MILKEN INSTITUTE

Nonprofits
A Growing Force in Drug Development

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with LaTese Briggs

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CONTENTS

1	Nonprofits: A Growing Force in Drug Development
4	Overview of Translational Drug Development
7	Drug Development Barriers: Why Does the Pipeline Stall?
12	Nonprofit Models: What Are They, and How Do They Help?
13	Funding Mechanisms: When Are They Used?
14	Model 1: Academic Support
15	Model 2: Supporter
16	Model 3: Incubator
17	Model 4: Contract Research Organization
18	Model 5: In-House Research and Development
19	Model 6: For-Profit Support
21	A Consolidated Model: Where Do These Activities Help?
24	Putting Pieces Together: A Decision Tree
28	Completing the Puzzle: Determining the Best Funding Mechanism
32	Champions of Drug Development

NONPROFITS

A Growing Force in Drug Development

Cara Altimus and Kirstie Keller with LaTese Briggs

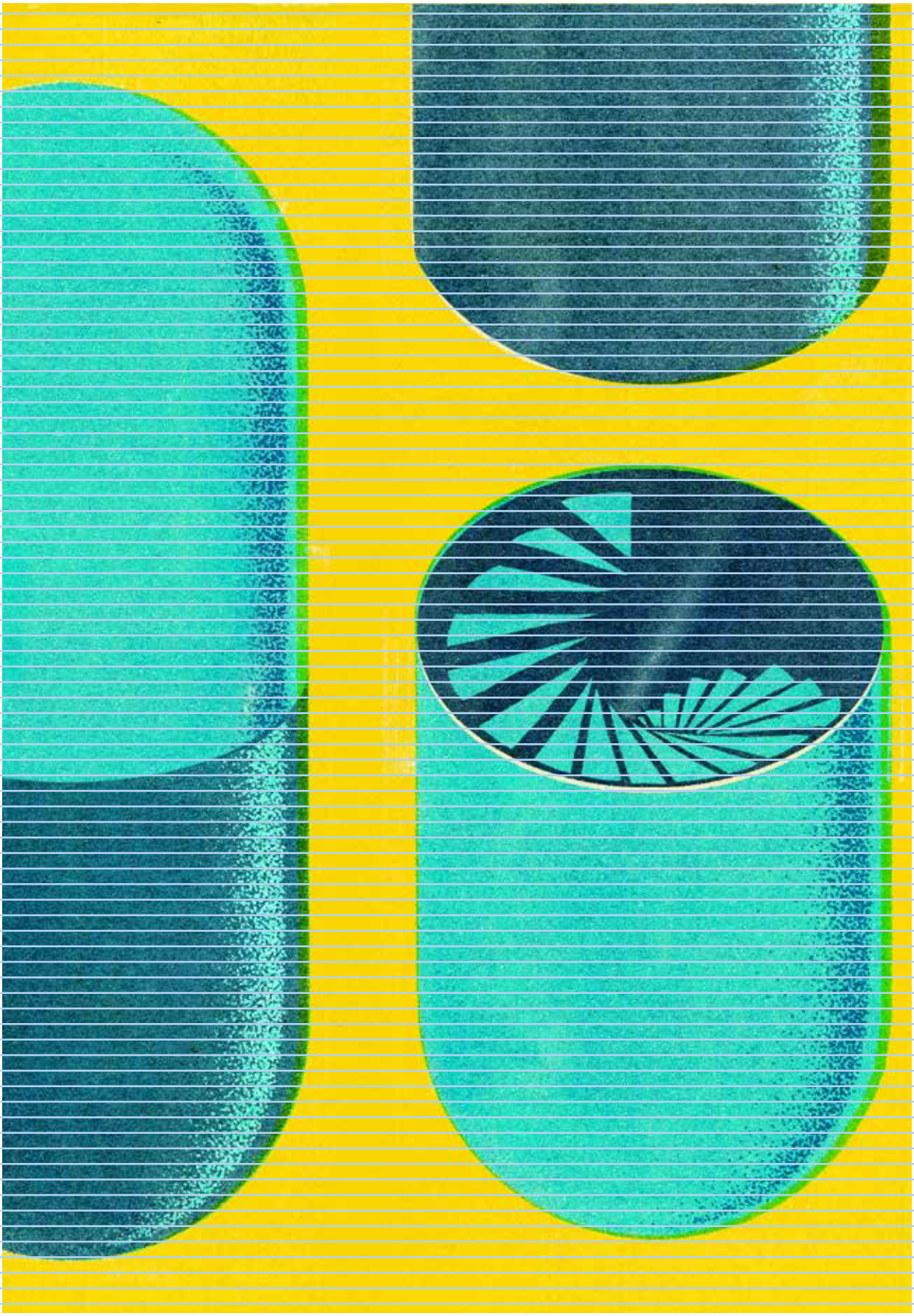
Shepherding a drug from discovery to the market is a complex process that involves many actors. The process often begins with academic researchers making a breakthrough discovery in the lab and ends with pharmaceutical companies running large-scale clinical trials to demonstrate that the drug is safe and effective. But what about the middle of this process—the point at which the discovery is translated into something that could be meaningful for treating patients? Who is responsible for the translational, or preclinical, part of the process? There is a lack of clarity about who should assume that role; translational research is often too expensive for academics to perform by themselves, but it is too risky for pharmaceutical companies given the uncertainty about the discovery's safety and market worthiness.

