Academic Drug Development: The DRIVE Model

Dennis Liotta^{*,†,‡} and George Painter[‡]

[†]Department of Chemistry and the Emory Institute for Drug Development, Emory University, Atlanta, Georgia 30322, United States

[‡]Department of Pharmacology, DRIVE, and the Emory Institute for Drug Development, Emory University, Atlanta, Georgia 30322, United States

S Supporting Information

ABSTRACT: Although there are hundreds of academic drug discovery centers open around the world, there are comparatively few academic drug development centers that contain the key core competencies needed to progress a lead compound into clinical trials. This is largely a consequence of operating in the “Valley of Death” (i.e., insufficient infrastructure, expertise, and funding). We have created an academic drug development center called DRIVE (Drug Innovation Ventures at Emory) that was designed to overcome many of the intrinsic and occasionally unintended barriers associated with academic drug development. Herein, we report a proof of concept that the DRIVE model provides a robust framework for pursuing university-based drug development, especially when the drugs in question target rare and neglected diseases.

KEYWORDS: Drug development, drug discovery, hit to lead development, lead to clinical candidate development, value inflection points

While the pace of new drug approvals was relatively flat for many decades, it increased significantly during the 2014–2017 time period, hitting a 21 year high in 2017. However, this good news must be tempered by a very sobering statistic: the cost for developing new drugs continues to increase at a staggering rate. According to a 2016 article, published by the Tufts Center for the Study of Drug Development, this cost, which eventually gets passed on to consumers, is just under three billion dollars per new drug approval, up from 1.9 billion in 2011.¹ Many experts believe that the problem has reached crisis proportions within the biotechnology and pharmaceutical industries and that the traditional pharmaceutical research and development operating model may no longer be financially sustainable. In some respects, this may be an overly gloomy assessment since we’ve witnessed amazing technological advancements in the pharmaceutical and biotechnology sectors over the past decade, the impact of which will not be fully understood for some time. These advances, for example, have already led to cell, gene, and immunotherapies that are being hailed as a new era in the treatment of serious disease. However, given the cost associated with the discovery and development of these breakthrough products, it is unclear if the world’s already overtaxed healthcare system can pay for them.

In response to the need for a new paradigm that increases the efficiency and consequently lowers the cost of new drug discovery and development, over 100 academic drug discovery centers have been established in the United States. By a large margin, these centers are focused on early stage discovery, which is generally defined as identifying compounds that have

an acceptable level of activity against a specific *in vitro* target (i.e., a “hit”). The degree to which these targets can be modulated can often be determined straightforwardly and relatively inexpensively by *in vitro* assay systems. The centers can then optimize the activity in the assay system in question using medicinal chemistry to generate a compound that is suitable for more advanced testing (i.e., a “lead”). Most universities have chosen to operate exclusively within this stage of the process because they can utilize the traditional extramural research sources that fund much of the basic biomedical research in the U.S. and around the world. This approach does not require large outlays of capital and only a minimal modification of the infrastructure found in a major research university is needed to be effective. However, since the costs of development beyond this point increase dramatically, this is generally where most of the academic drug discovery centers halt their activities. The inability to progress drug candidates beyond this point due to insufficient infrastructure, expertise, and funding is what the former NIH Director, Elias Zerhouni, famously termed the “Valley of Death”.²

Distinctive Features and Limitations of Academic Drug Development Units. *Lack of Experienced Development Personnel.* While funding and infrastructure limitations will, by definition, always be greater in universities than in their large pharma counterparts, the barriers to doing drug

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Table 1. Representative Academic Drug Development Centers

