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Drug discovery in academia

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Participation of academic centers in aspects of drug discovery and development beyond target identification and clinical trials is rapidly increasing. Yet many academic drug discovery projects continue to stall at the level of chemical probes, and they infrequently progress to drugs suitable for clinical trials. This gap poses a major hurdle for academic groups engaged in drug discovery. A number of approaches have been pursued to overcome this gap, including stopping at the production of high-quality chemical probes, establishing the resources in-house to advance select projects toward clinical trials, partnering with not-for-profit groups to bring the necessary resources and expertise to develop probes into drugs, and drug repurposing, whereby known drugs are advanced into clinical trials for new indications. In this review, we consider the role of academia in anticancer drug discovery and development, as well as the strategies used by academic groups to overcome barriers in this process.

Academic centers have always been significant contributors to the discovery of new anticancer therapies. Historically, these contributions have been focused on identifying and validating new therapeutic targets through biological studies and testing new drugs developed by the pharmaceutical industry in clinical trials. However, during the last 15 years, many academic centers have become increasingly involved in domains of drug discovery that were once confined to the pharmaceutical industry. For example, academic institutions have established high-throughput screening platforms, formed medicinal chemistry teams, and built capabilities in pharmacokinetic studies with the aim of developing small-molecule drugs. The ultimate goal of these projects is to advance compounds from academic institutions through preclinical and clinical development. Herein, we review some of the opportunities and challenges faced by academic investigators interested in drug discovery and development. We will focus on small-molecule anticancer drug development, highlighting strategies used by academic investigators to advance chemical compounds from the lab into clinical trials. We refer the reader to other sources that discuss the role of academia in the development of biological therapies, including antibodies and cell therapies [1,2].

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Unique opportunities for academic participation in drug discovery

Drug discovery in academic centers offers a number of unique opportunities not usually present in industry. For example, academic investigators can pursue drug candidates for targets of scientific interest without necessarily considering issues related to market share and profitability. In addition, chemical probes that do not reach the stage of clinical trials are important experimental tools, since the probes can be used to reveal new biological insights. Finally, academic investigators can make important contributions to the rationale for development of new therapeutic agents, even if the intellectual property rights of the drug are held by others.

Challenges facing academics participating in drug discovery

To understand the state of drug discovery in academia, Frye et al. conducted a survey focusing on academic centers in the United States where participants self-identified the existence of drug-discovery programs [3]. Of the 55 participating centers, the majority had established infrastructure to encompass the full drug discovery pipeline, including capabilities in high-throughput screening, medicinal chemistry, and pharmacokinetic analysis. These centers placed a high priority on their drug discovery programs to generate intellectual property. In fact, among the surveyed institutions, creating intellectual property ranked second in

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mission importance, behind only publications and ahead of training students. Yet, despite investing in capabilities to develop drugs for clinical trials, very few centers had developed drugs that reached clinical trials. In most cases, projects had only advanced to the stage of high-quality chemical probes.

This survey highlights one of the core problems in academic drug discovery programs: projects usually fail to advance to the clinic, stalling at the level of chemical probes, even with significant financial investment. Thus, obstacles remain in translating probes to drugs, often owing to difficulties in medicinal chemistry, pharmacology, toxicology, and formulation. This gap in advancing molecules from chemical probes to drugs is often called the "valley of death" [4], since most drug development projects fail to progress to the clinical stage and "die" as chemical probes. In order for academic investigators to remain relevant participants in the drug discovery process, they need to recognize this gap and develop strategies to overcome it. We propose three approaches to address the "valley of death" in drug discovery: stop before entering it, advance through it, and bypass it (Fig. 1).

