Novel drugs are not hiding in corners, waiting to be discovered. They are invented by scientists trained to identify which molecules are most likely to be potent and efficacious using medicinal chemistry and a range of in vitro and in vivo assays.

These early drug discovery efforts used to be generally confined to the early stage research divisions of Big Pharma, hallowed grounds where teams of in-house scientists identified promising drug targets and then determined if modulating them would have a therapeutic effect. A good example of this conventional approach can be found in the field of HIV/AIDS, where the discovery of protease inhibitors more than two decades ago ushered in the era of highly-effective antiretroviral therapy.

But today, pharmaceutical companies are more apt to share the reins of this high-risk, high-rewards ride. Most pharmaceutical companies have set up a network of collaborations with academic labs and small companies, but also with contract research organisations (CROs), an industry that historically has operated in the well-choreographed arenas of clinical and pre-clinical testing usually on a contract-by-contract basis, to supplement in house capabilities. Biopharmaceutical companies have been strategically using CROs for targeted segments of their discovery work to complement and augment internal capabilities, with some collaborations, including the one formed by Genentech and Argenta (acquired by Charles River Labs last year and now part of its Discovery Services Division), stretching back 10 years or more. Outsourced discovery services run the gamut – from medicinal chemistry, in vitro and in vivo biology, structural biology and computer-aided drug design that can identify a promising candidate – to process chemistry for scale up of promising candidates. If successful, the outcome is the identification of a compound that is druggable enough to advance to preclinical development, including preclinical toxicology studies – another activity that is frequently outsourced by biopharmaceutical companies to CROs.

This work is, technologically speaking, less empirical than the bench science that brought us drugs decades ago. Indeed, most drug discovery
efforts begin with a list of desirable attributes – a target candidate profile – and a range of in vitro assays, arranged in an efficient screening cascade, to help identify leads. Yet the odds of finding a blockbuster is as steep as ever, in part because the targets developers are seeking are harder to crack, and once cracked, the likelihood of target modulation resulting in the desired clinical efficacy is small.

So some CROs have taken a soup-to-nuts approach, creating integrated teams of industry-experienced scientists in all aspects of drug discovery that work synergistically to solve multi-factorial scientific issues for its partners in the pharmaceutical and biotechnology industry. The integrated services range from target identification and validation and the design and characterisation of molecules that interact with such targets, through scale up and preclinical toxicology testing. The chemistry services, in particular, can include everything from the synthesis of reference compounds and libraries, through the design of compounds that are specific for the target of interest and on through lead optimisation to deliver quality development candidates.

The key reasons behind these collaborations are well-documented. Everyone is familiar with how long it takes to get a drug to market (10-15 years), and how risky the stakes are. Figures cited by the Pharmaceutical Research and Manufacturers of America (PhRMA) suggest that for every 5,000 to 10,000 compounds that enter the pipeline, only one receives approval1. Even medicines that reach clinical trials have only a 7-15% chance of being approved2,3, in large part because it has been so hard to translate promising preclinical findings to efficacy in patients4.

Frequently, drugs fail in preclinical toxicology tests or are unsuccessful in clinical trials due to lack of efficacy or unforeseen adverse events. So if a CRO is able to demonstrate even minor improvements in the lead optimisation process, it could save time and money and help improve future business opportunities for its partners. These days, an additional and equally important reason for biopharmaceutical companies to engage CROs is to supplement limited in-house resources and the desire to keep their infrastructure lean.

The costs of drug development are also astronomical. One widely-cited figure last year from the Tufts Center for the Study of Drug Development in Cambridge suggests that it will cost as much as $2.6 billion to develop and win marketing approval for a single new prescription drug5. Even the more conservative figures that have been cited hover around $1 billion.

Between the steep costs, long development timelines and competitive environment, it is understandable why pharmaceutical and biotech companies desire more innovative and flexible models to
make the discovery process faster and more efficient, and they have turned to CROs to meet these goals. For their part, CROs that specialise in early drug discovery are eager to gain a stronger foothold in this decidedly less staccato section of drug development. The ranks of CROs are filled with scientists that began their careers at Big Pharma and, in the area of chemistry at least, employ more researchers today than many biopharmaceutical companies. A recent study by the business analyst Visiongain predicts that drug discovery outsourcing will reach $16.6 billion this year, with an increasing trend for pharmaceutical and biotech companies to form alliances and collaborations with CROs during the early drug discovery phase.

