



Feature

Academic drug discovery: Challenges and opportunities

Angela J. Murray¹, Liam R. Cox², Holly V. Adcock¹, Ruth A. Roberts^{1,3,4,*}

There are many different approaches to drug discovery in academia, some of which are based broadly on the industrial model of discovering novel targets and then conducting screening within academic drug discovery centres to identify hit molecules. Here we describe our approach to drug discovery, which makes more efficient use of the capabilities and resources of the different stakeholders. Specifically, we have created a large portfolio of drug projects and conducted small amounts of derisking work to ensure projects are investment ready. In this feature we will describe this model, including its limitations and advantages, since we believe the ideas and concepts will be of interest to other academic institutions and consortia.

Keywords: academic drug discovery; drug development; translation gap; dynamic investment; translational research; prioritisation

Introduction

The crisis in productivity of the pharmaceutical industry's drug discovery model^(p1) has driven an evolution towards academic partnership and collaboration. In turn, this has given rise to academic drug discovery centres (ADDCs), primarily across the United States, Canada, and the UK, whose aim is to bring drug candidates part way along the drug discovery pipeline to a state of maturity that will entice further substantial commercial investment into spinout companies or buyout of the intellectual property (IP). This model provides significant opportunities for translating academic innovation into patient benefits, and it is also attractive to the

pharmaceutical industry as the very early and riskiest part of drug discovery is outsourced.

The aim of ADDCs is to identify and develop drug candidates and tools to the point at which there is sufficient novelty and potential to attract commercial investment or, in the case of neglected diseases, make them potentially eligible for funding motivated by humanitarian concerns. This is achieved by recruiting those with drug-hunting expertise from industry to work alongside academics, usually complemented by specialised consultants. This model enables academics to focus on finding and validating novel targets and/or developing novel hits. One analysis from

2014^(p2) highlighted around 80 such ADDCs in the United States alone, with many more worldwide. A more detailed analysis of four of the ADDCs^(p2) concluded that they are good vehicles for alleviating risk and are well placed to bid for government and charity funding to carry out precompetitive research.

Although ADDCs represent an attractive model for academia, there are several challenges that need to be overcome. One of the most important is gaining funding to bridge the gap between areas traditionally supported by national institutes, government agencies, research councils, and charities and the investments needed to generate the data that

make a project attractive for commercial investment (Figure 1). For example, institutions and their resident academics/clinicians may be focused on novel research that breaks new ground and can generate high-impact publications; they might not be so inclined to invest time and resources in less exciting work, such as finding an appropriate formulation for a new molecule or predicting the likely pharmacokinetic properties of a series of compounds that have yet to be made. It is also challenging to get grant funding for this type of work, even from sources with a more translational mission. Conversely, this kind of enabling work is often seen as being too early for investment by pharmaceutical companies or venture capital (VC). There are further related challenges. Specifically, there is a tendency for academic scientists to overvalue their projects compared with the value that would be assigned by VCs (Figure 1), especially in the phase before *in vivo* profiling. A third major challenge is determining how resources are spent. As pointed out by Kirkegaard and Valentin,^(p2) a university is well placed to oversee a bench-to-bedside drug discovery pipeline held within its campus but there is a tendency for ADDCs to recapitulate the industry model of selecting a given area of disease research and then conducting a target–hit–lead approach, only on a smaller scale than is usually seen in large pharmaceutical companies. By the laws of probability, it is unlikely that this approach will yield results where large pharma has struggled. In academia, the area of disease research is frequently dictated by the areas of interest of the academic rather than by an up-to-date analysis of unmet medical needs, so the work generated might not always be selected for commercial investment. This is further confounded by a lack of expertise to assess project value,^(p3) leading to investment of limited resources in the wrong areas.

Birmingham Drug Discovery Hub

Back in 2015, a strategy review revealed that the University of Birmingham (UOB) has significant expertise in fields important for drug discovery, ranging from medicinal chemistry to computational biology, toxicology, screening, structural biology, discovery of new targets, and elucidation of disease mechanisms. UOB also

has a very strong clinical team with diverse clinical expertise and two world-leading clinical trials centres. However, there were only limited examples of successful translational to patient benefit, showing that this expertise alone was not enough to drive success in academic drug discovery.

