Filling the drug discovery abyss

novel business models to push through the valley of death

Over the past three years, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved around 200 novel drugs for human use[1,2]. Not a large number considering the Pharmaceutical Research and Manufacturers of America (PhRMA) citation that for every 5,000 to 10,000 compounds that enter the pipeline, only one receives approval[3].

By Dr Swati Prasad, Dr Charles McOsker, Professor Kathryn Chapman and Dr Michael Foley

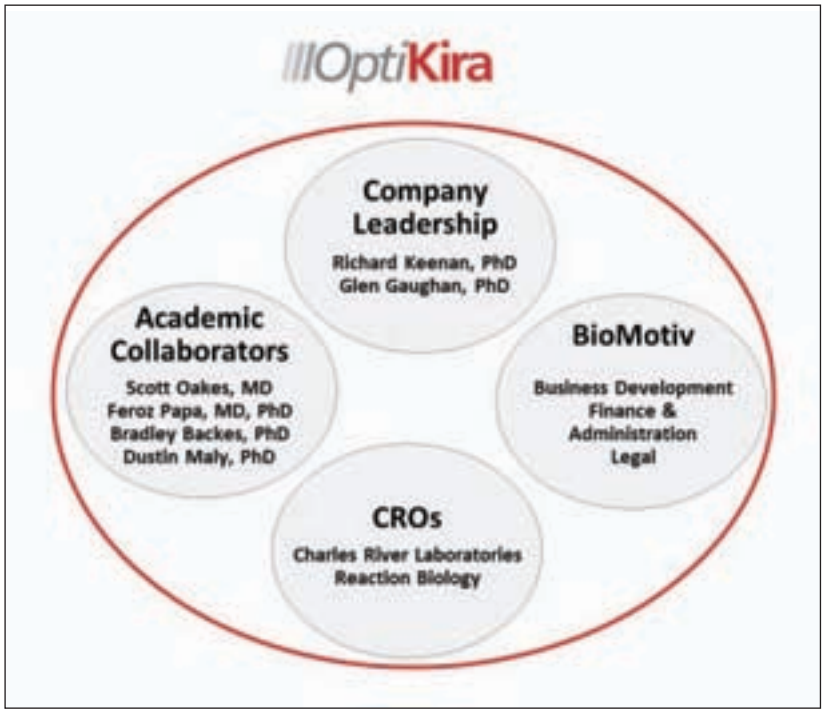
Even medicines that reach clinical trials have only a 7-15% chance of being approved[4,5], in large part because it has been so hard to translate promising preclinical findings to efficacy in patients[6].

One widely-publicised figure by the Tufts Center for the Study of Drug Development in Cambridge, MA, suggests it can cost as much as US$2.6 billion to develop and win marketing approval for a single new prescription drug[7] – that is to develop new molecular entities for which pharmaceutical companies did all of the research – and even the more conservative figures cited by industry suggest a price tag of around US$1 billion[8].

Today, the grim reality is that developing even the next first-in-class diabetes drug is really risky, and the risk is even higher for a disease such as Alzheimer's, where the overall success rate for drug candidates has been a dismal 4%[9]. The high cost of drug development along with regulatory and scientific challenges have put so much pressure on biopharmaceutical companies such that they are now focused on external collaborations for innovative ideas through the earliest and often stormiest phases of drug discovery – the three to five years between target selection and IND approval/Phase I studies.

This gulf between finding a promising new agent and demonstrating its safety is sometimes referred to as the 'valley of death', because the waning interest among drug developers to shepherd these discoveries has made it extremely difficult for academic scientists or start-ups to attract enough capital to prove that their ideas and platforms are commercially viable. Venturing into these badlands poses many challenges for academic investigators who lack experience in drug development and regulatory processes[10].

Elias Zerhouni referred constantly to the abyss (some accounts even say he coined the term valley of death) when he was Director of the US National Institutes of Health. He explored ways for the agency



The BioMotiv business model

to help companies and their technologies survive. One of his signature ideas as NIH Director was a roadmap for the agency in 2003 to tackle big science issues[11]. Five years later, and with his days waning at the NIH, he tried to bridge the divide between basic science and clinical research by creating 60 Clinical and Translational Research Centers at universities and medical centres across the country[12].

