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

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Introduction: Is academic research a valid source of novel medicines?

The 'claim to fame' in translation research

It is common knowledge across the biotech ecosystem - ranging from universities to pharma companies - that biomedical research from academia has been and will continue to be one of the most relevant sources of innovative future medicines. Is this premise really true?

While tangible statistics are surprisingly difficult to find, it has been previously reported that 13% of New Molecular Entities (NMEs) approved by the FDA from 1990 to 2007 originated from public-sector research institutions (Stevens et al., 2011). More recent publications show that academic inventors have contributed to a third or more of FDA-approved medicines since 2017 (Nayak et al., 2019; Kinch et al., 2020; Simoens & Hueys, 2022). On the other hand, it is well-documented that the relative impact of academia on drug development declines swiftly over the later-stage preclinical and clinical phases and a report concluded that between 1991 and 2010, there was not a single regulatory approval without industry collaboration (Takebe et al., 2018).

These data imply that academic and industrial researchers *must* collaborate in translational drug discovery if they want to develop novel medicines more effectively.

The *modus operandi* of academic researchers collaborating with industry partners to enable and advance drug discovery is multi-faceted and the subject of this mini-series of White Papers. It builds on the view that the global academic community is an unparalleled reservoir for drug discovery concepts, as appreciated by many industry leaders (Bergauer et al., 2016). Yet systematic probing of its full potential to accelerate the development of

novel therapeutics at a global scale has been hampered by multiple confounding factors ranging from 'cultural' to 'commercial'. Here, we aim to shed light on novel solutions for collaboration models that help to facilitate and accelerate the translation from academic idea to commercial reality in practice.

Academic ambitions do not meet regulatory realities

In modern drug discovery, a pivot point in developing first-in-class therapeutics is the identification and validation of a novel and ideally unique molecular target. Often, target candidates are initially discovered by academic researchers and are published in a peer-reviewed journal. The pathophysiological and molecular context as well as cellular and tissue distribution, molecular architecture and druggability of the target candidate will dictate the ensuing therapeutic format(s) as well as the potential use of biomarkers and the preclinical and clinical development plan (Dahlin et al., 2015; Emmerich et al., 2021).

In the last two decades, public funding of biomedical research by the National Institutes of Health and others has sought to promote potential strategies and policies to facilitate the translation of biomedical research into novel drugs and to help ensure that the public has affordable access to innovative medicines (Smith, 2011; McLean et al., 2018; Padilla–Cabello et al., 2022). These policies should have incentivized academic researchers to create biomedical impact by identifying targets with therapeutic utility.

In an attempt to assess the ambition of the academic community to identify novel targets, we screened 63 000 biomedical publications between 2000 and 2022 for references where the author(s) mention the term 'therapeutic target(s)' in the abstract or title. Interestingly, the relative proportion of publications making such reference increased from 0.03% in 2000 to 0.6% in 2019, an increase by approx. 20-fold over the last 20 years (Figure 1a). This indicates that academic researchers are increasingly focused on creating biomedical impact by identifying targets with therapeutic utility.

Following this logic, we would assume that the more well-defined targets the academic target-hunting community finds, the more modern medicines should be developed.

Scrutiny of public information shows, however, that the number of IND (Investigational New Drug) filings, a necessary step to start clinical development, as listed by FDA's CDER (Center for Drug Evaluation and Research) was basically steady between 2009 and 2019 (Figure 1b).