To realise the untapped potential, UOB developed an approach designed to overcome the challenges outlined above. Firstly, UOB appointed a Chair of Drug Discovery (RR) with significant industry experience in drug discovery, with the mission of leading and integrating drug discovery across campus. Important for success, this academic lead role did not encompass a lab or research theme; instead, efforts were entirely focused on supporting other academics and clinicians across campus.

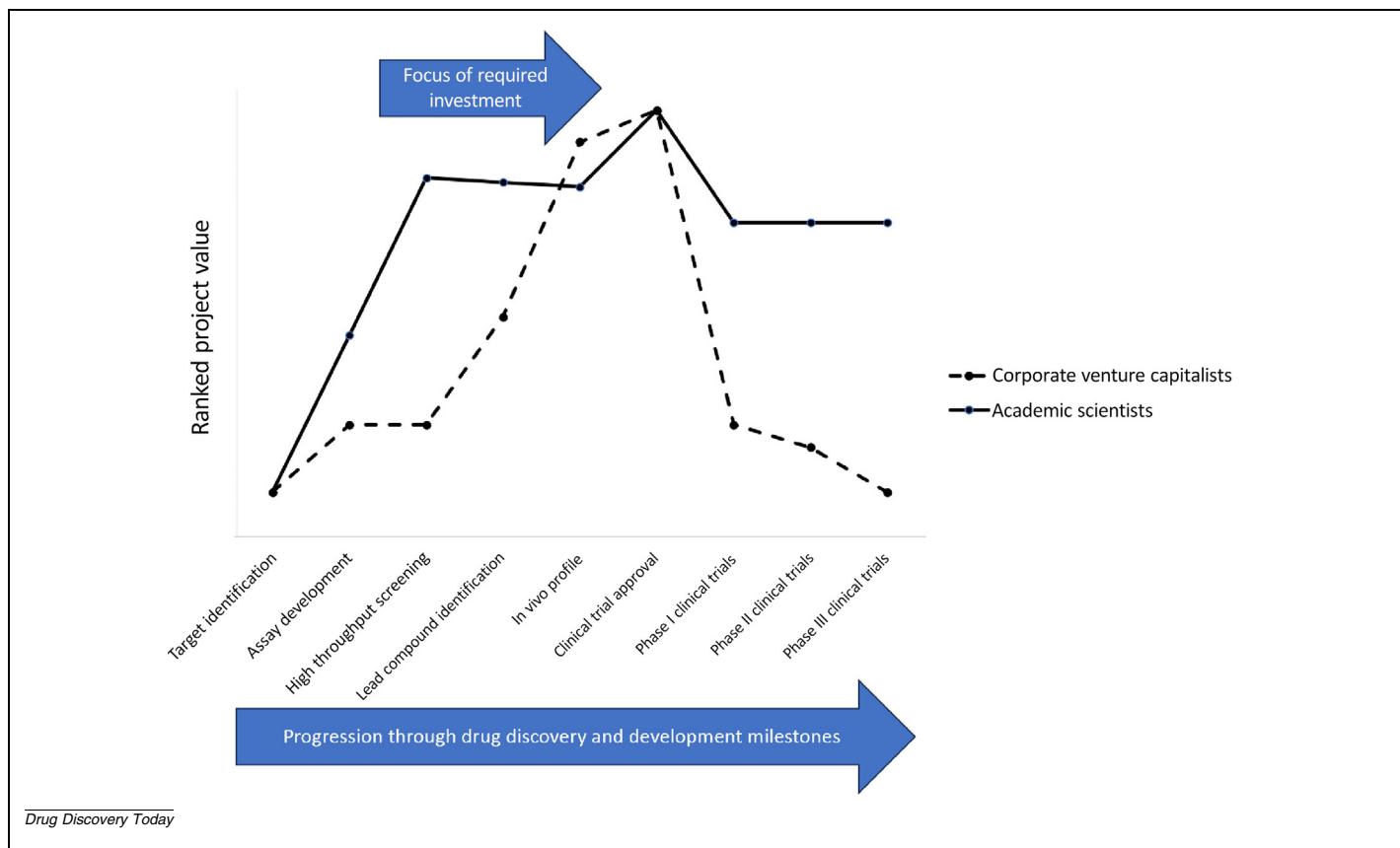
Secondly, UOB provided a ‘cornerstone’ investment (initially £0.5 million) from the University Dynamic Investment Funding (DIF) to support programme/project staff and to invest in projects. Unlike most university core or grant funding, the Drug Discovery 5-year DIF business plan proposed to operate more like a VC fund with a planned return on investment. Within the DIF business plan, investments provide a projected 30% return over 5–7 years via commercial investment from pharma/biotech, spinoffs, grant funding, and out-licensing. To date, we have invested £0.2 million in projects and have attracted £1.2 million direct income (industry funding brought directly to UOB), as well as direct and indirect income of £4.1 million (grants and industry awards that DIF funding has led directly to being awarded), and we have another £2.5 million of industry spinout funding currently undergoing due diligence and likely to be funded in Q2 of 2024. Therefore we have returns for UOB of 6, 20 or 30 times the amount invested by DIF in project funding to date (~£0.2 million), depending on how we count income. Overall, the DIF funds are quite small, or are comparable with other ADDCs, but they have yielded above-expected results due to our system for investment and return. Indeed, there are further funds available to us from DIF but, so far, we have not drawn this down due to the success of the programme in attracting external funding.