In this paper, we explore the multitude of methods that nonprofits use to support the translational drug development process in addition to when and where these models are most appropriate. To do so, we discuss several barriers to the translation of scientific discoveries to clinic-ready therapeutics and how nonprofits use their unique approaches to overcome these barriers. This work has led to the creation of a catalogue of activities for nonprofits to support drug development in their specific fields and of the financial mechanisms best suited to fund these activities.

This catalogue includes six main activities: academic support, supporter, incubator, contract research organization (CRO), in-house research and development (R&D), and for-profit development. Each of these activities provides the resources most needed to investigators, companies, or nonprofits themselves to drive drug development efforts forward (Figure 1).

Figure 1. Six Primary Ways Nonprofits Support Drug Discovery and Development

Finally, we paired these models to the most appropriate funding mechanisms and developed a decision tree to help nonprofit organizations determine how best to support drug development based on their field's drug development pipeline, the state of the science, and geographic constraints, as well as the necessary infrastructure and human capital. This paper showcases how nonprofits are tackling some of the most significant problems in R&D and bridging gaps in the pipeline to kick-start the development of new cures for the patient community.



OVERVIEW

of Translational Drug Development

The process of developing a new drug is long, costly, and risky. The Pharmaceutical Research and Manufacturers of America (PhRMA) estimates that, on average, it takes 10 years and $2.6 billion to bring a new drug to market.[1]

To develop a drug, researchers first identify a target or component of the biological system that could be modified to affect a disease. Then, they validate the target through several experimental tests and heavily scrutinize it to ensure that modification will not cause harmful repercussions. Next, researchers screen large libraries of drug-like compounds against the target to determine whether any have an effect that could be beneficial to treating disease. Once researchers identify a "hit," they chemically optimize the compound to maximize effectiveness while limiting any off-target interactions—a stage that is iterated multiple times until the best possible therapeutic is created. Finally, the researchers test the potential drug in animal models to ensure that it is safe and alters the disease state as expected.

The translational process is not only long and challenging but also marked by uncertainty and a low probability of success. Between 5,000 and 10,000 compounds are developed for each drug approved by the U.S. Food and Drug Administration (FDA). [2,3] Combined, these factors lead to lower levels of public- and private-sector investment compared to other drug development phases. This often kills the advancement of promising therapeutics, aptly earning translational research its colloquial name: the "Valley of Death."

1 PhRMA Chart Packs, "Biopharmaceuticals in Perspective," https://chartpack.phrma.org/2016-perspective/chapter-2/the-lengthy-costly-and-uncertain-biopharmaceutical-research-and-development-process.

2 JAMA, "Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016," https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2702287.

3 PhRMA, "New Medicines in Development for Diabetes," http://phrma-docs.phrma.org/sites/default/files/pdf/12-535phrmaoverviewdiabetes1109.pdf.

NARROWING THE VALLEY OF DEATH

Nonprofits are uniquely positioned to support the risky studies required for a drug to survive the Valley of Death—and they are doing just that. Over the past decade, we have witnessed blockbuster successes born from careful investments by nonprofits. One of the most notable of these investments was made by the Cystic Fibrosis Foundation, a long-time advocate of and participant in research and development (R&D) support of cystic fibrosis (CF) treatments. The foundation provided seed funding to Vertex Pharmaceuticals and earned a $3.3 billion payout from the success of the drug Kalydeco, which was recycled back into the R&D efforts within the CF community. Although this is an extreme case, it is a powerful example of how the venture philanthropy approach, adapted from the finance sector, is gaining popularity within the nonprofit sector, shifting the paradigm in developing treatments and cures. While venture philanthropy is a critical financial mechanism, it is only one of the many ways that nonprofits can shepherd a novel therapeutic through the valley.