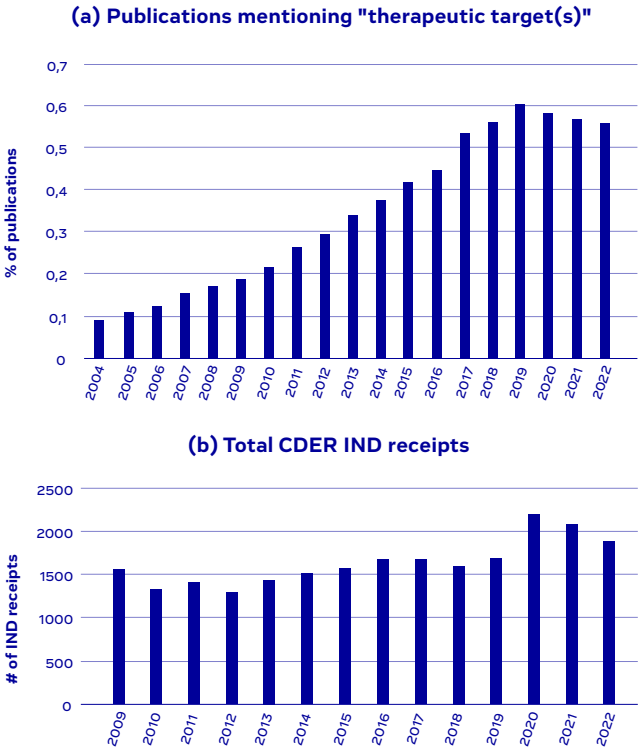

Figure 1 (a/b): Disentangling academic ambition and regulatory reality

Increase in publications mentioning "therapeutic target(s)"; stagnation in total number of CDER IND receipts. (a) Percent of publications listed in PubMed mentioning "therapeutic target" or "therapeutic targets" from 2000 to 2022. Excluded journal types: "Review", "Systematic Review", "Clinical Trial", "News", "Editorial" and "Published Erratum". (b) Total number of INDs received by the CDER at the FDA from 2009 to 2022. Data include drugs, non-biosimilar biologics, biosimilar biologics as well as commercial and research applications. Data was taken directly from the FDA website (https://www.fda.gov/drugs/ind-activity/ind-receipts).

Consequently, when analyzing the real-life transition from proclaimed therapeutic target to clinical actuality, we must conclude that the translation from academic ambition to regulatory reality is highly inefficient and in need of new solutions. This insight is not entirely new as the lack of productivity in translational research has been described previously, albeit typically focusing on other success criteria (Salman et al., 2014).

Identifying and addressing the root causes of inefficient translation

The high costs and significant risk associated with early-stage drug discovery has resulted in what is commonly described as the preclinical Valley of Death. The Valley of Death describes the challenges that researchers with a novel therapeutic hypothesis face when trying to find funding and, often more importantly, the right

expertise to build a commercially viable pre-clinical drug discovery program (Butler, 2008; Calza et al. 2021; Seyhan, 2019; Gbadegeshin et al., 2022). This impasse has persisted for several decades without obvious change. To overcome the dilemma of inefficient translation and to build bridges across the Valley of Death, it is important to understand the nature of the most prominent barriers to making cross-organizational drug discovery efforts more (cost-) effective and efficient.

Research over the last twelve years has identified the following key complications:

1. A misalignment between the culture and motivation of academic scientists and the expectations of investors, biotech and pharma partners (Lam, 2011; Sanberg et al., 2014; D'Este & Perkmann 2011; Huszár et al., 2016; van de Burgwal et al., 2019; Freedman & Mullane, 2017; Awasthy et al., 2020)
2. A lack of reproducibility of published academic data by the industry (Prinz et al., 2011; Begley & Ellis, 2012, Dirnagl et al., 2022)
3. A disparity in risk management between academic and industrial researchers (Dahlin et al., 2015)
4. A lack of access to drug discovery expertise and tools (Calza et al., 2021)
5. A lengthy and inefficient technology transfer process from academic licensors to commercial licensees (Awasthy et al., 2020)

BRIDGEs as a novel mechanism to improve translational efficiency

In the summer of 2016, drug discovery enthusiasts from the University of Oxford and Evotec were contemplating how to provide expertise and funding for drug discovery projects too mature to receive basic research grants but too immature for venture capital funding. The goal was to tackle several of the above-mentioned barriers in a new and systematic way, and in particular, to make industry platforms such as hit identification toolboxes accessible for academic entrepreneurs. To ensure a minimum likelihood of success (including generation of at least one spin-out company), a sizable funding volume and project portfolio was envisaged.

The considerations manifested in a first-of-its-kind umbrella collaboration between The University of Oxford, Oxford Sciences Innovation (now Oxford Science Enterprises) and Evotec; coined 'LAB282' (Oxford University Innovation, 2016). To date, LAB**282** has yielded 38 collaborative projects and a spin-out company that has licensed the Intellectual Property (IP) for six different target candidates.

Next, Evotec generalized the initial learnings into its 'BRIDGE' (Biomedical Research, Innovation & Development Generation Efficiency) concept which has appealed to an increasing number of internationally distributed academic institutions as well as early-stage investors and pharma partners with Bristol Myer Squibb being at the forefront of the latter. By mid-2023, eight publicly announced partnerships such as LAB**282**, LAB150, beLAB2122 and beLAB1407, together encompassing over 30 academic partners with triple-digit-million USD committed capital for translational research projects had been forged.

