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Maaïke Everts & Mark Drew

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META-OPINION



# Successfully navigating the valley of death: the importance of accelerators to support academic drug discovery and development

Maaïke Everts  and Mark Drew

Translational Therapeutics Accelerator (TRxA), Critical Path Institute, Tucson, AZ, USA

## ABSTRACT

**Introduction:** The drug discovery and development ‘valley of death’ remains a challenge for promising new therapies originating from academic research laboratories. Drug discovery support centers and accelerators have been established to provide monetary and scientific support, but limited available funding along with cultural and expertise gaps remain obstacles for many promising technologies.

**Areas covered:** In this meta-opinion article, the authors summarize the literature around obstacles that academic drug discovery projects face, along with potential solutions and best practices. Topics covered include funding challenges, regulatory education, reproducibility, along with cultural and organizational considerations. It describes one accelerator in particular-Critical Path Institute’s Translational Therapeutics Accelerator (TRxA)-that aims to overcome several of the mentioned challenges.

**Expert opinion:** The ‘valley of death’ remains a stubborn but not insurmountable part of the academic drug discovery and development landscape. Purposely designed accelerators can help, complementing more traditional intra- and extramural funding support.

## ARTICLE HISTORY

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## KEYWORDS

Drug discovery; valley of death; accelerator; regulatory science

## 1. Introduction: the stubborn valley of death

Translation from bench to bedside remains a significant opportunity for optimization in the process of discovering new pharmacological treatments for disease. Although truly disruptive medical innovation still tends to come from non-commercial research institutions, the bulk of academia-driven novel therapeutics remains in early development and, unfortunately, typically does not advance further [1]. The failure to progress fundamental basic research discoveries from the laboratory setting (bench) into treatment for human disease (bedside) is termed ‘the valley of death’ [2]. The translation of basic discoveries requires two fundamental activities. The first consists of defining proper regulatory and data strategies as early as possible in the discovery and development process. The second consists of identifying substantial additional investments beyond what is typically available in the academic environment. For the latter, there is a clear need for partnerships and the shouldering of the financial risk by the private sector, if therapies are to materialize as approved medicines that can benefit patients [3,4].

Fortunately, the pharmaceutical industry has realized that academia and not-for-profits significantly contribute to the discovery of new medicines and are funding collaborations and other initiatives to capture this innovation [3,5]. This is evidenced by the growing tendencies of pharmaceutical companies to license assets at earlier stages of development; yet, biopharmaceutical companies and venture capital firms remain most interested in assets with a clearly defined regulatory path [6]. Therefore, principal investigators must be able to articulate viable commercialization, clinical,

data and regulatory strategies for their discoveries, but a lack of expertise in these aspects of drug product development is a significant obstacle for most academic researchers [7].

There are many factors contributing to the failure to develop a properly informed regulatory strategy, for example a lack of understanding of regulatory science and requirements among academic researchers, aggravated by a gap in communication and engagement between the regulatory network and academia [1,8]. Compared to pharmaceutical companies, academic researchers are less aware of regulatory support tools that exist at the global, national and regional levels. The prevailing lack of understanding of regulatory science amongst academic researchers is exemplified by the frequent lack of a properly defined target-product-profile to help articulate the evidence-generation strategy for candidate products [8]. In another example, academic researchers are not usually aware that at the European Medicine Agency (EMA), the fee for scientific advice is waived for orphan and pediatric indications – therapeutic areas that are often a main focus of academic drug discovery research [1]. The Strengthening Training of Academia in Regulatory Science (STARS) project established via collaboration between 18 European National Competent Authorities intends to bridge the translational gap between regulators and academic innovators, by providing guidance on planning of relevant grant applications, strengthening regulatory knowledge in general scientific and qualification questions, facilitating bidirectional knowledge exchanges and ultimately improving the regulatory impact of results [1]. A recent US-based initiative is the Food and Drug Administration (FDA)’s Oncology Center of Excellence Project Catalyst, which provides guidance to, among

