University of Dundee
www.drugdiscovery.dundee.ac.uk

Drug Discovery Unit

Fixing a critical disconnect in drug discovery

By translating academic innovation and partnering with big pharma, the University of Dundee's Drug Discovery Unit (DDU) is developing novel therapeutic targets to a stage where they can be smoothly transitioned across to the pharmaceutical industry.

Priorities in the pharmaceutical industry are being shaped by two significant financial forces. On the commercial side, patent expirations are increasing the need for new pipeline products[1]; at the same time, the cost of drug discovery and development is rising. These trends are driving companies to look to academia for novel targets to replenish pipelines. This approach is effective, but it could be refined with the help of a smoother transition between academia and industry.

As it stands, the academic-industry relationship is often imperfect. Working at the frontiers of science, academics often discover biological processes with therapeutic potential. To gain access to such discoveries, the industry is working with academia and engaging in risk-sharing agreements. However, in doing so, the industry has learned that many novel academic targets require further validation to show that they are linked to a disease and are druggable before they can be deemed ready for direct insourcing. Targets that lack such validation represent a risk to pharmaceutical companies, which could invest in them only to later learn that they are nonviable. Further, worries about the reproducibility of academic discoveries[2] have made industry reluctant to insource them without evidence that the biology and associated assays are suitable for drug discovery projects.

"These are the studies the pharmaceutical industry relies on to identify new targets for drug development. But if you're going to place a $1 million or $2 million or $5 million bet on an observation, you need to be sure it's true. As we tried to reproduce these papers we became convinced you can't take anything at face value," C. Glenn Begley, former head of global cancer research at Amgen, told Reuters in 2013.

> "Having built a reputation for delivering preclinical candidates to industry, the DDU set up the Innovative Targets Portfolio in 2009

The consequences of these factors are severe. Charities and the public invest heavily in biomedical research—the annual total in the UK tops £2 billion—but much of the work they fund never fulfills its potential because of these translational shortcomings. These issues, which have become known as 'the valley of death', are centered on early-stage drug discovery, a field in which academic innovation meets professional medicinal chemistry and associated technologies.

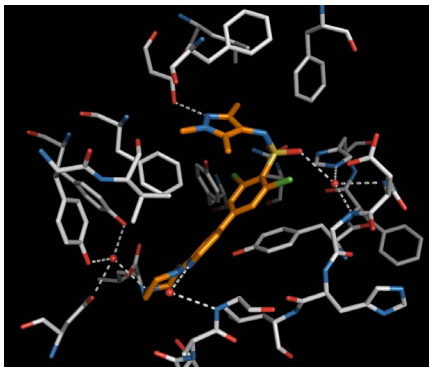

Figure 1: Chemical structure of lead molecule DDD85646 bound within the target enzyme N-myristoyltransferase.

Recognizing the need to further translate academic innovation, the University of Dundee set up its DDU (www.drugdiscovery.dundee.ac.uk) in 2006. The DDU is an integrated drug discovery engine housing a team of 85 staff, dedicated to small molecule drug discovery, the majority of who have built up expertise in the pharmaceutical industry. The capabilities of the DDU cover all stages of early drug discovery including hit discovery, medicinal chemistry, bioinformatics, computational drug design, structural biology and drug metabolism and pharmacokinetics. The DDU uses these capabilities to validate—or reject—potential drug targets, thereby bridging the gap between academic research and pharmaceutical development.

Bridging the academia–industry divide

The DDU is the most established university-based facility working across multiple therapeutic areas in the UK[3] that can take projects from target identification and hit discovery through to preclinical development. By pairing its capabilities with the resources of large pharma companies and funding from organizations including the Bill & Melinda Gates Foundation and the Wellcome Trust, the DDU has driven advances in the development of treatments for devastating diseases of the developing world, which it was originally set up to address.

A malaria drug developed at the DDU in collaboration with the Medicines for Malaria Venture is now in clinical development with Merck Serono and is due to start phase 1 in early 2017. The product of another DDU collaboration with GlaxoSmithKline (GSK) on visceral leishmaniasis, is also advancing toward the clinic.

Having built a reputation for delivering preclinical candidates to industry, the DDU set up the Innovative Targets Portfolio in 2009 to expand its reach to cover global diseases such as Alzheimer's disease, rheumatoid arthritis and other inflammatory diseases, antimicrobial resistance, and genetic skin diseases. The DDU team, many members of which built their reputations through work on such diseases, partners with academics to partly validate novel targets using industry-standard technologies and medicinal chemistry.

In developing molecules that demonstrate target engagement and the required phenotypic responses in appropriate models of disease, the DDU takes novel targets to a stage more suitable for licensing by industry. Because the DDU funds its work using research grants, it bears the risk that the pharmaceutical industry is reluctant to take. This has proven attractive to companies such as Pfizer and GSK, both of which have partnered projects with the DDU through its Innovative Targets Portfolio.

Expanding the scope of the DDU's work

Since the creation of the Innovative Targets Portfolio, the DDU has continued to search for ways in which it can better serve the academic researchers and pharmaceutical companies with which it works. The search has led the DDU to challenge traditional funding mechanisms and explore new translational models to accelerate the advancement of a pipeline of assets ready for development into new therapeutics by pharmaceutical partners.

The DDU is on course to become better positioned than ever to deliver on its respective promises to academic collaborators and the pharmaceutical industry. Academics will see their targets taken deeper through drug discovery, which in turn will enable pharmaceutical companies to pick up derisked programs that are closer to entering the clinic.

1. Harrison, C. *Nat. Rev. Drug Discov.* **10**, 12–13 (2011).
2. Begley, C. G. & Ellis, L. M. *Nature* **483**, 531–533 (2012).
3. Tralau-Stewart, C. *et al. Nat. Rev. Drug Discov.* **13**, 15–16 (2014).

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