Underscoring the momentum and global reach of BRIDGEs, we recently announced three novel BRIDGE partnerships: (i) with Novo Nordisk and Harvard, Yale, Mass General Brigham and Beth Israel Deaconess Medical Center in the US (LAB eN2 ; Evotec SE, 2023A); (ii) with Clavystbio, Lightstone, Polaris, Leaps by Bayer and NUS, Duke-NUS and A*STAR in Singapore (65LAB; Evotec SE, 2023B); and (iii) with Amplitude Ventures in Canada (Pre-Amp; Evotec SE, 2023C). Collectively, BRIDGEs are on the brink of becoming one of the largest translational accelerator programs around the world.

'The pharma industry is brilliant at activities requiring scale, large infrastructures and resources, and international coordination (e.g. HTS, lead optimisation, toxicology, ADME, multi-centre or multi-national Phase II and III trials). It also excels in non-traditional academic skillsets (e.g. regulatory). In academia it is easier to access innovation, deep target/ technology expertise, patient resources and broad clinical/ disease expertise. By pooling the capabilities of industry and academia, we are likely to increase innovation, probability of success and ultimately deliver many more new therapies for patients. Creating partnerships based on complementarity, mutual trust and an honest assessment of respective weaknesses, will improve efficiency, as amply demonstrated by Evotec's BRIDGE program. Access to funds, institutional track records, role models and REF deliverables, are accelerating a culture change across academia.'

Chas Bountra, Pro Vice-Chancellor for Innovation at the University of Oxford; Professor of Translational Medicine in the Nuffield Department of Clinical Medicine

Why?

Need to address major bottlenecks in translation and acceleration of drug discovery projects

- Systematically probe academic concepts on industry platforms
- Overcome poor reproducibility of published data from academia
- Cater to growing interest by top-tier universities to create sustainable start-ups
- Substantially shorten timelines from idea to Newco
- Facilitate follow-on funding for NewCos

What?

Strategic partnership with academic institution(s) and funder(s) to accelerate translation

- From academic concept to investable data point
- Using Evotec's technology platforms
- Over a portfolio of first-in-class therapeutic projects
- In a risk-shared scheme with pre-negotiated terms
- With the aim to co-create spin-out companies or licensable assets
- Generating long-term upside for all partners

How?

Close collaboration with academic researchers, TTO and funders

- Transparency and alignment on value-drivers and deliverables
- Regionally embedded 'Expert-in-Residence' for each BRIDGE
- Joint work-packages tailored for each project
- Regular and high-frequency touch-points of steering committees and joint projects teams
- Follow-on funding (Seed/Series A) for successful projects envisaged from Day 1

Box 1:. *BRIDGE hallmarks*

What to expect from this White Paper

This mini-series aims to exemplify new real-life solutions to improve collaborative translational research. It is co-authored by a small team of Evotec drug discovery experts and technology transfer professionals who are passionate about creating superior academia-industry partnerships. We will discuss how to improve the front-end of the drug discovery value chain by sharing key learnings from our collaborative efforts with academic researchers, technology transfer colleagues, venture capital professionals as well as biotech and pharma peers.

The series will have the following Chapters:

Chapter 1: Finding a winning formula to lower barriers for academic researchers. In Chapter 1, we will focus on the universities' and academic researchers' perspective.

Chapter 2: Creating impact by making industry platforms and know-how readily available for academic researchers. In Chapter 2, we will concentrate on the pharma / biotech viewpoints.

Chapter 3: Describing the Dos and Don'ts of an 'Expert in Residence'. In Chapter 3, we will provide insights on how Evotec's experts tackle day-to-day challenges in identifying, structuring and advancing academic drug discovery opportunities.

For each of the topics, we aim to distill the key blockades to greater efficiency, summarize what we consider to be today's best practices and describe the measures Evotec and its partners have taken and will continue to take for better solutions.