**Article highlights**

- The drug discovery 'valley of death' is well-recognized, and efforts have been initiated to bridge this gap.
- Obstacles remain, such as academic lack of regulatory knowledge, drug development expertise, funding, and reproducibility, along with cultural considerations.
- Reducing risk in drug discovery is imperative to garner follow on funding; mitigation strategies include appropriate collaboration around target selection, medicinal chemistry and preclinical pharmacology.
- Early engagement and dialogue with potential private funders as well as regulatory agencies helps to define the appropriate project plan to move a potential drug toward clinical utility and commercialization.
- An accelerator such as Critical Path Institute's Translational Therapeutics Accelerator (TRxA) has a critical role in bridging the valley of death, where in addition to funding, the accelerator brings scientific and regulatory expertise to selected projects.

others, academic life science incubators and accelerators to support anticancer therapy development to expedite the availability of novel cancer treatments to the public. Project Catalyst facilitates 'Accelerator Innovator Discussion' meetings, where investigators can ask questions about the regulatory plan at an early stage, prior to a pre-IND meeting. They also provide educational materials via a self-directed learning platform called 'Oncology Regulatory Expertise and Early Guidance (OREEG) [9].

These are great examples of regulatory outreach to academia, more of which would be welcome. Unfortunately, as of today, beyond the examples mentioned, there are no dedicated offices or departments within regulatory agencies at large that provide specific support to academic drug developers, as there is no legislative requirement to do so. The new draft regulation of the European Union that establishes rules governing the EMA does dedicate a specific article regarding providing scientific advice to nonprofit organizations, but this still needs to be approved by the European Parliament.

In addition to a lack of regulatory expertise, insufficient funding remains a major obstacle [10]. For example, of venture capital investments, only 3% of awards go to projects at the early stage of development [11]. This reality has led to significant growth in the number of regional or institutional translational research centers, incubators, and accelerator programs to help bridge this gap [12]. Motivations to start such centers include the altruistic desire to save lives, but also economic development opportunities through the creation of regional jobs, earning capital, as well as passing on and disseminating knowledge and education [10]. Examples are the United States' Centers for Translational Science Awards funded by the National Institutes of Health, Europe's Innovative Health Initiative, EATRIS, the European infrastructure for translational medicine and the European Lead Factory, spearheaded by Lygature. The expansion of these programs is illustrated by membership in the Academic Drug Discovery Consortium, which was established in 2012 by a handful of leading academic institutions and now, in early 2023, contains more than 150 centers or programs [13]. Nevertheless, the bandwidth for academic drug discovery support remains limited compared to the breadth and depth of projects that could

potentially be translated into novel therapies for unmet medical needs.

Although these translational centers are certainly helping to advance therapeutic development by providing infrastructure, knowledge, and funding, several challenges remain. For example, many targets, especially novel ones identified in academia, have little to no validation. Even beyond this issue, reproducibility of research findings is a major problem, with an estimate of only 20–25% being reproduced by an independent group [14]. Research findings are less likely to represent valid relationships if there is a small sample size, a small effect size, a lot of flexibility in assay designs or if there is great financial or other interest [15]. Also, good research practices such as double blinded studies are not often followed in preclinical studies. Unfortunately, as a consequence, for roughly two-thirds of projects, inconsistencies between reported effects and duplication efforts lead to long duration of target validation or, in most cases, termination of projects [14]. This aligns with the unspoken rule in venture capital firms that 'at least 50% of published studies cannot be repeated with the same conclusions' [14].

There are also cultural and organizational adaptations and competing academic responsibilities that need to be recognized when embarking on academic drug discovery projects. Academic environments traditionally reward personal goals and publications, whereas translational science requires a multidisciplinary approach and protection of intellectual property. Academics are often required to balance the need to disseminate novel research findings to gain support and funding with protecting intellectual property on their work and managing the patent clock. Specifically, in the chemical arts, even though provisional patent applications can be filed to protect a published disclosure, for strategic reasons it is sometimes advisable to postpone provisional filing until the technology is better understood. For example, when more in-depth Structure-Activity-Relationships have been generated, the applicant can file broader claims, supported by research, in more jurisdictions (to justify patent expense), and avoid potentially creating prior art to further iterations of their technology. There is additionally a duty to trainees to publish work in a timely manner to support career advancement beyond their current academic life. These cultural differences are not insurmountable but need to be kept in mind when designing and operationalizing translational support programs.

In summary, although progress is being made to overcome the drug discovery valley of death, lack of regulatory knowledge, drug development expertise, funding, and reproducibility, along with cultural considerations remain impediments to harness the promise of academic innovations.