Zerhouni, who is now President of Global R&D at Sanofi, remarked two years ago in a commentary that costly failures in late-stage clinical trials have stalled the translational pipeline and that these leaks have produced a biomedical innovation gap, with most newly-marketed drugs close relatives of already approved drugs rather than first-in-class entities. Meanwhile, he says, the medical landscape is characterised more by chronic diseases rather than acute illnesses, and our lack of understanding of these chronic diseases is costing society in both lives and dollars. "Deciphering the complexity of human diseases and finding safe, cost-effective solutions that help people live healthier lives requires collaborations across scientific and medical communities throughout the healthcare ecosystem," he says. "Indeed, we must acknowledge that no single institution, company, university, country or government has a monopoly on innovation"[13].

Given these realities, next-generation business models are emerging through collaborative networks to support frontier science and innovation, address the early drug development gap and help move a good idea through the rocky terrain that separates upstream research on promising genes, proteins and biological pathways from downstream drug candidates. Universities and hospitals are going beyond the practice of establishing centres for drug discovery, which traditionally has focused on screening through vast collections of chemical compounds to find lead chemical matter, and are now derisking lead candidates with 'proof of concept' studies that confirm that these candidates will successfully alter the course of a disease[14]. Rather than building additional in-house infrastructure, there has been a rise in collaborations among scientists at academic centres, Biopharma and CRO/CMO sectors. Alliances with CRO/CMOs is becoming an integral part of R&D approach as they contribute to building key scientific evidence for drug development programmes for clinical success and preserving intellectual property intact. CROs often have infrastructure to handle work that used to be the domain of basic science laboratories within Big Pharma. CROs also have highly-skilled workers. Many began their careers in Big Pharma in indispensable areas and during that time gathered deep clinical exposure.

The 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[15].

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 academic and hospital partners. Others are increasingly engaging in creatively structured financial relationships contingent upon advances in the pipeline. New business models are emerging that adopt non-traditional, venture type business arrangements to help manage R&D costs and share the associated risks in execution of scientific programmes.

These strategic arrangements can integrate with different business models, as we describe below, in a cost-efficient manner and allow access to well-established and validated platforms, technologies and expertise, to accelerate scientific assets and programmes forward.

The Harrington Project

The Harrington Project for Discovery and Development emanating from Cleveland is one initiative that is trying to accelerate breakthrough discoveries from research institutions into therapeutics. The Midwest city that borders Lake Erie is well-known for its symphony and, of course, LeBron James, but it also has great hospitals that work on the cutting edge of medicine and a vibrant bioscience innovation community.

The Harrington Project, a US$300 million international drug development effort to advance discoveries sourced from academic research and non-governmental organisations into new medicines, was launched four years ago by University Hospitals Cleveland Medical Center. A generous donation from the Harrington family of Hudson, Ohio jump-started the Project, which consists of two components:

- The Harrington Discovery Institute, which provides translational grants of up to US$700,000 to physician scientists to advance translational research addressing unmet clinical needs and also provides access to its Innovation Support Center, which provides the selected physician scientists with access to experienced drug developers to guide the development of their innovative therapies.
- BioMotiv, a for-profit accelerator, that is mission-aligned and positioned to continue early stage development projects through an innovative business model that provides a novel link between academic projects and late-stage commercialisation partners.

Since its inception just over four years ago, BioMotiv has raised US$145 million in capital from strategic and impact investors, formed partnerships with non-profits, investors, drug companies and life science companies to develop pioneering discoveries in cancer, ophthalmology, immunology, neurology, inflammation and cardio-metabolic diseases and helped launch 10 start-ups in the US and Europe that are developing drugs in these areas. A key part of BioMotiv's strategy is to forge partnerships with CROs to provide discovery and preclinical services to help advance discoveries sourced from academic research organisations into novel medicines.

BioMotiv sounds a lot like a venture capital fund, but is actually quite different. Most venture capitalists invest in a management team and expect results in five to seven years, putting pressure on the companies in the portfolio to earn significant returns through an exit. BioMotiv invests in a technology or a specific platform – an interesting compound, a novel pathway – and they work closely with investigators to develop a plan of action, with go/no-go milestones built into the plan based on technical progress and market conditions, towards early commercialisation partnerships. BioMotiv reinvests a significant portion of profits earned through such events to fund additional projects and expand its mission impact.

OptiKira, a start-up formed in 2015 by BioMotiv and two Harrington Scholars at the University of California-San Francisco (UCSF) – Scott Oakes, MD and Feroz Papa, MD – is a good example of how these new business models can work. Oakes and Papa, along with two other scientists from UCSF and the University of Washington, were studying a pathway that leads to progressive cell death in diseases such as diabetes, retinitis pigmentosa and amyotrophic lateral sclerosis (ALS), and had identified prototype compounds that inhibited this pathway. BioMotiv formed and funded OptiKira to develop this technology; the founding scientists continue to work closely with the company to increase understanding of the underlying science. In addition, BioMotiv recruited two scientists with more than 20 years of experience in drug discovery and development to provide tactical leadership for the company, and secured several CROs, with Charles River playing a major role, to conduct the preclinical work. Finally, BioMotiv provides ongoing business development support to OptiKira and takes a hands-on role in guiding both the technology's and the company's development.