Thirdly, the University created a virtual hub, the Birmingham Drug Discovery Hub

(BDDH), with two fulltime posts, a programme manager and a project officer. Finally, we developed a system for identifying and evaluating all projects across campus, including targeted investment from DIF. Thus BDDH is disease agnostic and embraces the entire university and associated hospitals to identify good-quality research with translational potential (Figure 2).

To identify those projects that merited further evaluation and investment, we assembled a team of people with diverse expertise in different aspects of drug discovery and development, primarily but not exclusively drawn from outside the university. The virtual team included drug project leaders, biologists, chemists, clinicians, formulation specialists, DMPK specialists, toxicologists, and experts in IP, as well as disease area specialists. Much like an industry project team, this group was assembled from an extensive pool of experts across the university and hospitals and used in a flexible way as needed depending on the project stage, therapy area, modality and key identified risks. After an initial triage, for projects that merited further evaluation, we used an evaluation form known internally as TCP (target–chemistry–patient) (Figure 3). TCP proved highly effective in capturing academic drug projects in a format more familiar to industry and, crucially, was very efficient in derisking projects (Table 1) by identifying data gaps. Small investments from DIF of around £5000 to £50 000 over 1 to 12 months were made to address these data gaps and address concerns, such as additional target validation work, the need for novel formulations, computational modelling of novel pockets on the target, and evaluating unwanted on-target safety risks via a target safety assessment.^{(p4),(p5)} Based on the outcome of the work, as outlined in the three examples in Table 1, we would decide if the project meets key criteria. If yes, then we would develop and deliver a project plan with costings, milestones, and timelines alongside a plan for engaging with potential investors.

Once the value of BDDH to the University was established, the University also part-funded the programme and project posts via various internal funds, including the Higher Education Investment Fund (HEIF), a campus-wide fund that supports projects with high potential for societal

**FIGURE 1**

The translation gap between academic research and the data required for preclinical proof of concept: this is the focus of the investment required. Adapted from McCammon *et al.*^(p3)

and educational impact. The expert BDDH team has now established a searchable portfolio of ~240 projects assembled over 3 years, categorised by therapy area, project type, project stage, and supporting information such as IP position and past/current funding sources. This allows us to evaluate and demonstrate what is needed to achieve preclinical proof of concept (Table 1). For each entry, there is a hyperlink to the completed TCP and any other documents allowing all functions across campus to search for and access details of specific projects/themes to present to investors.

