From academic concept to commercial reality: How to accelerate translational drug discovery

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Chapter 1: Finding a winning formula to lower barriers for academic researchers

Recognizing the 'academic perspective' to identify hurdles

Translating new academic insights in disease biology into new therapeutic targets and agents is for most institutions and academic researchers a journey into the unknown – or at least the unfamiliar. It relies on a highly collaborative approach, as each stage requires access to new expertise that may not reside in the institution. As academic researchers represent the starting point for the discovery of many new therapeutics (see Introduction), ensuring that they are motivated to engage in the process is vital if we are to realize the full translational potential of academic biomedical research.

We will therefore first consider the incentives and disincentives faced by academic researchers who consider setting their early discoveries on the pathway to translation, starting with the role of academic culture.

Academic researchers are not being career-incentivised to engage in translation

Academic culture has frequently been cited as a challenge for translating research into drugs or drug discovery programs (Sanberg et al., 2014). Traditionally it prioritizes activities leading to tenure including publishing in high-impact papers, obtaining grant funding, and teaching - rather than commercializing research findings (Sanberg et al., 2014; Mantai & Marrone, 2022; Mantai & Marrone 2023). A survey of 35 US Technology Transfer Offices (TTOs) reported that 75% considered the primary barriers to completing more [licensing] projects to be the lack of entrepreneurship amongst faculty (46%) or academic resistance to commercialization efforts (29%) (Deerfield Institute report, 2019). In the shadow of this prevailing culture, the proportion of academics who devote time to translational activities is small; with studies in Europe and the US reporting

single-digit percentages (Lissoni et al., 2008; Bozeman & Gaughan, 2007).

How entrepreneurial universities are creating incentives

Despite these cultural countercurrents, some universities are now including consideration of translational outputs/ commercialization activities in relation to academic career progression (Sanberg et al., 2014, Perkmann et al., 2013) and are making genuine efforts to inculcate and celebrate a more entrepreneurial institutional culture (Bezanilla et al., 2020; Meyers & Pruthi, 2011).

The majority of universities also implement policies under which academic innovators benefit financially from successful Intellectual Property (IP) commercialization. Typically, this involves receiving a share of any licensing revenues associated with IP from their laboratories and/or receiving equity in new companies (NewCos) formed around their discoveries (Ouellette & Tutt, 2020). However, published evidence suggests that personal financial gain may be a less powerful incentive than factors such as institutional recognition, increased funding or intrinsic satisfaction (Ouellette & Tutt, 2020; Huszár et al., 2016). Improved translational cultures in academia therefore require both multifactorial incentives at an individual institutional level and national policies intended to encourage universities to demonstrate that they are maximizing the societal impact of their research (Sanberg et al., 2014).

Translation risks disproving a hypothesis that might otherwise remain unchallenged

A more speculative cultural disincentive for academics may lie in the risk that their published academic research findings are found to be unreproducible or disproven when subjected to translation from academic paper to industrial laboratory. The challenges of pharmaceutical companies being unable to replicate academic findings are well described and have probably not gone unnoted by academic researchers (Prinz et al., 2011; Begley & Ellis, 2012, Dirnagl et al., 2022). However, since there is no institutionalized incentive for academic researchers to have their published hypotheses reassessed by peers or by a commercial drug discovery partner, it should not be surprising that few academics venture this path.

Practical hurdles for academic drug discoverers

Beyond cultural challenges, academic researchers face practical barriers specific to drug discovery when engaging in translational efforts – in particular, the following:

1. **Minimal institutional support for early therapeutic concepts**

   When academic researchers identify new potential drug targets, the options to progress towards a new drug are often limited or challenging to access. Such discoveries typically fall short of patentability and are given a lower priority by the academic's local TTO (Bohrer, 2008). As a result, there can be little incentive for an academic to voluntarily disclose such discoveries in the absence of access to suitable internal translational support mechanisms. In practice, most academics rely either on sporadic calls for proposals for external public translational funding programs or on finding a pharma company willing to sponsor future research on the target in the institution (Franzoni et al., 2022). Either may represent the proverbial needle in a haystack.