## 2. Current status: the building of sturdy bridges

As mentioned earlier, multiple academic drug discovery support centers have been established in the last two decades. It has been suggested that academic drug discovery is particularly well suited to de-risk novel targets, focus on neglected and orphan diseases, develop new methods and approaches, and provide training for the next generation of scientists [16]. Although most initiatives were initially established to focus on

high throughput screening of chemical compound collections, they have matured to support development of initial ‘hit molecules’ to true ‘lead molecules’, with proof-of-concept studies in predictive animal models confirming that these compounds can alter the course of a disease [17].

In these programs, reducing risk is a key activity to increase the likelihood of a commercial partner being interested in the technology, and thus funding its further development. Dahin et al. propose several mitigation strategies in several categories. These include 1) organizational, where it is imperative to establish a culture of collaboration and have the right individuals and expertise as part of the project team; 2) target selection, where druggability and the role of the target need to have been clearly delineated; 3) assay design, where the use of orthogonal assays is strongly encouraged; 4) medicinal chemistry, where forming partnerships with experienced individuals is key, as well as making sure compounds are fully characterized and 5) preclinical pharmacology, where demonstrating target engagement and selectivity is just one of the many aspects to keep in mind [12].

To further highlight the importance of target selection and validation, it has been suggested to introduce ‘preclinical trial’ requirements, where novel therapies undergo rigorous and independently performed studies to confirm the robustness of the research findings, prior to advancing to clinical trials [18].

It should also be recognized that, even with the best risk management, 95% of all early phase drug development projects will not result in a new therapy reaching clinical reality. Nevertheless, at minimum, quarterly project reviews involving all relevant experts will help these efforts stay on track with respect to scientific progress, an understanding of the competitive landscape as well as identification of potential funding and partnership opportunities [12]. Considering the latter, although different programs and centers are built around a variety of business models, it is expected that charity, government and private foundations will remain the dominant supporters of this translational science [16]. To complement these sources, over the last two decades, research institutions and partners have evolved gap funding programs to address critical elements of technology development, including discovery and development of new drug products [11].

Gap funding and accelerator programs can be segmented, depending on the stage of technology development they support, and include 1) translational research grants; 2) proof of concept programs; 3) startup accelerators and 4) philanthropic venture funds. Each have their unique characteristics, structures, and commercialization priorities, but all are mission-driven to innovate and attract more outside capital, with a secondary goal of longer-term return-on-investment through licensing royalties and equity positions. Beyond these priorities, these types of programs have varying expectations toward education and job creation, depending on their environment and funding sources [11].

The Bayh-Dole act, a federal law enacted in 1980 enables universities and nonprofit research institutions to own and patent technology developed under federally funded research programs within their organizations and benefit from any resulting licensing revenue. Universities began setting up technology transfer offices in droves [19] to take advantage of the potential profits from their

research. Deans and chancellors have often been criticized for profiting from research without providing the critical structure to help academics overcome the valley of death [20]. Although internal gap funding is available to academics to carry out key translational proof of concept experiments, advice as to what those experiments are, is often not available. Instead, the intellectual contribution provided by technology transfer offices is primarily focused on commercial viability of the technology (competitive intelligence, patent landscape research, etc.). The availability to engage with external experts to develop strategies to overcome the valley of death is seen as a secondary concern for internal university funding.

Regardless of the translational science funding source, engagement with the pharma and biotech sectors is critical, as they will ultimately fund and execute the later stages of drug development. Ideally, a drug discovery project is at Technology Readiness Level (TRL) 4 or 5 before private investment is deemed prudent, with TRL4 representing selection of a clinical candidate with appropriate drug-like properties, and TRL5 having completed appropriate good laboratory practice (GLP) animal toxicity studies and chemistry, manufacturing and control (CMC) studies [21]. These TRLs can more easily be achieved if accelerators do not operate in a vacuum. Rather, early interactions and feedback are critical to ensure translational projects proceed toward building data packages that are appropriate for handoff to a commercial partner [16]. Some sophisticated models of early and coordinated integration between academia, foundations, federal government and industry can be found in several therapeutic areas, including cystic fibrosis, multiple myeloma and type 1 diabetes [3], illustrating that this can be practically implemented, provided it is actively managed.