Integrating the science

So how are these collaborations structured and how do they, well, collaborate?

The partnership between Genentech and Argenta began in 2005 with a single project trying to identify suitable inhibitors of the kinase target MEK, an important link in a chain of proteins that dial up tumour cell proliferation and survival. Around six to eight Argenta medicinal chemists spent three years working with its Genentech colleagues to progress early hits all the way through to a development candidate.

From those relatively small beginnings the collaboration expanded, adding multiple projects – largely in the realm of oncology and immunology – and drawing on the extensive expertise of dozens of chemists and biologists as well as scientists representing drug metabolism and pharmacokinetics, pharmaceutical sciences and structural biology. These partners now provide a lot of the innovation within projects while more mundane activities are outsourced to other CROs. The collaboration has worked on nearly a dozen targets, including JAK, a driver in autoimmunity, and EGFR, which is responsible for the growth and progression of tumour cells and is the target of Genentech’s lung cancer therapy Tarceva.

How the collaboration is structured and how it functions can be illustrated by the retinoic acid receptor-related orphan receptor or ROR project. The science behind this endeavour hinged on RORs, in particular RORc, which helps drive the differentiation and function of certain pathogenic immune cells and tumour cells produced by the protein IL-17.

The RORs are relatively new members of the nuclear hormone receptor family (others include the hormone estradiol) that help regulate gene
expression. RORs are somewhat of a mystery, and their biology has not yet been fully elucidated. But discoveries made by other groups linking monoclonal antibodies that target IL-17 with effective treatments for autoimmune disorders, most notably Novartis’ recently-approved psoriasis drug secukinumab, created a buzz in the field. There is now considerable interest among a number of different biopharmaceutical companies in advancing RORc modulation to the next level, with a new piece in the biology of the RORc jigsaw being the identification of small molecule inhibitors of RORc against autoimmune diseases that was the focus of a collaboration between Genentech and Argenta.

To study RORc, Genentech generated crystal structures of the receptors and then transferred the technology and all the structural biology to Argenta, which enabled structure-based design. Argenta provided substantial drug design input, medicinal chemistry, in vitro biology and structural biology support, and took the lead in optimising one of the two chemical series that had promising activity against the biological target. Genentech took the lead with the other chemical series, with some input from Argenta and help from their in vitro and structural biology resources. This approach led to the generation of a number of patent applications surrounding these novel inhibitors and co-authored publications focusing on the drug discovery science that has evolved from this collaborative project.

The collaboration worked as follows. A Genentech scientist headed up the ROR project and was the final decision maker. Argenta had a project leader acting as the medicinal chemistry lead to make sure all the activities undertaken by Argenta were in line with the project’s overall expectations. Senior scientists from different Genentech and Argenta disciplines met biweekly (by webex) to discuss the latest data and next steps. Infrastructure was set up for seamless data transfer and both parties had access to all relevant in vitro and in vivo data using shared databases. The latter, while technically complicated, is essential to enhance design and decision making by both parties. Another essential component was a comprehensive screening cascade which described the various assays in place at Genentech and Argenta and their sequence as well as success criteria for a compound to progress down the cascade. All of this created a very transparent and collaborative environment, further illustrated by Argenta’s name on patents and as a co-author on publications and presentations at scientific meetings.

Good communication was essential throughout the process. Senior team members provided quarterly face-to-face updates to a management committee comprised of three high-level managers from both companies who were responsible for
providing strategic input and making sure the work was moving forward, and identifying and addressing resource bottlenecks while staying on budget. The senior management committee also resolved occasional scientific disagreements among the scientists.

**Different strokes**

Not every project is as integrated as this one was, nor do perfect collaborative models exist. Virtual companies outsource all discovery activities while maintaining a level of management oversight. Other companies are more hesitant and only outsource specific activities on a less exclusive fee-for-service basis after extensive qualification of the CRO in question. Indeed, the type of interaction between the partner and the CRO reflects the internal resources at the partner, but also its culture.