So far, we have attracted ~£7 million investment into projects as a consequence of our work. It is too early to evaluate how this will translate into tangible patient benefit, but we are tracking metrics around new targets, new chemical entities, and progress towards clinical trials. In addition, two funded DIF projects are expected to form joint ventures with pharmaceutical investors in 2024.

Setting up BDDH as separate and distinct from existing academic working units, such as schools and colleges, was vital to its success; it ensured BDDH experts formed a community that is truly interdisciplinary and agnostic to university architecture, overcoming academic silos, preventing duplication, and making it easy to quickly gain access to the skillsets that were required to answer the next key go/no-go decision point for each project.

Ultimately, the Chair of Drug Discovery is accountable for all the different strands of drug discovery at UOB such as the portfolio, the BDDH, and returns on DIF.

Enabling chemistry and the Haworth Compound Collection

In addition to DIF, agile funding was also secured for BDDH from the Wellcome Trust for two specific projects, enabling medicinal chemistry and the establishment of the Haworth Compound Collection. For the supported medicinal chemistry initiative, we employed a full-time skilled medicinal chemistry postdoc-

torial research fellow. Academics could bid for this person's time (via a competitive and independent application process) to undertake molecular synthesis projects to overcome issues such as solubility and formulation, and molecular design and synthesis, enabling hit-to-lead and hit-to-tool programmes to move forward. This investment in a dedicated expert medicinal chemistry research fellow was transformative in that the biggest hold-up to such projects can be a dependency on someone 'knowing someone else' within the university who is willing to help out. Now we have a formalised and rapid way to get the medicinal chemistry support needed to move a project forward and to avoid potentially lengthy delays pending more substantial funding. Clearly, one single postdoc cannot serve all needs so we are moving towards a cost neutral model where we conduct the upfront work at no charge to the project, but projects then use these pilot data to secure other funding for subsequent medicinal chemistry.

