# Collaboration for innovation is the new mantra for the pharmaceutical industry

In order to maintain a flow of innovative medicines there is a growing realisation that companies cannot allow the status quo to remain as it is and the need to identify sources of appropriate knowledge and expertise outside of their own organisations is paramount. This article discusses some of the challenges in arranging collaborative arrangements with each other and academia.

**By Professor Jackie Hunter**

Much has been talked about the crisis in new drug development and the lack of productivity in the Pharmaceutical industry[1]. However, the crisis is also true for the biotechnology firms which the large pharmaceutical companies have come to rely on as a source of pipeline sustainability[2].

This has prompted an examination of all aspects of the biomedical research and development (R&D) process in recent years to try to cut costs and improve efficiency and productivity. Although this has led to mergers, reorganisations and tens of thousands of job losses in the industry, so far it does not seem to have created the radical shift required. If a radically different model is needed for companies to survive and thrive, what might that look like? Some authors have proposed abandoning the current system of patented medicines altogether and introducing the funding of pharmaceutical R&D through taxation or prize-based funding systems[3]. Another approach that has been adopted by other industries to solve similar problems in terms of lack of productivity and innovation is to build strategies around pre-competitive collaboration and open innovation[4]. Many large pharmaceutical companies are now espousing the virtue of these approaches but will they work if adopted inconsistently by the industry and not adopted or supported by academia and research funders?

Pre-competitive research has been recently defined by Janet Woodcock as "science participated in collaboratively by those who ordinarily are commercial competitors"[4]. Open innovation, on the other hand, although defined in many different ways, is basically the proactive use of a company's intellectual property (IP) and resources to create new innovations and generate new products and accompanying IP. It promotes both external and internal sources of innovation and thrives in an environment where ideas are spun in and out of a company in a very dynamic way. To create this environment needs strong senior management support as it requires a culture very different from the more controlling, hierarchical R&D culture that still existed in many companies at the turn of the century. By definition, it also requires much more proactive management of, and communication about, a company's unused IP. Many companies have begun to explore what this means in a pharmaceutical context but it is clear that such a radical new approach will require more time, effort and resources. However, the benefits of adopting these different ways of collaborating could be extensive in both tangible and intangible ways – reducing cost of failure through predictive biomarkers, leveraging

of unused IP and external funding mechanisms, access to networks of talent and innovation and increased trust and transparency with patients and other stakeholders. These benefits will be realised not only for pharmaceutical companies but also for academics and other collaborators.

## Internal innovation

One way of experimenting with these new concepts is to trial relevant tools and technologies internally to drive cultural change within a company before 'going external'. It is always a challenge for large organisations to be able to harness the knowledge of their employees and bring people together to share insights and information, breaking down barriers and challenging silo mentalities. The advent of computing platforms such as Microsoft's Share Point have facilitated data sharing and exchange and pharmaceutical companies would do well to emulate companies from other sectors such as Arup, which has developed excellent systems for accessing knowledge across an organisation.

Companies such as Lilly and Pfizer have put in place internal systems for seeking solutions to problems across their organisations and these have demonstrated the power of this approach. However, many companies struggle when reorganisations occur to retain the links and knowledge that has been built internally. Robust systems need to be put in place to maintain this knowledge base but these are also important for optimising and managing links between the internal and external environment. Companies such as Procter and Gamble have an excellent track record in doing this and their approach may also be applicable to large pharmaceutical companies.

## Why should companies collaborate with each other and academia?

At first sight it seems counter intuitive that companies would want to share data and potentially give away competitive advantage. However, this assumes two things: firstly that the possession of such data does indeed give a competitive advantage and, second, that such a closed operating model is financially sustainable. The drugs that do make it to market have to fund the cost of failure of those compounds that did not make it. As a recent Morgan Stanley report pointed out[6], the current success rates of the pharmaceutical industry are not sufficient to sustain large internal R&D organisations and the current operating model is not financially viable. Thus it is essential that companies either improve success rates or decrease the cost of failure. The two major causes of compound failure are lack of efficacy in man and unexpected toxicity either in animals or man. Therefore it is not surprising that the major areas of collaboration have been in the development of tools and technologies for target validation and the discovery and validation of biomarkers for efficacy and toxicity. Many large public private consortia have been formed, eg the Innovative Medicines Initiative (IMI) and the Serious Adverse Events Consortium, but there is a need to co-ordinate and integrate these multiple efforts within companies so that the maximum possible benefits are obtained.