References

1. Awasthy, R., Flint, S., Sankarnarayana, R., & Jones, R. L. (2020). A framework to improve university–industry collaboration. *Journal of Industry-University Collaboration*, 2(1), 49–62. https://doi.org/10.1108/jiuc-09-2019-0016

2. Begley, C. G., & Ellis, L. M. (2012). Drug development: Raise standards for preclinical cancer research: Drug development. *Nature, 483*(7391), 531–533. https://doi.org/10.1038/483531a

3. Bergauer, T., Ruppert, T., Essioux, L., & Spleiss, O. (2016). Drug target identification and validation: Global pharmaceutical industry experts on challenges, best strategies, innovative precompetitive collaboration concepts, and future areas of industry precompetitive research and development: Global pharmaceutical industry experts on challenges, best strategies, innovative precompetitive collaboration concepts, and future areas of industry precompetitive research and development. *Therapeutic Innovation & Regulatory Science, 50*(6), 769–776. https://doi.org/10.1177/2168479016651298

4. Butler, D. (2008). Translational research: crossing the valley of death. *Nature, 453*(7197), 840–842. https://doi.org/10.1038/453840a

5. Calza, F., Ferretti, M., Panetti, E., & Parmentola, A. (2021). Moving drug discoveries beyond the valley of death: the role of innovation ecosystems. European Journal of Innovation Management, 24(4), 1184–1209. https://doi.org/10.1108/ejim-11-2019-0342

6. Dahlin, J. L., Inglese, J., & Walters, M. A. (2015). Mitigating risk in academic preclinical drug discovery. *Nature Reviews*. Drug Discovery, 14(4), 279–294. https://doi.org/10.1038/nrd4578

7. D'Este, P., & Perkmann, M. (2011). Why do academics engage with industry? The entrepreneurial university and individual motivations. *The Journal of Technology Transfer,* 36(3), 316–339. https://doi.org/10.1007/s10961-010-9153-z

8. Dirnagl, U., Duda, G. N., Grainger, D. W., Reinke, P., & Roubenoff, R. (2022). Reproducibility, relevance and reliability as barriers to efficient and credible biomedical technology translation. Advanced Drug Delivery Reviews, 182(114118), 114118. https://doi.org/10.1016/j.addr.2022.114118

9. Emmerich, C. H., Gamboa, L. M., Hofmann, M. C. J., Bonin-Andresen, M., Arbach, O., Schendel, P., Gerlach, B., Hempel, K., Bespalov, A., Dirnagl, U., & Parnham, M. J. (2021). Improving target assessment in biomedical research: the GOT-IT recommendations. *Nature Reviews. Drug Discovery,* 20(1), 64–81. https://doi.org/10.1038/s41573-020-0087-3

10. Evotec SE. (2023A, September 26). Evotec and Novo Nordisk launch LAB eN2 to accelerate translation in cardiometabolic diseases. Evotec SE. https://www.evotec.com/en/investor-relations/news/corporate-news/p/evotec-and-novo-nordisk-launch-lab-en2-to-accelerate-translation-in-cardiometabolic-diseases-6324

11. Evotec SE. (2023B, October 5). Evotec, ClavystBio, Leaps by Bayer, Lightstone Ventures and Polaris Partners launch "65LAB". Evotec SE.https://www.evotec.com/en/investor-relations/news/corporate-news/p/evotec-clavystbio-leaps-by-bayer-lightstone-ventures-and-polaris-partners-launch-65lab-6330

12. Evotec SE. (2023C, October 11). Evotec and Amplitude Ventures launch partnership for Pre-Amp". Evotec SE. https://www.evotec.com/en/investor-relations/news/corporate-news/p/evotec-and-amplitude-ventures-launch-partnership-for-pre-amp-6334

13. Freedman, S., & Mullane, K. (2017). The academic-industrial complex: navigating the translational and cultural divide. *Drug Discovery Today, 22*(7), 976–993. https://doi.org/10.1016/j.drudis.2017.03.005

14. Gbadegeshin, S. A., Natsheh, A. A., Ghafel, K., Mohammed, O., Koskela, A., Rimpiläinen, A., Tikkanen, J., & Kuoppala, A. (2022). Overcoming the valley of death: A new model for high technology startups. Sustainable Futures, 4(100077), 100077. https://doi.org/10.1016/j.sftr.2022.100077

15. Huszár, S., Prónay, S., & Buzás, N. (2016). Examining the differences between the motivations of traditional and entrepreneurial scientists. *Journal of Innovation and Entrepreneurship, 5*(1). https://doi.org/10.1186/s13731-016-0054-8