We define nonprofits as organizations that are dedicated to furthering a particular cause, such as medical research. They recycle any excess capital back into their organization to further their mission, rather than distributing profits to shareholders, leaders, or members.

CHAMELEONS OF DRUG DEVELOPMENT

Unfortunately, there is no “one-size-fits-all” model to bolster drug development; each disease-focused field has its own unique set of challenges that shift over time as the science evolves and the funding environment changes. These changes require flexibility, which is a fundamental principle of nonprofits. Nonprofits act like chameleons as they tailor their solutions to the specific challenges of their scientific field at any given time.

To further our understanding of this broad and changing landscape, we studied the barriers to drug development, along with nonprofit drug development models utilized across disease areas. We interviewed more than 20 academic investigators and 15 for-profit entities, as well as profiled 48 nonprofits engaged in drug development to obtain a holistic perspective on both the barriers to the advancement of therapeutics through the pipeline and how nonprofits overcame these barriers. In the following sections, we highlight each of the identified barriers and provide the six models that nonprofits use to guide compounds through drug development to ultimately accelerate the process of finding treatments and cures, along with the appropriate funding mechanism. The combination of these diverse activities and funding mechanisms provides a multitude of ways that a nonprofit can support drug development to overcome common yet diverse challenges.

DRUG DEVELOPMENT BARRIERS

Why Does the Pipeline Stall?

Therapeutic development is challenging and requires a concerted investment, as emphasized by the numerous models nonprofits have adopted to advance the process. But what exactly makes this process so challenging?

In Figure 2, we highlight barriers that hinder the advancement of therapeutics through the drug development pipeline and the effect on the process. These issues represent some of the common threads that impact many scientific fields as they attempt to move therapeutics through the preclinical stages.

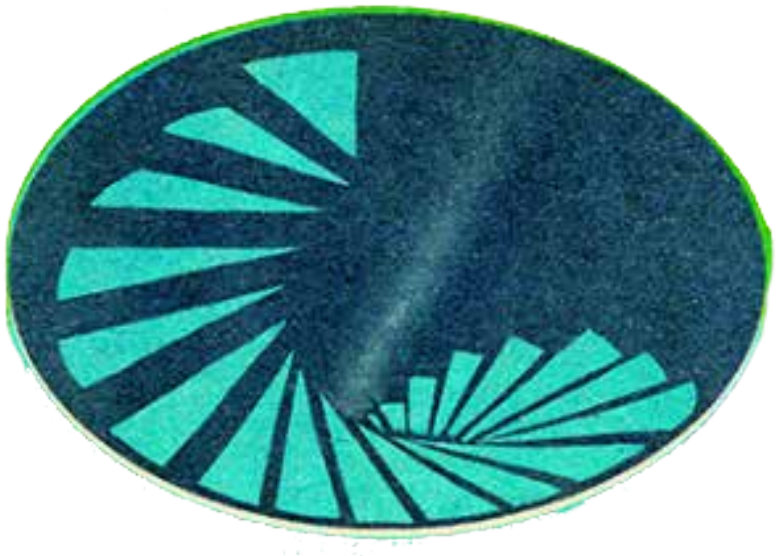


Figure 2: Challenges in the Drug Development Process and Their Impact

Challenges	Results
1. Insufficient funding for validation and translation studies	- Limited number of validated therapeutics available for investment - Overall drug development pipeline shrinks
2. Few medicinal chemists are integrated into academia	- Compound development is stagnated, ceased, or outsourced
3. Lack of drug development expertise and access to resources	- Researchers must outsource activities for increased expense - Insufficient data are available to advance therapeutic to next stage
4. No consensus on intellectual property management	- Publishing or patenting do not occur at the right time, negating the possibility of future partnerships or killing a future program
5. Limited knowledge of business strategy and development	- Investors and partners do not engage to take an asset to the finish line - Project timeline increases due to inefficiencies or lack of know-how
6. Difficulty identifying the right partners at the right stage	- Project data do not align with needs of investors or partners - Programs or projects are abandoned or taken over by parties with other interests

CHALLENGE 1: INSUFFICIENT FUNDING FOR VALIDATION AND TRANSLATIONAL STUDIES

Many therapeutic areas experience limited support for preclinical studies, which pose the highest risk of failure. Public funding sources, such as the National Institutes of Health (NIH), traditionally support basic or discovery science and fund more established ideas.[4] A focus on mainstream ideas may advance scientific knowledge, but it ignores the flexibility and risk-taking needed for preclinical work. While some efforts reflect a renewed focus on translational science, for example, the development of the NIH's National Center for Advancing Translational Sciences (NCATS), translational science continues to attract a small percentage of public funds for biomedical research. Private companies also minimize investment because of high failure rates and the concomitant impact on their valuation. However, without investment in the translational stage, potential therapeutics cannot be properly validated and cannot advance to later development stages.