In the future, the effective pharmaceutical companies will find themselves as hubs at the centre of a network of collaborators and suppliers, focusing internally on their core competencies which might include medicinal chemistry, clinical trial execution and sales and marketing. They will facilitate interactions across their network to stimulate the development of innovation ecosystems. The opportunities that this will bring to expand beyond traditional products and markets will enable pharmaceutical companies to evolve into companies that offer a range of healthcare solutions. These will include not only prescription medicines but also diagnostics, branded generics and technologies that support personalised medicine as well as potentially nutraceuticals and other 'wellness options'. Although the internal size of many R&D organisations will inevitably decrease, the complexities of managing and maximising the impact of this external web of relationships will demand new skills and capabilities over and above those of excellent science – developing and rewarding employees who possess such skills will be an additional challenge. One important question is what is the optimal size of internal R&D activities given this new environment – there is a certainly a critical mass of expertise required to both attract new collaborators and be sufficiently knowledgeable to identify and interrogate new opportunities. Furthermore, those companies that excel in the development of these new collaborative models will have a significant competitive advantage in being able to work across sectors to deliver more innovative healthcare solutions.

So what current collaborative models are being explored by pharmaceutical companies and how successful have they been?

## Collaborations based on sharing of expertise and resource

One of the companies that has used resource sharing as a way of driving their open innovation strategy is Lilly. In 2009 Lilly launched PD2, a portal

**Table 1:** Open innovation assays at Lilly

| DISCOVERY APPROACH | ENDOCRINE/CARDIOVASCULAR | ONCOLOGY | NEUROSCIENCE | TUBERCULOSIS |
|---|---|---|---|---|
| Phenotypic drug discovery | Insulin secretion<br>Wnt pathway activator<br>GLP-1 secretion | Anti-angiogenesis | | TB screening module (IDRI) |
| Target drug discovery | GPR119 agonist<br>APJ agonist<br>NTP inhibitor | HK2 inhibitor | mGluR2 allosteric agonist<br>CGRP antagonist | |

*Details available online: https://openinnovation.lilly.com/dd/science-of-open-innovation/strategic-areas-of-interest.html*

which allowed scientists to have their compounds screened against phenotypic, disease-relevant assays that were already established within Lilly. In addition for interesting compounds relevant secondary assays can also be made available to provide additional biological characterisation. Lilly provides all the data free of charge and with no obligation to the investigator and the investigator retains the IP rights to the chemical entity tested. Within a couple of years it had allowed Lilly to create a network of 70 small biotechnology companies and 174 academic institutions. Data presented by Lilly showed that the compounds submitted were structurally diverse from the Lilly compound collection and a reasonable percentage had biological activity in one or more assays[7]. The initiative has already led to the establishment of new collaborations with academia.

In 2011 Lilly also introduced the TargetD2 initiative. In this programme, Lilly will give external access to a panel of well-validated target-based assays across five targets of interest. Importantly, they say that they will also provide access to relevant computational methods to let investigators carry out structure-based research on the initial results (see https://openinnovation.lilly.com/dd/). Therefore this model of sharing appears to be delivering value for Lilly.

Another example of resource sharing is where collaborators can access expertise and know-how. Glaxosmithkline (GSK) has established a group called Scinovo (http://www.scinovogsk.com). This group sits within the R&D organisation of GSK with access to GSK experts across the whole R&D continuum. The terms under which this advice is provided are flexible and allow GSK to build strong links with collaborative partners. The unit has been operating for several years and has strong links with Stevenage Bioscience Catalyst, the recently-established open innovation campus adjacent to GSK's UK Pharma R&D site. A more tangible example of resource sharing by GSK is the Open Innovation Labs at Tres Cantos in Spain. Here the focus is on neglected diseases and the labs are run by a non-profit foundation. Investigators from around the world can come and work in the labs and gain access to GSK's expertise, processes, facilities and infrastructure, including an ultra-high-throughput screening facility and Biosafety Level 3 *in vitro* and *in vivo* laboratories. GSK has put £10 million to date into the organisation and other funders have also provided financial support (https://www.openlabfoundation.org). There are three disease areas that have been prioritised and investigators have to undertake research projects that are in line with the foundation's mission. It will be interesting to see if there are any insights from this open innovation activity that could be more widely applied in other areas of drug discovery and development.

Takeda has announced that it is providing incubation facilities for academics and biotech companies in its Shonan research Centre in Japan, where external investigators will be able to work side by side with Takeda investigators. UCB has also announced that it will make some of the new mammalian cell culture bio-pilot plant available to potential partners together with some in-house expertise. These examples show how companies are seeking to leverage their in-house expertise and resources to expand their collaborative networks. These companies will evaluate the success of the resource sharing efforts in terms of access to new partners and technologies.