In addition, proactive communication with regulatory authorities should not only be encouraged, but it should be facilitated and fostered. This could be incentivized by funding bodies by requiring regulatory considerations (such as a well-defined target-product-profile, a sound translational strategy, envisioned clinically meaningful endpoints, etc.) to be included in grant proposals, progress reports and decision-making. For example, funders can request that scientists seek regulatory dialogue in advance of a grant submission and/or during the research project, thereby increasing the likelihood that the findings can be translated to clinical care [1].

Initiatives and suggestions such as these should contribute to a more rigorous ecosystem in which academic drug discovery projects are given the highest chance of success and, consequentially, resulting in more innovations crossing the valley of death and reaching patients’ bedsides.

### 3. Expert opinion: C-Path’s Translational Therapeutics Accelerator (TRxA)

One program that aims to be a bridge across the valley of death is Critical Path Institute (C-Path)’s Translational Therapeutics Accelerator (TRxA), launched in 2022 (Figure 1). TRxA is a global academic drug discovery and development support program focused on supporting scientists with funding and guidance for the advancement of novel therapeutics from the lab to clinical trials and, ultimately, commercialization and patient care. Projects are solicited via an annual request for applications and academic investigators can

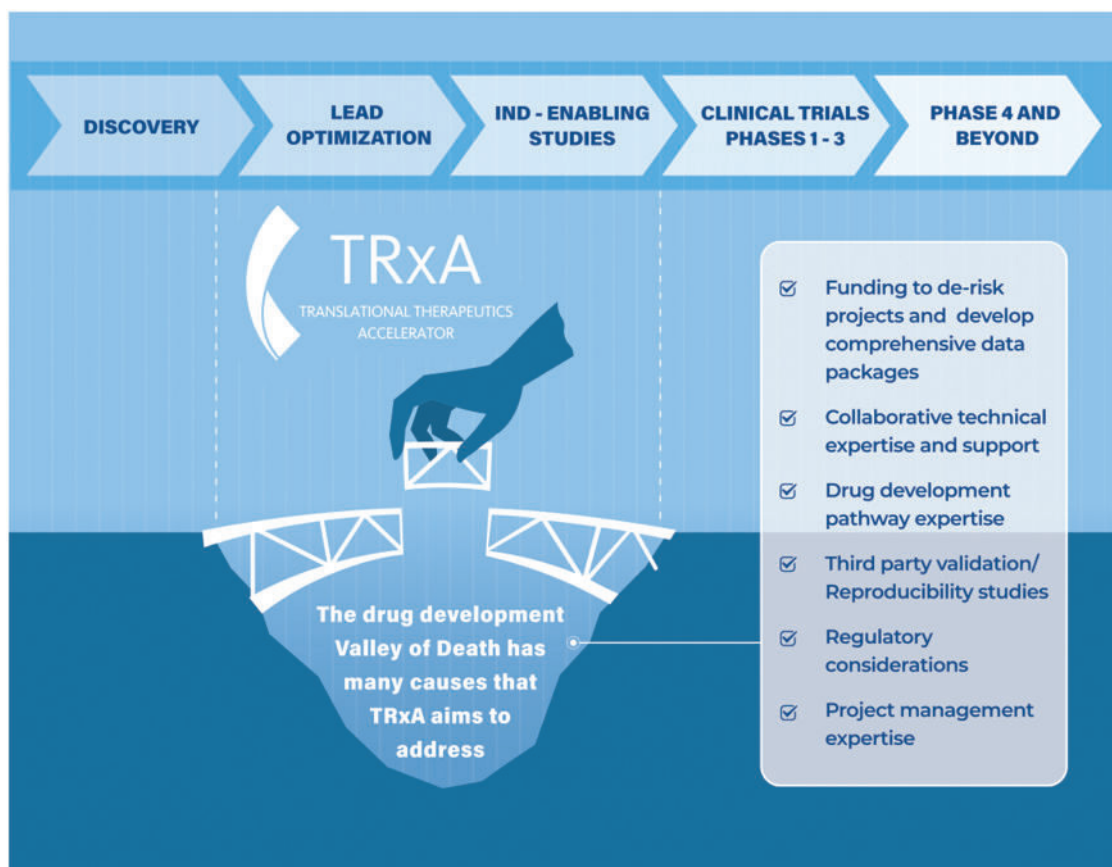
apply for support of lead optimization or IND-enabling studies. Aspects of the program take into account considerations mentioned earlier, specifically:

- The program supports neutral, third-party validation of key experimental findings, by engaging independent contract research organizations to reproduce pivotal observations.
- Interdisciplinary research teams guide funded projects, with expertise in, for example, target biology, pharmacology, medicinal chemistry, regulatory and data science, clinical care and commercialization. Cultural and organizational differences between different stakeholders are proactively addressed based on C-Path's deep experience in forming inter-institutional consortia. These consortia encompass members with very different backgrounds and perspectives, such as pharmaceutical companies, patient organizations, and federal agencies. Yet, they manage to find common ground and approaches to tackle universal problems in drug development, together.
- Research teams meet frequently to keep the project focused and on track toward an IND. As the development of drugs needs to start with the end in mind, including clinical end points that would lead to approval, the TRxA model provides unique access to individuals and teams with appropriate regulatory knowledge.

TRxA is embedded within C-Path, which has deep expertise in data science, quantitative medicine, biomarker qualification, clinical outcome assessments and regulatory science. Being situated within this organization, TRxA can capitalize on a wide range of subject matter experts for various steps in the drug discovery process. These experts reside within C-Path but can also be identified via its numerous consortia with members from industry, academia, patient advocacy groups, governmental funding agencies and regulatory bodies to ensure, for example that gold standard translational models are incorporated into research development plans.

TRxA is an example of a proof-of-concept type of gap funding and accelerator program, not affiliated with any academic institution, or even geographical region, and is positioned to support drug product development and bridge projects to attract additional capital via either venture-backed startup formation or a license to a commercial biopharmaceutical partner.

This funding mechanism allows development of the program within the PI's laboratory before the necessity of company formation and/or out-licensing to a separate business entity. It ensures continued access to guidance, expertise, and funding mechanisms available only to academic groups, aimed at strengthening relevant aspects of evidence generation linked to key regulatory science aspects of drug development. Furthermore, it delays the burden of carrying and maintaining costs associated with, for example, patent prosecution and



**Figure 1.** Critical Path Institute (C-Path)'s Translational Therapeutics Accelerator (TRxA) helps bridge the valley of death, focusing its support on academic lead optimization and IND-enabling studies.



maintenance, to a time when the technology is mature enough to justify out-licensing and the burden of substantial costs to progress to toxicological studies, IND filings, etc.

To date, TRxA has provided funding to academic researchers focusing on (1) the development of a series of small molecule pleiotropic brain-penetrant kinase inhibitors for the treatment of glioblastoma and (2) proof of concept studies of a series of epigenetic modulators of histone H3 lysine 9 (H3K9) methyltransferase for the treatment of Prader-Willi syndrome. TRxA expects to provide funding and guidance to several additional academic projects in financial year 2023 and beyond.

With academic investigators at the forefront of early drug discovery, accelerator programs like TRxA have a critical role in bridging the valley of death so that new compounds targeting novel modes of action can be developed for patients in need of therapies. In addition to addressing the funding gap so often experienced in the academic environment, providing principal investigators with direct access to a team of scientific and regulatory experts can help ensure that well-planned studies result in quality data packages, thus increasing interest amongst pharmaceutical companies in licensing and further investment. In the end, it is a win-win for everyone, as new therapies with a validated data package and increased chance of success make the long journey from bench to bedside.

TRxA's funding mechanism operates on an annual recurring cycle, for which details can be found at [22].

## Conclusion

The 'valley of death' remains a stubborn but not insurmountable part of the academic drug discovery and development landscape. De-risking projects by identifying suitable data packages and determining the appropriate regulatory pathways will help garner interest for commercial development outside of the university's walls. While efforts are underway to ensure scientific, financial and cultural alignment with various stakeholders in the drug discovery process, accelerators such as TRxA can help, complementing more traditional intra- and extramural funding support.

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## Declaration of interest

M Everts is an Executive Director and M Drew is the Director of Drug Discovery and Development at the Critical Path Institute. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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## ORCID

Maaike Everts  <http://orcid.org/0000-0001-7421-4691>

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