Center Name	Therapeutic Approaches	Therapeutic Areas of Expertise	Center/Program Highlight
BRITE (Biomufacturing Research Institute and Technology Enterprise) Facility, North Carolina Central University	Small Molecules	Multiple disease indications	Drug discovery/development and biomanufacturing
BSI (Brain Science Institute) Neuro-Translational Drug Discovery Program, Johns Hopkins School of Medicine	Small Molecules, Bio-markers	Neurological and Psychiatric disorders, Ophthalmology, Pain, Neuro-Oncology	Medicinal chemistry, pharmacokinetics and drug metabolism, animal pharmacology/toxicology and assay development
CD3 (Center for Drug Design and Development), University of Toledo	Small Molecules, Bio-markers, Drug Delivery	Oncology, Multiple disease indications	From concept to IND submission (excluding GMP synthesis and GLP toxicology)
DRIVE/Emory University Institute for Drug Development (HIDD)	Small Molecules	Virology	Medicinal chemistry, virology, DMPK, Managed by a veteran development team with prior successes in HIV, HBV, and HCV to address diseases with significant morbidity and mortality
Institute for Therapeutics Discovery and Development	Small molecules, Pro-drugs	All major therapeutic areas, including pain, neurological disorders, oncology, nonhormonal contraception, epilepsy, glaucoma	Team with industrial expertise in drug discovery and development. Medicinal Chemistry, Lead and Probe Discovery, High Throughput Screening, Pharmacology, Chemical Process Development, GMP Manufacturing
National Center for Natural Products Research, University of Mississippi	Small Molecules, Natural Products, Herbal Supplements	Immunology, Infectious diseases, Neurological disorders, Oncology	Natural products for use as pharmaceuticals, dietary supplements and agrochemicals
SciLifeLab Drug Discovery & Development Platform, Consortium of Swedish Universities.	Biologics, Small Molecules, Antibodies	Multiple disease indications	Combines frontline technical expertise with advanced knowledge of translational medicine and molecular bioscience
SPARK Translational Research Program, Stanford University School of Medicine	Biologics, Small Molecules, Vaccines, Antibodies	Any indication with an unmet medical need	Translates academic discoveries into drugs or diagnostics that address clinical needs
UCL TKO Drug Discovery Group, University College of London, UK	Small Molecules	Multiple disease indications	Project development, compound design and synthesis; hit discovery and hit to lead optimization. Part of the wider UCL Drug Discovery Cluster
Drug Discovery Unit (DDU), University of Dundee	Small Molecules	Diseases of the developing world, antibacterial drugs	A fully integrated drug discovery group working across multiple disease areas
University of Iowa Pharmaceuticals	Biologics, Small Molecules, Vaccines, Antibodies	Multiple disease indications	Contract organization for formulations, small scale commercial manufacturing, analytical method development/validation, API and excipient release testing
Translational Drug Discovery Group, University of Sussex	Small Molecules	Infectious diseases, Neurological disorders, Oncology	Medicinal chemistry and molecular pharmacology
Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center	Small Molecules	Neurological and Psychiatric disorders	Managed by a focused veteran drug discovery team, closely integrated with infrastructure for basic, translational and clinical research

development in academia go well beyond a lack of resources. While academicians delight in talking about translational research, i.e., research that progresses a product or service from “benchtop to bedside”, most lack experience in the highly specialized field of drug development to do this. This lack of experience virtually guarantees that novices venturing into the “Valley of Death” will make mistakes somewhere in the development continuum, which may dramatically increase the time and the cost of moving a promising drug candidate forward, thereby increasing the probability of failure.

Cultural and Governance Issues. Drug development companies operate in a very specialized arena. Their success depends on the ability to execute complex business plans, to provide quick and appropriate responses to unforeseen problems and to capitalize on unexpected opportunities. This is an endeavor where the “time cost” of money is extremely impactful. Conversely, academic scientists have research, teaching, and service responsibilities that prevent them from focusing exclusively on drug development. Moreover, academicians usually lack the business expertise and universities lack the governance structures that are needed to succeed in the development of therapeutics.

Unintended Consequences of University Intellectual Property (IP) Policies. Virtually all research universities have enacted IP policies to ensure that, *inter alia*, licensing revenues derived from university technologies get distributed to various stakeholders. These typically include the technology inventors, their departments, their schools and the university’s central administration. This practice effectively concentrates drug development activities in the early stage invention space since no provisions are made to allow a return on investment from later-stage activities performed by noninventors.