Companies are also engaging more strategically in large networks of academic collaborators. For example, in 2010 Pfizer announced plans to establish Centres for Therapeutic Innovation (CTIs) which had the remit to build open innovation partnerships with academic medical centres globally.

**Table 2:** Rational for academics to be involved in Pfizer's centres for therapeutic innovation

**Acceleration of scientific progress**
- Unprecedented access to Pfizer's world-class antibody libraries and technologies
- Dedicated support and expertise in drug development and protein sciences
- Potential use of Pfizer assays and high-throughput screening, biophysical and/or animal modelling, cell-line development, protein/mAb engineering and humanisation or other technologies
- Intellectual property ownership and license rights to support continued experimentation and exploration

**Career enhancement**
- Reasonable publication rights
- Association with a highly competitive, well-resourced programme
- Diverse training experiences for PIs and postdocs

**Financial incentives**
- Well-funded fellowships for PIs and their teams
- Flexible funds to support the preclinical and clinical advancement of promising projects
- Milestone payments and royalties, as appropriate, upon the advancement of programmes

*Source: http://www.pfizer.com/sites/default/files/research/partnering/cti_brochure_9x12_v12single.pdf*

The academic partners would have access to antibody tools and technologies and to work alongside Pfizer staff in dedicated laboratories. The advantages for academics in working with the CTIs are shown in **Table 2**. To date Pfizer has established 20 collaborations with major academic medical centres in the USA and has four dedicated CTI labs in Boston, New York, San Francisco and San Diego. They have received more than 300 research proposals and from these 20 projects were selected for support. Although the academic retains the right to patent and ownership of the patent, Pfizer has first rights to license any clinical probes that arise from the collaboration, although if they decline to license the academics are free to progress the probe themselves or via further partnerships. If Pfizer really is making resources and tools available in this way, rather than solely providing cash, then this does represent a change in the collaborative model between Pharma R&D and academia which hopefully will accelerate progress.

More recently in 2013 the Karolinska Institute and AstraZeneca have established a joint venture called the Karolinska Institutet/AstraZeneca Integrated Cardio metabolic Centre. This centre will conduct both clinical and preclinical studies for AstraZeneca's two biotech units – AstraZeneca Innovative Medicines and MedImmune. In the centre scientists from the company will work side by side with those from academia and they will be able to access all the facilities of the university. The cost to AstraZeneca is up to $20 million per year[8].

Some resource-sharing collaborations have already been established for a while. For example, GSK announced in 2008 a five-year, $25 million collaboration with the Harvard stem cell institute in Boston where participants would spend time in each other's laboratories and resources as well as cash be made available to Harvard by GSK. Unfortunately, internal research priorities changed within GSK and many of the key personnel, and areas of research, involved in establishing the collaboration changed. Whether this led to a reduction of the benefits for both parties is unknown although it must have had some impact. Indeed, feedback from academia groups involved in such collaborations suggests that industry participants can change rather frequently and when they do this, it can have major changes on the dynamics of the collaboration as well as affecting the deliverables.

## Using compounds to drive collaboration

While Pfizer is clearly making its antibody tools and technologies available, including their phage libraries, as part of the CTIs, other companies have made their chemical compound collections available to biotechnology companies and academic collaborators for preclinical screening. For example, Merck Serono is providing a Mini Library, comprising former Merck Serono development or research compounds and derivatives, free of charge to investigators for use in their assay systems. Eisai has established a strategic collaboration with the John Hopkins Brain Science Institute (JHBSi). In this collaboration researchers at JHBSi build assays against neuroscience targets of agreed interest. These are then transferred to Eisai for high throughput screening. JHBSi may then carry out further hit-to-lead work with milestone payments for successful projects[9].

Previously JHBSi had signed a deal with Biogen-Idec which included research support for proposals chosen on a competitive basis by a joint Biogen Idec-BSi steering committee. The agreement was it streamlined intellectual property and reduced regulatory barriers. The first two awards were announced in 2007 and a third project award was announced in 2009. Target research areas included Multiple Sclerosis, Alzheimer's disease and pain.

Astra-Zeneca has worked with the MRC to give access to 22 clinical and preclinical compounds to UK-based researchers. Although only brief details of the compounds are available on the MRC website, more details will be given under confidentiality if a proposal is of interest. This has some parallels with the much larger NCATS initiative in the

USA where a number of compounds are providing more than 50 clinical compounds (http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/directory.html).