4 NIH supports preclinical and clinical work through NCATS. However, for 2019, the NCATS budget is $685 million (approx. 1.9 percent of the $34.8 billion NIH budget across all disease fields for both preclinical research and clinical trials). Department of Health and Human Services, "2019 Budget in Brief," https://www.hhs.gov/sites/default/files/fy-2019-budget-in-brief.pdf.

CHALLENGE 2: FEW MEDICINAL CHEMISTS INTEGRATED INTO ACADEMIA

Early in the translational development process for small molecules, researchers use large-scale screening to identify compounds that have the desired effect on a molecular target of interest, known as a "hit." However, these hits must be chemically optimized to improve their therapeutic properties and their chances of being translated into a drug that can be tested in humans. This optimization process requires the interdisciplinary science of medicinal chemistry, which combines organic chemistry, biochemistry, and structural biology, and uses chemical principles to design effective drugs. While lead optimization is critical to drug development, few academic scientists have the requisite knowledge or access to medicinal chemists within their labs. Consequently, the drug development process stagnates because the compounds are not adequately de-risked and require significant additional investment to become a "drug-like" molecule.

CHALLENGE 3: LACK OF DRUG DEVELOPMENT EXPERTISE AND ACCESS TO RESOURCES

The many experimental steps on the pathway from target discovery to clinical use involve a broad range of scientific expertise and an understanding of the entire preclinical development system. In addition, the steps require tools not typically available in an academic setting, such as high-throughput screening capabilities or large-scale absorption, distribution, metabolism, and excretion testing. The lack of experience and access to resources often stagnates progress or requires outsourcing of experiments, which may involve contracts and expenditures that are not covered by a typical grant agreement.

CHALLENGE 4: NO CONSENSUS ON INTELLECTUAL PROPERTY MANAGEMENT

Nuanced legal hurdles require clear guidance for each project. The research community has not arrived at a clear consensus about best practices to resolve the publishing vs. filing for a patent dilemma, and tension may exist between a nonprofit's desire to share knowledge and the necessity to protect intellectual property (IP). Meanwhile, the current incentive structure in academia is solidly anchored in scientific publication. Combined, the lack of consensus about best practices and the conflicting incentive structures present an obstacle to early-stage drug development. Specifically, academics and industry may be reluctant to form partnerships, which can lead to the premature termination of a program if the asset is not appropriately protected.

CHALLENGE 5: LIMITED KNOWLEDGE OF BUSINESS STRATEGY AND DEVELOPMENT

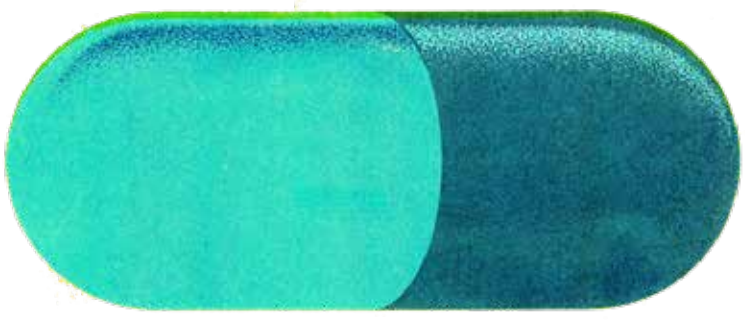
As therapeutics reach the later stages of preclinical development, the original inventor often seeks outside investment to support the high costs of testing and validation. However, promising science cannot stand on its own. Investors also seek a strong business and development plan and a team with a successful record of accomplishment. Unfortunately, most scientists are unequipped to develop the necessary proposal materials on their own. Unless they involve an experienced entrepreneur, scientists might not secure funding because their proposals have missing or weak business components.