2. **Lack of expertise how to efficiently bring a project to 'industry standard'**

   It is also generally challenging for an academic researcher with no commercial experience to devise a project plan that meets – or at least approaches - industry standards. While some larger research institutions may have employees or consultants with commercial drug discovery experience, many lack such expertise, particularly spanning different therapeutic modalities (Roy, 2018; Frearson, 2010; Boguszewicz-Kreft, et al., 2021). Translational project plans, experiments and disease models must align with the needs of potential future investors. If not, they are unlikely to secure support.

   There is the additional risk to academics that where translational funding is secured, their project is 'thrown over the fence' to a commercial partner (or contract research organisation) and that the translational activities therein remain a black box. This is, of course, a missed opportunity for both parties to learn from each other. In addition, it undermines trust and respect between academic and commercial teams and reinforces the informational and cultural barriers existing between universities and companies.

3. **Insufficient funding to achieve meaningful proof of concept**

   Translational funding schemes must provide access to enough funding to achieve a level of proof of concept sufficient to subsequently attract a commercial partner. Bona fide drug discovery is inherently expensive and as far back as 16 years ago, the absence of such funding for academic drug discovery projects was

recognized as a market failure (Moran, 2007). While the early-stage funding environment has improved since 2007, there remain relatively few funding mechanisms that can provide the magnitude of financial support required (Seyhan, 2019), and less than 25% of 35 major US TTOs surveyed in 2017 had access to funding to support therapeutics translation (Deerfield Institute report, 2019). By way of example, the funding necessary to go from a novel small molecule target via high throughput screening approaches to an early lead candidate with pharmacodynamics or robust preclinical in vivo proof of concept data can easily exceed one or even two million dollars.

In the absence of suitable stand-alone funding options, academic researchers must fall back on accessing multiple smaller funding sources to reach robust proof of concept. The often-sequential nature of this approach can greatly prolong timelines, involve considerable administrative time, and ultimately lose competitive advantage against others working on the same target.

4. **Protracted timelines and lack of clarity regarding downstream commercial terms**
   Even with strong proof of concept data in hand, finding the right investors or licensee can be a difficult and time-consuming process, both for the academic(s) involved and the institution's TTO (Smith, 2011). While the TTO can take on some of the work, the academic researcher will typically need to invest time presenting to potential investors and being consulted about various aspects of the contracts. When it comes to the creation of a NewCo in which the academics will be shareholders, the time requirements are typically significantly higher than for a stand-alone license, due to the extra complexity. Even once an interested investment partner is found, due diligence may take several months.

   It can also take a long time to agree deal terms between an institution and an investor. Protracted negotiations are often required to agree not only financial terms such as milestones, royalties and pre-money valuations, but also other key terms such as scope of license rights, management of IP, termination rights and liabilities (Great Britain. Dept. for Business, Energy and Industrial Strategy, 2018).

   Academic researchers are also understandably concerned about protecting certain academic interests such as the rights to publish on funded work and to use arising IP for non-commercial research in their institutions. Such rights are per se immutable but may still delay negotiations with potential investors. Protracted negotiations risk frustration amongst all parties, erosion of relationships and the deal falling through. Even if an agreement is ultimately reached, the associated opportunity cost may be a disincentive for academics to attempt similar translational endeavors in the future.

Overcoming key obstacles by building BRIDGES

So how can academic institutions better inspire, ignite and incentivize their biomedical researchers such that more of the drug discovery potential is realized? Based on Evotec's experience of operating BRIDGE partnerships for more than 6 years across as many different countries, we propose the following measures to have positive impact by addressing practical barriers and helping develop a culture that more readily catalyzes translation:

1. **Make it a conversation**
   Evotec has found that an embedded expert model with a designated Expert-In-Residence (EIR) can be transformative in identifying new targets for translational support. A BRIDGE EIR represents a dedicated, in situ expert with whom an academic researcher can develop an ongoing in-person dialogue. Such roles typically operate under blanket confidentiality agreements and we find that the quality of relationship that develops at TTO and researcher level is enabling both in terms of sourcing projects and in providing a highly effective rolling informal triage of potential opportunities.

   Moreover, as forward-looking work plans and project proposals are being built, the EIR acts as a facilitator to convene a project proposal team comprised of both industry and academic colleagues. This ensures that experimental plans are constructed with the right commercial input to align with downstream (pharma) partner expectations. The EIR model also is evident in other pre-seed initiatives, most notably Apollo Therapeutics' and Deerfield Management's academic partnerships (Senior, 2019; Apollo Therapeutics, 2022). We will describe 'a day in the life of an EIR' in greater detail in Chapter 3.