Companies are also starting to provide a selection of their compounds directly to academic organisations. AstraZeneca has added 250,000 high-quality compounds to the Lead Discovery Center based in Germany (LDC) to enhance its compound collection. The LDC will then identify compounds from the combined collection that show activity against a portfolio of targets. These will be selected by the LDC from its range of academic partner institutions which includes members of the Max Planck Society, Germany's leading basic research organisation. AstraZeneca will have a preferred right to obtain a licence for pre-clinical and clinical development and commercialisation with terms agreed individually for each project.

Although in the above examples the pharmaceutical companies still retain rights and some controls on the use of their compounds via joint steering committees, making compounds available can be a powerful force for driving collaboration. There are also examples of companies sharing compounds with each other such as AstraZeneca and Bayer, allowing companies to greatly expand the range of compounds they can screen their targets against. However, this only makes sense when there is little redundancy between the collections, as was the case with AstraZeneca and Bayer[10].

More recently in 2013, the Innovative Medicines Initiative launched a project called the European Lead Factory (http://www.europeanleadfactory.eu). The aim is to build a Joint European Compound Library which can be accessed by both private and publically funded institutions. It has 30 public and private partners, including seven pharmaceutical companies and will establish a European Screening Centre. It is hoped that this will act as a catalyst for further drug discovery in Europe.

## Precompetitive activities

The European Lead factory is an unusual form of collaborative activity as it involves compound generation and sharing. Most precompetitive activities

have been focused on areas that are traditionally seen as being safer areas for collaboration, eg biomarker identification and validation, preclinical safety and toxicology, method development and the design and validation of patient reported outcomes. Such activities certainly form the bulk of precompetitive collaboration today – some would even call this 'non-competitive' rather than 'precompetitive'. However, the boundaries for such collaborations do appear to be shifting. Within the umbrella of the IMI, for example, the NEWMEDS project in schizophrenia has pooled data from clinical trials and this data has enabled a better and shorter trial design thus saving time and costs. Data from genetic studies has also been pooled to allow correlations of genotype with phenotype which will be important for target validation. To date more than 4,500 researchers are involved in IMI projects from private and public organisations, including SMEs and patient groups. This in itself is a considerable achievement and the advent of projects such as the European Lead Factory will continue to expand the impact on the whole R&D continuum (see http://www.imi.europa.eu). IMI is already providing a valuable template for public-private partnerships in biomedical science[11] and learnings from the consortia will be important to incorporate in future initiatives.

## The rise of crowd sourcing

Crowd sourcing approaches have been used internally by a number of companies such as Roche and Pfizer (https://www.innocentive.com/files/node/casestudy/roche-experience-open-innovation.pdf). Roche Diagnostics actually compared the effectiveness of internal and external crowd sourcing using the same problem. Internally they took six problems out to more than 2,400 people and, although less than 20% of those contacted actually engaged with it, they received nearly 50 proposals, one of which was "truly exciting". They then took one of the six problems externally working with Innocentive, an open innovation intermediary. Within 60 days they had 113 detailed proposals with a solution to a problem the company had been wrestling with for 15 years.

Other companies have also used this approach – Pfizer's Neusentis business unit posed a recent challenge on the Nature/Innocentive Open innovation platform. They were looking for novel means of measuring the interaction between a drug and its targeted ion channel. Although they were looking for a solution which would be applicable across all ion channels, they would also consider proposals specific to voltage-gated channels. Obviously this is also a good way to allow Neusentis to identify potential collaboration partners (https://www.innocentive.com/ar/challenge/9933445 via @innocentive). GSK has canvassed for new therapeutic concepts as well – ideas are submitted to a panel of judges and 10 from Europe and 10 from the USA will be selected to 'win' a collaboration with GSK. The winners will work with GSK scientists to advances their ideas, eg by screening against the GSK compound library (www.gsk.com/discovery-fasttrack).

Experience with the use of these types of challenges both within and without the pharmaceutical industry has shown that the more specific the question, the more likely that a good response will be forthcoming. Poorly articulated or very broad challenges frequently do not produce good solutions because it is not clear what is required.