Because regulatory approval for a drug technology largely depends on later stage development activities, one of two outcomes is virtually guaranteed by these IP policies: (1) the technology will be licensed to a third party at an early stage of development before the full potential of the technology can be established, thereby resulting in suboptimal realization of value; or (2) the technology will never be developed by the inventors because the necessary resources cannot be obtained. In this latter situation, the inventor’s initial competitive advantage can erode relatively quickly, e.g., publication of a patent application 18 months after it was filed provides others with detailed information about the technology, thereby enabling them to springboard their own proprietary advances.

Lack of Experienced Leadership Teams. According to the Web sites of various centers, as well as a 2011 article, fewer than half of the U.S. academic drug discovery centers are involved in developing drugs.³ Only about 25% have appropriately trained personnel and any of the laboratory capabilities needed to extend drug development beyond the lead identification stage. Fewer still have leadership teams with experience in all of the scientific, commercial, and regulatory nuances of drug development.

An up-to-date, but informal overview of academic drug development units, compiled by us using a variety of Internet resources,⁴ is shown in Table 1. A more comprehensive survey of drug discovery units (including Web site information) is listed in the Supporting Information section. While many drug discovery units contain a number of the features present in a fully integrated drug development center, most lack the key core competencies (whether internal or through partnering arrangements) needed to progress a lead compound into

clinical trials. Table 1 lists the relatively small number of centers that, in the opinion of the authors, are representative of the scope and diversity of academic drug development initiatives. From this data, we conclude that, while drug discovery is alive and well at a large number of research universities around the world, comprehensive academic drug development centers are few and far between.

In an effort to circumvent the deficiencies described above, in September 2012 the authors of this article created DRIVE (Drug Innovation Ventures at Emory). DRIVE, LLC, a wholly owned subsidiary of Emory University, was organized as an independently managed, virtual, not-for-profit drug development company with an exclusive focus on developing therapeutics for viral diseases of global concern. Importantly, without shareholders or investors, DRIVE can address the most critical unmet needs rather than those that might produce the highest profits.

The commercial entity, DRIVE:

- is run by a highly experienced management team that has successfully developed and commercialized multiple FDA-approved drugs;
- is guided by a world class Advisory Board, composed of three venture capitalists and a highly regarded infectious disease physician;
- can in-license therapeutic opportunities from Emory University on commercially reasonable terms;
- can negotiate *directly* with other commercial or academic entities to in- or out-license technologies;
- advances drug candidates to a higher value stage of development (i.e., a value inflection point) with the help of its academic partner, the Emory Institute for Drug Development (EIDD), which is managed by the DRIVE leadership team and housed in a state-of-the-art facility in the Yerkes National Primate Center;
- maintains a strict focus on the development of antiviral drugs to address unmet medical needs (no “non-virology” opportunities are pursued);
- can form its own for-profit spinouts to accommodate private investments;
- has ready access to the intellectual and physical assets of Emory University, which provides a major advantage relative to traditional for-profit university spinouts.

We believe that the DRIVE model provides a number of unique advantages relative to other academic drug development centers. First, although not necessarily unique to the DRIVE model, it is hard to overstate the importance of having an experienced leadership team and personnel in any drug development center. In order to successfully progress a drug candidate through the development continuum, a leadership team must comprehend the subtle interdependence that often exists among the scientific, business, legal, and regulatory issues associated with the drug candidate in question. An issued patent, for example, while an essential component of a commercially viable (hence financeable) licensing package, does not necessarily provide freedom to operate. Similarly, an ill-conceived regulatory strategy can result in costly delays or even termination of what might otherwise have been a successful development program. Thus, while prior experience is no guarantee of future success, many investors consider the experience of the management team to be the single, most important derisking factor in a successful biotechnology venture. It is the seamless interaction of a team of highly

innovative research scientists with experienced drug developers that we believe makes the DRIVE model well suited for developing drugs in an academic environment.