2. **Make it feasible**
   In drug discovery, feasibility is inherently linked to funding. When starting from a novel target, the cost of achieving robust proof of concept with a new therapeutic candidate against that target – whether small molecule, antibody or another modality – is substantial. Innovative translational schemes such as

BRIDGES offer project awards of sufficient magnitude, in the case of current BRIDGES up to – or in some cases exceeding – $ 1.5 million per project. This provides potential academic applicants with the confidence that there is a clear route to robust preclinical proof of concept, and no need to spend significant time stitching together a patchwork of smaller awards to achieve the same goal.

In addition, Evotec finds that giving academic researchers access to a funding mechanism that can approve and initiate projects much more quickly than public (translational) funds – reducing such period from months to weeks – can also be a powerful incentive.

3. **Make it a collaboration**

Few academic researchers possess material experience of commercial drug discovery, but most are aware that the chances of a given drug discovery program yielding a marketed product are very low. The potential holistic return on investment for an academic considering engaging in translation can therefore be uncertain at best. However, in Evotec's experience with the BRIDGE partnerships, participating academics derive significant value from the opportunity to learn about commercial drug discovery. Whether or not a funded project is successful, the researchers can apply their new insights both into future translational opportunities and in addressing new questions in the context of their basic and applied research.

'The LAB282 partnership award (one of the first funded BRIDGE projects) provided me with the unique opportunity to generate proof-of-concept data in collaboration with Evotec. Their experience in assay development and validation was invaluable to progress our project into a fully-fledged drug discovery programme and spin-out.'

Christian Siebold, Professor of Structural Biology, University of Oxford

Over time – and if implemented at scale – this collaborative approach can lead to a cultural shift in academic institutions as the collective understanding increases in terms of how basic biology can translate to focused drug discovery.

4. **Make it rapid and transparent**

There are distinct advantages to translational structures where potential future investment partners are already integrated and contractual terms associated with translational funding are pre-defined (see Introduction, Box 1). An academic researcher can thereby understand the likely downstream trajectory, partners and benefits even before they accept associated funding. Pre-seed examples beyond Evotec's BRIDGEs include, but are not limited to, Deerfield Management's academic collaborations in the US (with Deerfield as seed investor), Epidarex Exceed in the UK (a pre-seed mechanism for Epidarex's main fund) and FutuRx in Israel (including Orbimed, Takeda Ventures and JJDC) (Senior, 2019; Weinreb, 2017; Epidarex exeed, 2019).

From the academic perspective, there is a reduced likelihood of needing to spend time finding investors once a project has completed. From the investor perspective, at the point at which NewCo formation is being considered, they will already be very familiar with the project(s) in question and the academics' views, expediting the decision process by reducing the need for further due diligence. We will explore further the investors' perspective in Chapter 2.

The principle of transparency is enshrined across Evotec's BRIDGE portfolio. For individual partnerships, we pre-define the financial terms associated with either downstream licensing or spinout creation, such that our academic research partners can be clear on the long-term goals and 'who receives what' should a program be successful. We will revisit the benefits of pre-defined terms in Chapter 2.

In BRIDGEs, we also pre-define other contractual terms beyond the financials, including those important to academics such as publication rights and licenses to the institution for non-commercial use of associated IP. This has proven to enable rapid progression from completed project to operational NewCo.

Conclusions and outlook

Academic researchers face material cultural and practical challenges to translate their biomedical discoveries into projects that match industrial standards, validate targets and generate clinical-stage projects. Lowering the entry barrier for academics requires the provision of appropriate mechanisms, resources and expertise to enable them to engage in translation while allowing them to remain focused on their core academic research priorities.

Publications from the last decade indicate that these barriers are still sky-high. The good news is that a growing number of pre-seed funding initiatives provide academic researchers with a winning formula, Evotec's BRIDGEs amongst them.

In the next Chapter, we turn to the perspective of the industry and examine the challenges investors, biotech and pharma partners face in accessing and assessing translational opportunities arising from academic research. More specifically, we will discuss best practices in how industry scouts, evaluates, negotiates, finances, reproduces, advances or 'kills' translational projects of academic origin.

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