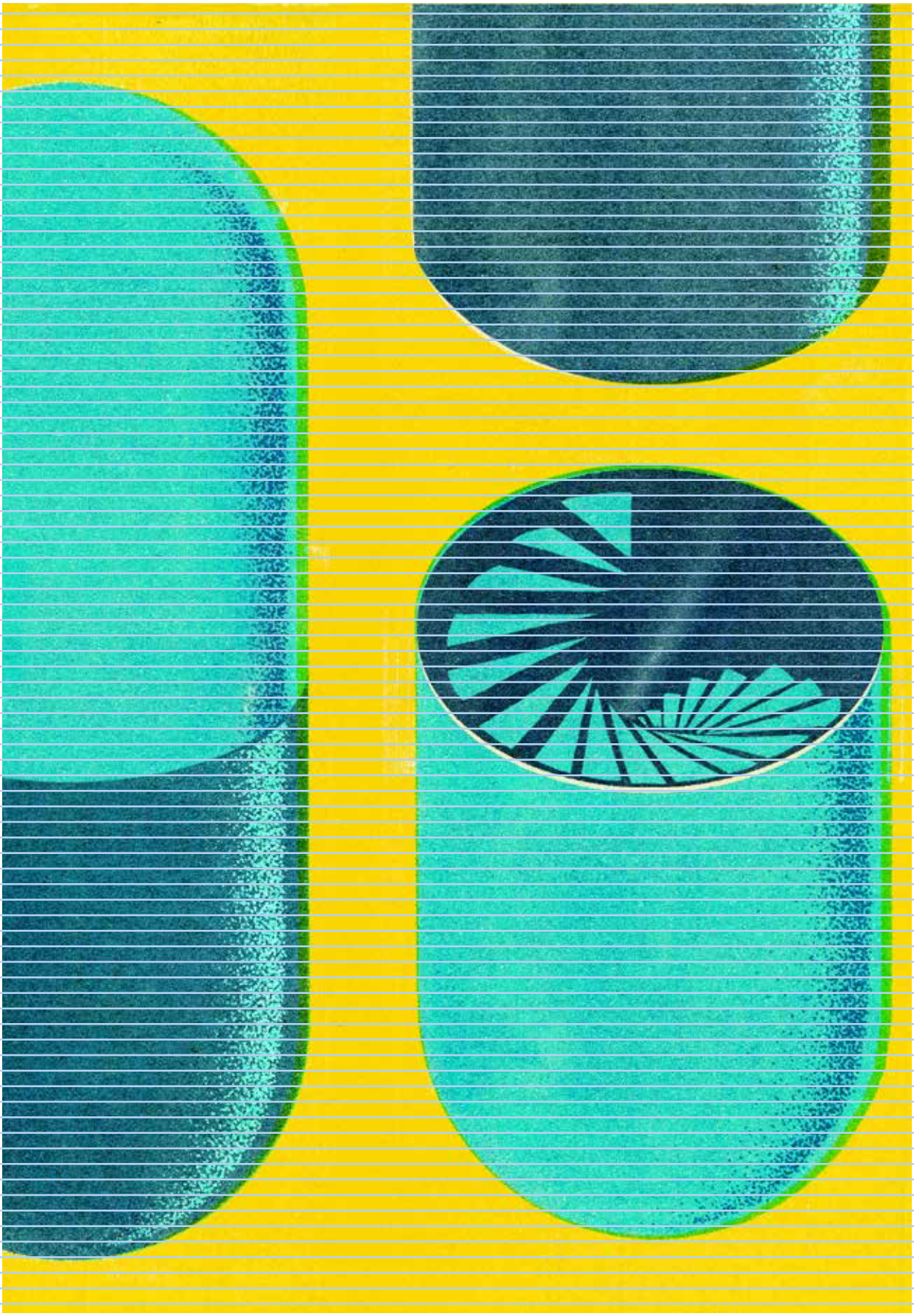
CHALLENGE 6: DIFFICULTY IDENTIFYING THE RIGHT PARTNERS AT THE RIGHT STAGE

Generally, academic researchers rarely interact with investors or potential industry partners. However, these interactions can provide access to funding and key insights into the drug development process. Attracting the right partners in advance can streamline the drug development process by creating clear paths to funding and ensuring that the therapeutic meets all guidelines necessary to advance to the next stage.