Multiple factors influence how a particular partnership is structured, how it functions and how long it lasts. The level of scientific expertise has to meet, if not exceed, expectations and the projects have to add value to the sponsor’s portfolio. While it is easy to make compounds, synthesising the right compound is another matter entirely; perhaps the ultimate proof of success being the number of development candidates that are delivered and the amount of time it takes to deliver them. The average industry success rate for delivering a development candidate for a drug discovery project is around 45% right now according to a Nature Drug Discovery study, but is more likely around 35%. To date, the Genentech/Argenta collaboration has generated seven quality development candidates out of 11 projects.

Even more importantly, perhaps, are the percentage of development candidates that progress to clinical proof-of-concept or beyond, which is now between 12 and 24%. Extensive experience provides greater innovation and problem-solving, reducing delivery times for candidates. And the ability to run integrated projects within a single CRO significantly reduces client management time. This is one reason why Charles River Discovery has been able to deliver 61 development candidates in the last 15 years, with 28% reaching clinical proof of concept studies.

Another important factor that affects the utility of these collaborative arrangements is the ability to remain flexible. Today’s ultra competitive landscape requires both parties to be able to respond quickly to developments in the preclinical and clinical pipeline. This can be somewhat tricky in the world of bench science, where scientists loathe giving up on a good idea. But the fact is that throughout industry developers are opting out of otherwise promising projects because a competitor turns out to be too far ahead in the game to make the investment worthwhile. While this situation is not unique to these collaborations with CROs, it does mean that partners must be able to adapt quickly to the changing environment. Indeed, the Genentech/Argenta collaboration has encountered this situation, but there is sufficient scientific depth and flexibility to quickly swap out targets as needed.

The costs of CRO services can also vary widely within the collaboration due to their level of expertise and the range of services provided. For instance, Western providers tend to be two to three times more expensive than Eastern providers but they also generate two to four times more compounds per scientist than Eastern CROs and their impact on drug design is much greater.

With regard to staffing levels, the critical mass of scientists employed by Asian CROs are generally quite capable of replicating well-established models and have a good track record of delivering on high volume routine projects, but they lack the research depth and experience to handle the more challenging upstream work. As an example, half the scientists on Argenta projects have a PhD compared to around 10% at Asian CROs. Moreover, high turnover of staff at Asian CROs is of concern with rates on the order of 20% to 30% a year. On the other hand, Western CROs are more stable and have the innovation, industrial experience and expertise, and the scientific management to deliver on challenging projects, but they are also more expensive. Thus, the ideal collaboration includes both a Western CRO and an Asian CRO – each focusing on their respective strengths.

The non-regulated research space of early discovery is also, paradoxically, more challenging to navigate for collaborations. By necessity, the relationships must be more fluid and flexible due to the different kinds of technology and models that are employed to collect the data used in making crucial go/no go decisions which are frequently somewhat subjective and associated with a level of uncertainty.

It also takes time to build partnerships around mutual interests, expertise and trust. Finding the scientific equivalent of that perfect eHarmony match – one that lasts a long time and is mutually satisfying – often hinges on chemistry, both on and off the bench. Frequent communication and honest feedback is essential to make the collaboration work and last – especially in light of the non-linear and non-precedented nature of drug discovery.
Some sponsors want their CRO partners at the table, others prefer to call the shots and keep their distance. On the other hand, some CROs are not shy about offering their opinions and actively pursue a bigger role in how the projects are managed. Others are less forceful. Finding the right balance of personalities takes time and some match-ups – like any relationship – inevitably lack the right ingredients to make the collaboration work. Recognising and adapting to the cultural differences within each organisation can help relationships thrive, though, and learning from each project is one reason why some collaborations are so durable.

In short, much of this early discovery work is complex and difficult to execute. It sounds obvious, but cross-communication and regular conversations between the two entities matter, whatever the collaboration’s structure or scope. When constructive dialogue is lacking, stuff happens and projects become difficult to manage.

It is better to be ‘brothers in arms’ in the pursuit of innovation to allow valuable drugs to reach patients quicker.