Just as biotech start-ups need to be nimble and decisive in order to successfully deal with unexpected issues (both problems and opportunities), so too do academic drug development centers. “Nimble” and “decisive”, however, are not adjectives one associates with typical academic governance systems (at least none that these authors have encountered). Often, the oversight arrangements, particularly those affecting negotiations with external commercial entities, can be tediously slow since they are often done by overworked (and sometimes inexperienced) university technology transfer personnel. In the DRIVE model, all interactions with outside entities are handled by DRIVE personnel, which dramatically reduces negotiation times. The DRIVE management reports to Emory Innovations, Inc., whose board of directors is composed of Emory’s three executive vice presidents and its general counsel.

While there are no intrinsic differences in the chemistry component of a “lead to clinical candidate” campaign for different therapeutic areas (e.g., the basic methodology used to synthesize an oncology drug is the same that is used to make a cardiovascular or neurologic agent), the biological infrastructure needed to pursue drug candidates in different therapeutic areas can be vastly different. Additionally, the associated costs required to maintain this infrastructure across multiple therapeutic areas can be prohibitive. In our opinion, by failing to select one or two focus areas, many academic drug development units dilute their resources and development expertise, thereby limiting their chances of success. Indeed, the academic penchant for creating committees to develop solutions to current problems may work well for developing collegiality, but not for developing drugs. For this reason, DRIVE focuses exclusively on its area of expertise, i.e., the development of antiviral therapeutics.

Because DRIVE is a legal entity, distinct from Emory University (in our case a single member LLC), it can enter into a fair market value license with Emory for technology that it would like to advance to a value inflection point. Once the license has been executed, DRIVE can develop the technology in question unimpeded by University intellectual property policies in much the same way that an outside licensee might do. If DRIVE achieves a revenue-generating milestone, it first pays the University its share of the revenue (as mandated by terms of the license) and ploughs the remaining revenue back into its research and development efforts. This feature has proven to be particularly useful for funding the development of therapeutics for treating rare and neglected viral diseases. Specifically, by targeting a mixed portfolio of major market and rare/neglected viral diseases, DRIVE is able to use revenues obtained from licensing a large market drug candidate to subsidize research on rare and neglected viral diseases.

In our opinion, the DRIVE model provides a useful template for universities interested in drug development, particularly for diseases that the pharmaceutical industry is unlikely to pursue because of their small market potential. While these endeavors are unlikely to provide large, new revenue streams for universities, they have the potential of saving many lives. The mission of all research universities is to create and disseminate knowledge. We cannot think of a better example of doing this than to take a scientific hypothesis and ultimately transform it into a medicine that improves the health of people around the world.

At this point we suppose the reader may ask: “the model sounds interesting, but does it work?” DRIVE was initially funded by an \$8 M investment from intramural Emory funds. Since its founding, DRIVE has sustained itself by raising over \$40M in funding from government and industry sources without any additional Emory support. Some of the more advanced drug candidates DRIVE has developed include:

- *EIDD-2801*: an orally available, broad spectrum antiviral for the prophylaxis and treatment of the biodefense threat, Venezuelan Equine Encephalitis virus (VEEV), as well as for the treatment of Chikungunya infection, a devastating polyarthritic disease that has spread around the world at an alarming rate (note: *EIDD-2801* also potently suppresses the replication of the Ebola virus);
- *EIDD-2173*: an orally available development candidate capable of providing a sustained virologic response (SVR) in hepatitis B (HBV) patients while simultaneously eliminating its replication template, HBV, cccDNA; and
- *EIDD-2023*: an orally available treatment for rhino- and enteroviruses with extensive and positive safety data (12-week GLP-toxicology studies in two species that show a favorable profile).

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acsmmedchemlett.8b00124](https://doi.org/10.1021/acsmmedchemlett.8b00124).

A 12 page overview of academic drug discovery and development centers ([PDF](#))

■ AUTHOR INFORMATION

ORCID

Dennis Liotta: [0000-0002-7736-7113](https://orcid.org/0000-0002-7736-7113)

Notes

The authors declare no competing financial interest.

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