a more open and collaborative way of working. The Wellcome Trust in the UK is also known for funding this type of research.

“The European Commission is a major force in driving collaborative research and has been for some time. In order to generate a proposal, four or five centres need to come together from three or more member states. This does much to address the Lisbon Treaty of Productivity and Scientific Quality in Europe. It works well to bring together centres of excellence who can then collaborate on a project funded by the European Commission.”
There is considerable uncertainty about how this new model could be adopted within the pharmaceutical industry, however.

“We are seeing a change; Pfizer now has their designer chemists in Britain work virtually and a large amount of the wet chemistry is done by chemists in labs in Shanghai in China. Pharmaceutical giants could become more like the Wellcome Trust and the European Commission, which are developing a looser network of entities that can respond to change more rapidly.”

The need to deliver results is, however, always going to be a fact of life.

“If you’re providing money you like to know your compound will be in phase 1 within 10 months, say two studies completed within three years and there’s a chance of a return by a certain time after that. Very few investors are comfortable with ‘Well it might work, we don’t really know where we’re going, and it’s interesting and we like it and if something does happen you might get some of your money back’. It doesn’t quite work from an investor perspective but the current system is not delivering new drugs, so we need to try a new approach.”

**Collaborative research and information exchange**

Graeme, like many researchers, is inundated by new research papers on a daily basis and finds it difficult to keep up with the pace of developments.

“It is impossible to read all the papers you should read and although biology is relatively text-based, when you move into medicinal chemistry and drug design, you need to move beyond text searches. Being able to search structures would be ideal but it’s difficult to do that in any database outside Reaxys. I think this is the ideal model that we should be looking at as a way to interchange information on new drug candidates and their analogues.

“All electronic data associated with an article should be retrievable and searchable electronically, even screening information using pixel maps.”

Graeme foresees a time in the near future when it will be possible to search research papers by chemical structure with a sub-structure or similarity search, both in terms of the biology that is known about that structure, and any toxicology data.

“Electronic publishers are sitting on a mine of information; they are working on putting it into more useable databases for drug discovery research and, although it is a big task, I think they know how to do it.”

“There is widespread acceptance that change is inevitable, but we must first overcome the inertia that our fear of change creates. If publishers were to change the way they provide data so that this fuelled a knowledge sharing and knowledge sharing approach, this could be a great catalyst to get things moving.”
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