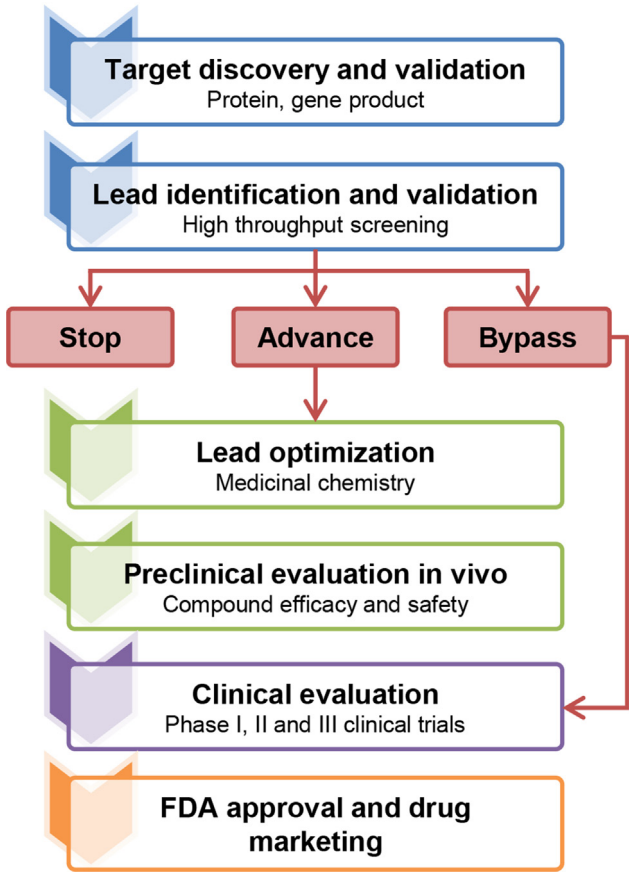

Figure 1. Three approaches to address the "valley of death" in the drug discovery process in academia. Most academic centers are efficient at reaching the stage of high-quality chemical probes, but very few are successful in progressing new drugs to clinical trials. This barrier in advancing molecules from chemical probes to drugs is called the "valley of death." This review proposes three different approaches to address the "valley of death" in the drug discovery pipeline in academia: (1) stop before entering it, (2) advance through it, and (3) bypass it.

Stopping at the valley of death and focusing on the development of chemical probes

Although developing drugs for clinical trials is an exciting initiative, there remains significant value in producing high-quality chemical probes. These molecules serve as important tools for exploring biological questions and can serve as leads for future therapeutic agents. Thus, one approach to addressing the "valley of death" is to stop at the stage of a chemical probe. This strategy has been successfully employed by groups such as the Division of Signal Transduction Therapy Consortium (DSST) located in Scotland. DSST is established as a collaboration of University of Dundee, the Medical Research Council, and six pharmaceutical companies to conduct early-stage research in cancer and inflammatory and degenerative diseases. The project has accumulated the world's largest collection of drug targets relating to kinases and ubiquitylation systems.

Another example is the Structural Genomics Consortium (SGC), located in Toronto, Canada. The SGC is an international public-private partnership whose goal is to conduct basic science in support of drug discovery. Using structural biology, high-throughput screening, and medicinal chemistry, SGC develops small-molecule chemical probes targeting proteins of medical relevance. For example, this consortium has recently developed specific inhibitors of the following lysine methyltransferases: Enhancer of zeste homolog 2/1 [5], G9a (also known as KMT1C (lysine methyltransferase 1C) or EHMT2 (euchromatic histone methyltransferase 2)) and GLP (also known as KMT1D (lysine methyltransferase 1D) or EHMT1 (euchromatic histone methyltransferase 1)) [6], and setd7 2 [7]. These probes are made available to academic investigators and industry without patent restrictions. In addition, data generated by SGC are deposited in public repositories. Through this approach, SGC hopes that academic investigators will use the chemical probes to understand the biology behind the targets and that industry will modify the chemical probes to generate drugs protected by intellectual property that are suitable for clinical trials. This consortium receives funding from academic granting agencies as well as from multiple pharmaceutical partners who recognize the potential value of SGC's open-access work. This open-access approach stands in contrast to the goals of most academic centers engaged in drug discovery.

Advancing through the valley of death

Another approach to overcoming the "valley of death" in drug discovery is to bring sufficient resources to the problem, particularly in the areas of medicinal chemistry and pharmacology. Here, we outline three strategies that have been successfully adopted.