It is still early days for BioMotiv, but two of its portfolio companies, one focused on cancer and the other on chronic inflammatory diseases, have been advanced into commercialisation partnerships with pharmaceutical companies.

Milner Therapeutics Institute

The UK-based Milner Therapeutics Institute, launched a year ago with a £5 million donation from Jonathan Milner, the co-founder of the antibody producer Abcam, is an example of how academia and industry are pairing up to accelerate drug development. The Institute is fully integrated within the University of Cambridge, directed by Professor Tony Kouzarides and consists of two parts:

- Academic drug discovery research laboratories on the Cambridge Biomedical Campus.
- An outreach programme that involves a consortium of seven pharmaceutical companies (AstraZeneca, Astex, GlaxoSmithKline, MedImmune, Pfizer, Otsuka and Shionogi) and

The Milner business model

three academic institutions (Sanger Institute, Babraham Institute, University of Cambridge) and 29 affiliated partner companies, Charles River included, that focus on therapeutic development.

Milner's two overarching principles are to lower the barriers for interaction between academia and industry and to actively put programmes together that lead to drug discovery. Milner uses two different business models to try to achieve these goals.

The first model allows drug companies to turn to academic scientists for help during the early stages of drug discovery – such as target identification and improving understanding of the target pathway in disease. Here is how it works. Drug companies that belong to the consortium provide materials, compound libraries or just compounds to scientists at Cambridge academic institutions and fund the work as well. When the work is completed, the research goes back to the pharmaceutical company for preclinical development.

The other model is designed to work kind of in reverse. The Institute's affiliates provide assistance – chemical screening or end-target validation, for instance – to academic scientists throughout Cambridge and in the future directly to the Institute's research labs. The goal here is to help the academic scientists derisk their projects and get them to the point where a pharmaceutical company, venture capitalist or other research scheme will be willing to license the technology and take it to the next level.

Milner is very new. Its building on the Cambridge Biomedical Campus, one of the largest medical research and biotech clusters in Europe, is not completed yet and the research labs will not be operational until 2018. But the academic institutions that belong to the consortium are already doing early drug discovery work on five projects – two in oncology, two in infectious diseases and one in neuroscience – in collaboration with pharmaceutical companies.

Tri-Institutional Therapeutics Discovery Institute

The NYC-based Tri-Institutional Therapeutics Discovery Institute or Tri-I TDI is leveraging the scientific discoveries from three research powerhouses in New York City: Memorial Sloan Kettering Cancer Center (MSKCC), The Rockefeller University and Weill Cornell Medicine. The trio are in the heart of the Upper East Side's science corridor, and while they compete for research dollars they also collaborate on projects. They launched the independent, non-profit Tri-I TDI in 2013 – with charitable gifts from two benefactors – to focus on the early stages of developing compounds that make possible all-important proof-of-concept studies – those that increase the likelihood that targeting a specific biologic pathway can favourably alter the course of a disease. They also partnered with Takeda Pharmaceuticals to help develop small chemical molecules emerging from these laboratories.

Last year, they built on the work being done at Tri-I TDI by establishing a new drug discovery company called Bridge Medicines in partnership with Takeda and the healthcare investment firms Bay City Capital and Deerfield Management. They now have a seamless and fully-funded system to efficiently and rapidly develop innovative therapeutics for treating human diseases.

Here is how it works. If a scientist affiliated with MSKCC, Rockefeller or Weill Cornell identifies a disease target that might lead to a novel drug they can seek drug discovery support from Tri-I TDI. The discovery institute provides latest generation medicinal chemistry techniques and technologies through strategic partnerships with academic and industrial partners, such as Charles River. Tri-I TDI oversees all aspects of the drug discovery process and by providing industry-level support, toxicology studies being one example, they can rapidly assess whether the compound should advance further downstream. Projects that 'graduate' from Tri-I TDI are eligible to enter Bridge Medicines, where they can continue along the drug develop-

ment pipeline without interruption and be professionally managed in a venture capital setting. The goal is to graduate 12 new projects a year from Tri-I TDI to Bridge Medicines.