16. Kinch, M. S., Horn, C., Kraft, Z., & Schwartz, T. (2020). Expanding roles for academic entrepreneurship in drug discovery. *Drug Discovery Today,* 25(11), 1905–1909. https://doi.org/10.1016/j.drudis.2020.09.004

17. Lam, A. (2011). What motivates academic scientists to engage in research commercialization: 'Gold', 'ribbon' or 'puzzle'? *Research Policy,* 40(10), 1354–1368. https://doi.org/10.1016/j.respol.2011.09.002

18. McLean, R. K. D., Graham, I. D., Tetroe, J. M., & Volmink, J. A. (2018). Translating research into action: an international study of the role of research funders. *Health Research Policy and Systems,* 16(1). https://doi.org/10.1186/s12961-018-0316-y

19. Nayak, R. K., Avorn, J., & Kesselheim, A. S. (2019). Public sector financial support for late stage discovery of new drugs in the United States: cohort study. *BMJ (Clinical Research Ed.)*, 367, l5766. https://doi.org/10.1136/bmj.l5766

20. Oxford University Innovation. (2016, November 10). LAB282 - *Accelerating drug discovery at Oxford to benefit patients, healthcare and society.* Oxford University Innovation. https://innovation.ox.ac.uk/news/lab282-accelerating-drug-discovery-oxford/

21. Padilla-Cabello, J., Santisteban-Espejo, A., Heradio, R., Cobo, M. J., Martin-Piedra, M. A., & Moral-Munoz, J. A. (2022). Methods for identifying biomedical translation: a systematic review. A*merican Journal of Translational Research, 14*(4), 2697–2708.

22. Prinz, F., Schlange, T., & Asadullah, K. (2011). Believe it or not: how much can we rely on published data on potential drug targets? *Nature Reviews. Drug Discovery, 10*(9), 712. https://doi.org/10.1038/nrd3439-c1

23. Salman, R. A.-S., Beller, E., Kagan, J., Hemminki, E., Phillips, R. S., Savulescu, J., Macleod, M., Wisely, J., & Chalmers, I. (2014). Increasing value and reducing waste in biomedical research regulation and management. *Lancet, 383*(9912), 176–185. https://doi.org/10.1016/s0140-6736(13)62297-7

24. Sanberg, P. R., Gharib, M., Harker, P. T., Kaler, E. W., Marchase, R. B., Sands, T. D., Arshadi, N., & Sarkar, S. (2014). Changing the academic culture: valuing patents and commercialization toward tenure and career advancement. *Proceedings of the National Academy of Sciences of the United States of America, 111*(18), 6542–6547. https://doi.org/10.1073/pnas.1404094111

25. Seyhan, A. A. (2019). Lost in translation: the valley of death across preclinical and clinical divide – identification of problems and overcoming obstacles. *Translational Medicine Communications, 4*(1). https://doi.org/10.1186/s41231-019-0050-7

26. Simoens, S., & Huys, I. (2022). How much do the public sector and the private sector contribute to biopharmaceutical R&D? *Drug Discovery Today, 27*(4), 939–945. https://doi.org/10.1016/j.drudis.2021.11.027

27. Smith, C. D. (2011). Your idea and your university: issues in academic technology transfer. Journal of Investigative Medicine: *The Official Publication of the American Federation for Clinical Research, 59*(5), 752–757. https://doi.org/10.2310/JIM.0b013e31820d0fdf

28. Stevens, A. J., Jensen, J. J., Wyller, K., Kilgore, P. C., Chatterjee, S., & Rohrbaugh, M. L. (2011). The role of public-sector research in the discovery of drugs and vaccines. T*he New England Journal of Medicine, 364*(6), 535–541. https://doi.org/10.1056/NEJMsa1008268

29. Takebe, T., Imai, R., & Ono, S. (2018). The current status of drug discovery and development as originated in United States academia: The influence of industrial and academic collaboration on drug discovery and development. *Clinical and Translational Science, 11*(6), 597–606. https://doi.org/10.1111/cts.12577

30. Van de Burgwal, L. H. M., Dias, A., & Claassen, E. (2019). Incentives for knowledge valorisation: a European benchmark. *The Journal of Technology Transfer, 44*(1), 1–20. https://doi.org/10.1007/s10961-017-9594-8