Other companies are using the web for soliciting collaborative proposals, although the way the collaborations are executed seems to be along traditional lines in most cases, ie the company solely provides money rather than expertise or other in-kind contributions. Academia is also using crowd science to progress drug discovery projects, eg the India-based consortium Open Source Drug Discovery (http://www.OSDD.net). The Medicines for Malaria Venture (MMV) and the EBI have created resources and easy-to-use data repositories for groups working on malaria to speed up the drug discovery process (http://www.ebi.ac.uk/chembl/malaria). Preliminary data suggests that an open source, crowd-based approach can certainly increase efficiency and reduce costs to milestones. The best practices and lessons learned from these endeavours will be valuable if made public and certainly the MMV is beginning to do this[12]. It has six key laws to abide by for these open source projects:-

- First Law: All data are open and all ideas are shared.
- Second Law: Anyone can take part at any level of the project.
- Third Law: There will be no patents.
- Fourth Law: Suggestions are the best form of criticism.
- Fifth Law: Public discussion is much more valuable than private email.
- Sixth Law: The project is bigger than, and is not owned by, any given laboratory.

Clearly these laws are not all applicable for precompetitive collaborations or other forms of open innovation, but other lessons learned from the MMV studies may be applicable, eg ways of

tracking contributions, the optimum use of collaborative tools and management methods.

## Conclusions

The boundaries for collaboration between companies and academia are being expanded and new models are being explored. For example, it is becoming possible to develop collaborations around compounds and other IP sensitive areas in ways that would have been unthinkable a decade ago. There is still some way to go – many companies close down areas of research and terminate compounds for a particular indication, but do not spin-out these assets or make the associated reagents (antibodies, cell lines, etc) available. The reasons for this are many, but the main one is that companies have a 'fear of success' – that the assets will make a lot of money and therefore a lot of attention is required to ensure that no 'crown jewels' are given away too cheaply. However, as stated at the beginning of this article, most compounds do not make it!

The IMI and other public-private collaborations are beginning to build trust and understanding between the various stakeholders as well as delivering some real tangible benefits. There are still challenges:

- Lack of standardisation in terms of data collection, storage and annotation will hamper data sharing and collaboration, but again some steps are being taken to address this, eg the formation of TranscelerateBiopharma as a not-for-profit organisation to address standards in a range of areas including clinical trials (http://transceleratebiopharmainc.com/). Likewise, the Pistoia Alliance is trying to do the same in the preclinical arena http://www.pistoiaalliance.org/.
- Logistics – including everything from how best to track compounds, contributions to who should be the medical sponsor for collaborative clinical trials. TranscelerateBiopharma will address some of the issues, but this is much wider than clinical trials and the acquisition of clinical data.
- Assessing the value in the short term of collaboration. The R&D process is a long one and it will be important for the IMI and other large scale collaborations to devise short to mid-term metrics or key performance indicators to show how valuable they can be.
- Aligning internal and external objectives – in many companies employee bonuses and promotions for example are more dependent on internal objectives than externally focused ones.

Certainly there are some new models of interaction, eg the IMI, but whether these are really producing a radical change in the way companies do the business of R&D and how academics interact with industry is still open to debate. DDW

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## References

**1** Pammolli, F et al (2011). The productivity crisis in pharmaceutical R&D. Nat. Rev. Drug Discov. 10, 428-438.
**2** Pisano, G. Can Science Be A Business? Harvard Business Review, Oct 2006.
**3** Herper, M. Biology Goes Open Source. Forbes Magazine. February 12, 2007.
**4** Hunter, AJ and Stephens, S (2010). Is Open Innovation the way forward for big Pharma? Nature Drug Discovery 9, 87-88.
**5** Woodcock, JA (2010). Precompetitive research: A new prescription for drug development? Clin. Pharmacol. Therap. 87 (5) 521-523.
**6** Morgan Stanley report 'Pharmaceuticals: Exist research and create value'. Jan 2010.
**7** Lee, JA et al (2011). Open Innovation for Phenotypic Drug Discovery: The PD2 Assay Panel J. Biomol Screening, Volume 16 (6) 588-602.
**8** Bouchie, AJ (2014). Seizing opportunities in cardiovascular disease. Nature Rev Drug Disc. 13(3)B7.
**9** Simpson, PB and Reichman, M (2014). Opening the lead generation tool box Nature Rev Drug Disc. 13 3-4.
**10** Kogej, T et al (2013). Big pharma screening collections: More of the same or unique libraries? The AstraZeneca-Bayer Pharma case Drug Discov. Today 18: 1014-1024.
**11** Papadaki, M (2012). Assessing the boundaries of precompetitive collaboration initiatives in biomedical research using the Innovative Medicines Initiative as an exemplar. MPhil Thesis, Cambridge University.
**12** Robertson, MN et al (2013). Open source drug discovery – a limited tutorial. Parasitology FirstView Article pp 1-10.