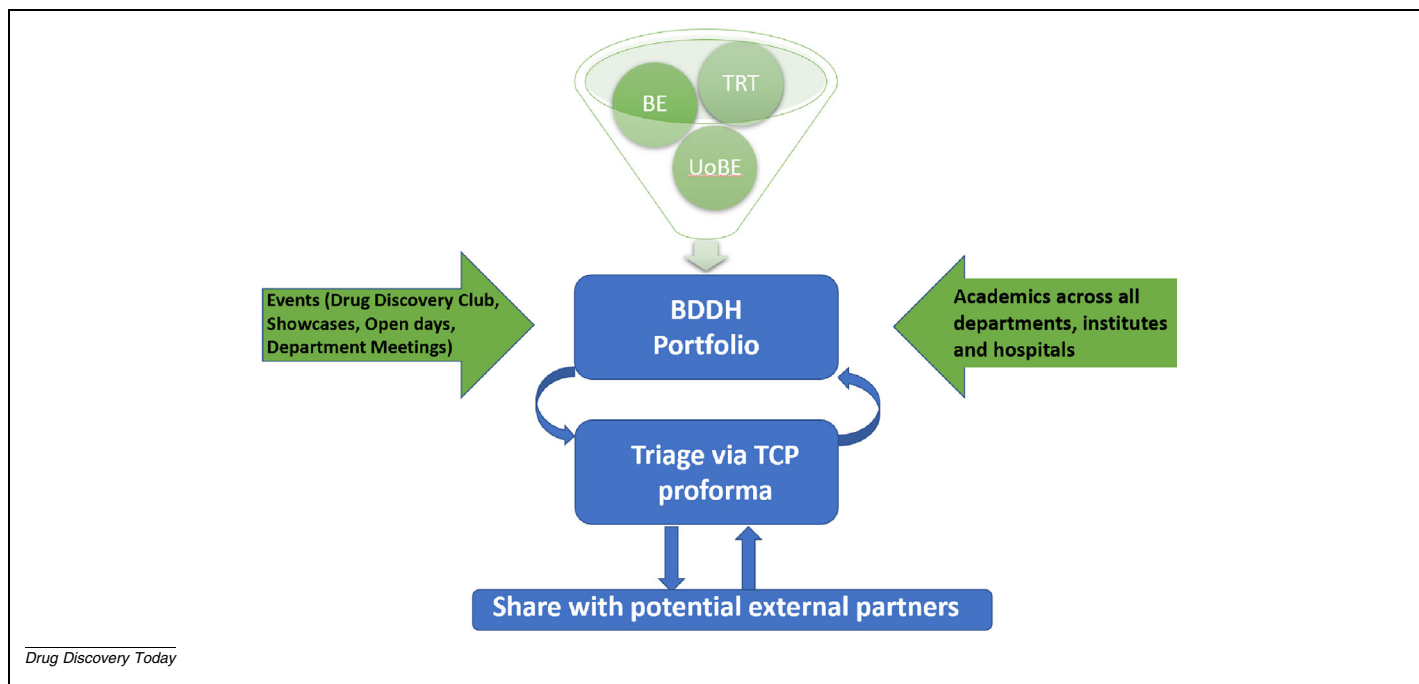


FIGURE 2

The drug discovery project funnel. Projects are identified by University of Birmingham Business Engagement and Research Impact (BERI), the Translational Research Team (TRT) and University of Birmingham Enterprise (UoBE) as well as from outreach events and directly from academics. These are brought into the Birmingham Drug Discovery Hub (BDDH) portfolio for triage of novelty and data gaps identified via the TCP proforma (see Figure 3).

Enabling chemistry was employed in several projects, three of which are outlined here. One project was focused on new molecules to improve radioiodine treatment of thyroid cancer. Radioiodide is used to treat thyroid cancer but uptake is poor in around one third of patients, limiting efficacy. Some compounds have been reported to improve uptake but are associated with significant side effects. We identified several novel compounds that induce radioiodide uptake into thyroid cancer cells. *In vivo* studies have now shown significant effects on the uptake of radionuclides into mouse thyroids. Next steps will involve carrying out studies in mouse models of human thyroid cancer.

A second project was developing a novel diagnostic tool for Parkinson's disease. The currently available radionuclide imaging techniques used for imaging patients with Parkinson's Disease have major drawbacks including cost, poor uptake, and poor spatial resolution. We designed and synthesised a novel MRI probe for labelling dopaminergic neurons in Parkinson's disease with increased sensitivity. We have demonstrated uptake by PC12 cells using NMR spectroscopy. Next steps for this are to assess labelled DOPA uptake in rat brain using MRI imaging. If

we demonstrate increased MRI signal in known dopaminergic brain areas, then we will compare distribution in images from rats with experimental Parkinsonism.

A third project is looking for novel formulations of prednisone for local delivery in the treatment of inflammation. Current prednisone formulations have low solubility, limiting the ability to administer at sufficient doses for improved efficacy over current standards of care. The aim of this project was to overcome this limitation by developing steroid gels that are activated within the joint by endogenous metabolism. The enabling chemistry scheme developed a novel salt formulation that improved solubility of the drug substance, allowing its incorporation into a gel to overcome this limitation. An animal model confirmed efficacy of the formulation in an *in vivo* disease model of inflammation.

In addition to and in support of enabling chemistry, we gained funding to assemble an institutional physical and virtual compound library, the Haworth Compound Collection. These are high-quality and highly curated collections of compounds displaying drug-like properties that have been synthesised in schools (primarily chemistry and pharmacy but also

others) across campus. The majority of compounds in these libraries have been made using bespoke chemistry and developed within the institution; therefore they are unique and distinct from commercial compound libraries. The hit rate when screening these libraries has proven to be higher than we see with commercial libraries and has enabled several projects to move forward within our portfolio. Lockdown actually had unintended benefits here as the Collection was originally proposed to be fully physical; however, when laboratory facilities were closed, we transitioned to a virtual format where PhD theses from the past 25 years were mined for suitable compounds; these compounds, alongside compounds that had already been deposited in the physical collection, were uploaded to a database using their Simplified Molecular Input Line Entry System (SMILES) identification code, enabling *in silico* screening. This virtual collection has brought diverse and novel chemistry to a far wider audience within the university.