The projects Tri-I TDI and Bridge Medicines focus on include cancer, neuropsychiatry, infectious diseases and rare diseases such as Niemann Pick c Disease or diseases in developing countries that large pharmaceutical companies have typically stayed away from because they cannot reclaim their investment.

Because Bridge Medicines projects are funded as a group, risky but potentially transformational ideas can obtain financial support and shave a decade off the typical process from promising discovery to medical use. Projects are supported through filing of an investigational new drug (IND) application with the US Food and Drug Administration, and Bridge Medicines then works with the participating scientists to establish and fund biopharmaceutical companies responsible for managing individual projects and advancing them to clinical trials, with the intention of basing the new companies in New York City.

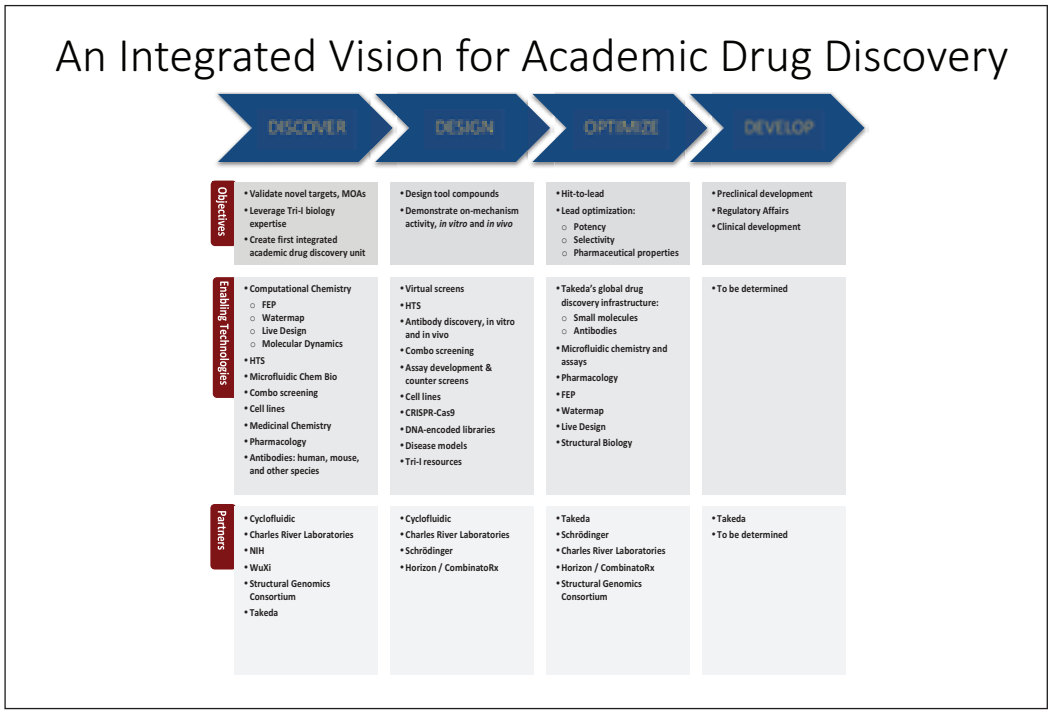
New Strategies, new challenges

While the money spent on early drug discovery work does not come close to the cost of a human efficacy trial, it is still an expensive, high-risk venture. It does not take long to spend down your capital. Finding a steady stream of investors, both public and private, willing to work within these models takes a long time. Finding the right mix of players that can contribute and make the models work is also a challenge.

The non-regulated research space of early discovery is also, paradoxically, more challenging to navigate. 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 and risk [16].

Getting academic researchers to think like an entrepreneur can also be hard. They may not be so comfortable navigating the hyper-staccato world of product development – when drug discovery begins to move downstream and into the more regulatory-driven requirements of preclinical testing. Safety programmes for new investigational drugs must follow rigid objectives and study designs, and be conducted under Good Laboratory Practice (GLP) regulations to ensure repeatability and reliability of the data [17].

And no matter how much you try to derisk a project, there is still a lot of judgment involved in determining if a project works and is eventually worthy of FDA approval. So it is important, perhaps, to manage the expectations of the scientists involved and to have standards and criteria in



The Tri-I TDI business model

Continued on page 30

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Continued from page 29

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place to make those difficult no/no-go decisions that make the asset worthy of further investment.

But if executed properly, these novel business models also offer a path forward for research stuck in the trenches and destined to die of neglect. Who knows? Perhaps these models can provide some projects a 'safe-conduct' through the valley of death and successful translation to breakthrough new drugs. DDW

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