Ideas to consider for academic drug discovery success

The UOB Drug Discovery Hub has brought together many approaches used in other

Project Title / Aim		Target e.g. <i>c-Myc, IL6R, GSK3</i>	
PI name		Mechanism e.g. <i>inflammation, ageing</i>	
PI email		Disease Area e.g. <i>Oncology, arthritis, ophthalmology</i>	

T: Is it the right target?	
1. How well do we understand the target and its properties?	
2. Detail the existing evidence that demonstrates a link between the target and the disease condition.	
3. What is the intrinsic variability of the target in the population? (Stratification)	
4. To what extent do <i>in-silico</i> / <i>in-vitro</i> / <i>in-vivo</i> models demonstrate likely efficacy?	
5. What are the safety implications of modulating the target? (Activation or inhibition)	
C: Is it the right chemistry?	
1. What are the likely pharmacokinetic / pharmacodynamic properties and are they compatible with a 'drug-like' molecule?	
2. What is the activity against the target and related targets that may play a role?	
3. Will it formulate for <i>in-vivo</i> delivery? Is it stable?	
4. What are the safety risks associated with the chemistry? (Structural alerts)	
5. What are the likely secondary pharmacology (off-target) signals?	
P: Is it the right patient population?	
1. What is the intended patient population? (Disease condition, demography, co-morbidities)	
2. Describe the current standard of care, likely co-morbidity and clinical outcome.	
3. Considering the future needs of the patients, what is the potential impact on care providers, budget holders and wider society?	
4. What is the current IP position? Is there likely to be any novel IP developed by the team? How does this technology compare to competing approaches (existing therapies and those in development)?	

Drug Discovery Today

FIGURE 3

The target–chemistry–patient (TCP) proforma.

academic institutions to develop a portfolio of drug projects that can be shared with the right funding partner at the right time and in a format familiar to the pharmaceutical industry. Keys to success that might be considered by other academic institutions and consortia are (i) to have an academic lead who is purely focused on assisting others and does not have their own research interests; (ii) to have a dynamic investment fund for targeted derisking; and finally (iii) to focus these limited funds on translating existing research rather than setting up new areas of discovery.

Concluding remarks and future perspectives

There are many ADDCs across the world, with one analysis^(p2) highlighting 80 ADDCs in the United States alone. ADDCs are a great vehicle to translate academic discoveries into new medicines but they face three major challenges:

- Lack of funding to cross the translation gap between basic research and investment-ready research

- Lack of expertise within universities to assess project value and identify data gaps
- An overfocus on recapitulation of the industry model within academia but on a smaller scale

BDDH has been designed to overcome these challenges by assembling the right funding and the right team of experts to drive research from the bench to preclinical proof of concept, thereby maximising both our intellectual and financial capital. We now have a diverse portfolio of projects across many therapy areas, including oncology, inflammation, ageing, women's health, and infection, covering all stages from target identification to clinical development. With our inclusive philosophy, we are also open to all modalities from traditional small molecules through to antibodies, CarT, and nanobodies.

We also have a strong outward looking approach where we actively engage with investors to map what projects and areas they are seeking. Therefore our strategic reviews of our portfolio are more efficient since we are providing projects to several

different funders at once, but with each project tailored to the needs of each investor.

Nonetheless, the valley of death (VoD) concept (where projects fail to make it from discovery to marketed product) is still with us and it would seem is no longer primarily an academic problem. Indeed, converting new technology concepts into marketable products is also proving difficult for companies that struggle with transitioning projects from knowledge discovery to product development.^(p6) Also, similarly to the challenges in academia, at least some of these failures are attributed to organisational complexity leading to the suggestion of a motivation–opportunity–ability framework that to some extent resembles our BDDH evaluation process.

Declarations of interest

RAR, AJM, LRC, and HA are all employees of the University of Birmingham, UK. RAR is also an employee of ApconiX, an integrated ion channel research and toxicology consultancy that provides expertise to academia, industry, NGOs and

TABLE 1

Concepts important to the Birmingham Drug Discovery Hub with examples.

Concept and definition	Example 1	Example 2	Example 3
Derisking refers to identifying key risks in a project and carrying out 'fit for purpose' risk mitigation work.	An academic believes their protein could be a drug target. DIF would support <i>in silico</i> work to assess disease linkage, expression, and the consequences of genetic manipulation.	A repurposed drug requires a novel formulation to deliver peak dose at bedtime, tailing off towards morning. <i>In silico</i> modelling would be used to generate possible formulae that can then be tested <i>in vitro</i>	A new drug for cancer is highly efficacious in <i>in vitro</i> and <i>in vivo</i> mouse models but the target is also expressed in the brain. A small <i>in vivo</i> 'mini-tox' study would establish whether there is penetration of the blood-brain barrier with any adverse CNS signs.
Preclinical proof of concept (POC) refers to a dataset that would be required to establish confidence in the potential of a project to enter clinical trials.	A project has identified several molecules that inhibit a target of interest where disease linkage is already established. POC would require the ADME (absorption, distribution, metabolism, excretion) profile, an assessment of on- and off-target safety risks, and a dose range-finding study in two toxicology species to establish the maximum tolerated dose (MTD) and to reveal any 'stop' toxicology signals.	A project aims to better existing therapies via a new approach that requires clinical validation. POC would require a translatable biomarker that can be used in early clinical trials.	A project has identified a new therapeutic opportunity and requires toxicology bridging studies to demonstrate that the existing toxicology package can support patient safety.

governments on all aspects of nonclinical program design and delivery.

CRedit authorship contribution statement

Angela J. Murray: Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. **Liam R. Cox:** Conceptualization, Data curation, Supervision, Writing

– review & editing. **Holly V. Adcock:** Data curation, Investigation, Methodology. **Ruth A. Roberts:** Conceptualization, Formal analysis, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by the Wellcome Trust (204846/Z/16/Z) and by the University of Birmingham internal Dynamic Investment Fund. The authors would also like to acknowledge Professor Chris McCabe and Dr. Rowan Hardy at the University of Birmingham for their contribution to the case studies in this article.

References

- Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. *Nat Rev Drug Discov*. 2011;10:428–438. <https://doi.org/10.1038/nrd3405>.
- Schultz Kirkegaard H, Valentin F. Academic drug discovery centres: the economic and organisational sustainability of an emerging model. *Drug Discov Today*. 2014;19:1699–1710. <https://doi.org/10.1016/j.drudis.2014.06.011>.
- McCammon M, Pio E, Barakat S, Vyakarnam S. Corporate venture capital and Cambridge. *Nat Biotechnol*. 2014;32:975–978. <https://doi.org/10.1038/nbt.3029>.
- Brennan R. Target safety assessment: strategies and resources. In: Gautier J-C, ed. *Drug Safety Evaluation: Methods and Protocols, Methods in Molecular Biology*. Springer Science; 2017.
- Roberts RA. Understanding drug targets: there's no such thing as bad news. *Drug Discov Today*. 2018;23:1925–1928.
- Dean T, Xhang H, Xiao Y. The role of complexity in the Valley of Death and radical innovation performance. *Technovation*. 2022;109 102160.

Angela J. Murray¹, Liam R. Cox²,
Holly V. Adcock¹, Ruth A. Roberts^{1,3,4,*}

¹Birmingham Drug Discovery Hub, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

²School of Chemistry, University of Birmingham, Birmingham, UK

³School of Biosciences, University of Birmingham, Birmingham, UK

⁴ApconiX, Alderley Park, Macclesfield, UK

* Corresponding author.