AND MANY MORE

Although these six barriers are critical to address, they do not comprise an exhaustive list. Each field experiences its unique hurdles in addition to those that we have described. Furthermore, the issues described here may not resonate with all nonprofits and their missions. Each nonprofit should perform an analysis of the barriers specific to its field and focus its efforts to overcome those barriers to have the maximum impact. The Milken Institute Center for Strategic Philanthropy follows a systems-based approach to understand the landscape of scientific fields—identifying the most prominent challenges affecting progress and uncovering solutions to overcome these challenges. We then use this understanding to guide nonprofits and philanthropists to make high-impact investments within a field. Other groups can adopt this methodology to examine the unique hurdles and opportunities in their fields as a first step on the best pathway for future investments.





NONPROFIT MODELS

What Are They, and How Do They Help?

Nonprofits use six distinct and creative models to overcome these seemingly insurmountable barriers to drug development. The first four models strengthen the development of the asset itself, while also providing support to the development of human capital in the field by providing researchers with access to the tools and expertise they need to participate in the drug development process. These four models are as follows:

1. Academic Support: Nonprofits provide funding to academic scientists to conduct translational drug development work, such as target identification, within their laboratory and home institution.
2. Supporter: Nonprofits act as project manager, educator, or matchmaker to fill knowledge gaps and ensure that the path forward is unencumbered.
3. Incubator: Nonprofits provide physical space, equipment, reagents, and expertise to researchers who seek to spin-out their work into new companies. However, this needed assistance is meant only to jumpstart companies and therefore is usually time-restricted.
4. Contract Research Organization (CRO): Nonprofits provide funds to researchers to use a CRO to conduct the necessary preclinical experiments that are not feasible in an academic setting. Alternatively, nonprofits themselves can act as a CRO, offering their services to users at a discounted rate.

The final two models focus more on how a foundation can assume complete control of drug development.

5. In-House R&D: Rather than outsourcing or gifting grants to external sources, some nonprofits use capital to engage in traditional R&D in a nonprofit setting. The activities can span much of the drug development process, from discovery to Phase II, but typically do not include Phase III, which exceeds the financial capacity of nonprofits and requires partnership with industry.

6. For-Profit Support: Nonprofits provide financial support to a young biotech company to bolster a translational development project or an established company to start a new program within its R&D arm. Nonprofits can use these models individually or in combination to support the different stages of drug development, regardless of the field of study. Ultimately, the adoption of these models narrows the Valley of Death and brings patients closer to a treatment or cure.

FUNDING MECHANISMS: WHEN ARE THEY USED?

Nonprofits adopt not only new activities in the drug development space but also explore innovative financial tools to fund their programs. In addition to the tried and true methods of traditional grantmaking, they have bolstered their financial toolkits to include venture philanthropy and self-funding:

Funding Mechanisms: A Quick Glance	
Gifts/Grants	**- Funds or resources given without an expectation of return**
Venture Philanthropy	**- Investments made with an expectation of a return** **- Return can be through IP ownership, equity, royalties, etc.** **- Return can also be through simple repayments**
Self-Funding	**- An entity provides funding to its own internal drug development programs**

Gifts/Grants

Philanthropic investments are typically made through financial grants or resources to principal investigators or institutions to support research on a specific topic. Resources may include compound library access, research models, datasets, or a patient registry. The funder provides capital with no expectation for IP or a return on investment. However, grantors can restrict the use of funds for a specific purpose.

Venture Philanthropy

This approach balances the funding models of traditional grantmaking and venture capital. It incentivizes high-risk approaches to research with the goal of developing a marketable medical product. In contrast to grants, the funder expects a return on investment through IP ownership, equity, or royalties. Any potential earnings from the end product can be returned to the research fund to support future studies.

Self-Funding

In some cases, nonprofits support drug development through internal R&D programs, which typically require research infrastructure and scientific staff to perform the experiments. In this case, the nonprofit manages the infrastructure, employs scientists, maintains the IP, and can earn a profit from assets resulting from the work.

Determining the best path forward requires an understanding of the greatest barriers to therapeutic development in a field and layering on specific support mechanisms to overcome these barriers. The following sections explore each model in detail.

MODEL 1: ACADEMIC SUPPORT

Nonprofits have provided funding to academic scientists for decades. These gifts are typically awarded to advance the fundamental understanding of a specific disease. However, increasing recognition of the challenges unique to the Valley of Death has led some nonprofits to pivot their financial support from basic research to translational efforts. This model, referred to as "academic support," is primarily used to support scientists conducting drug development research within academic institutions. Typically, these awards fund further validation of a biological target or are used to identify compounds that could be effective against the target of interest.

This model is best suited to provide the resources needed in the early stages of preclinical drug development. While many academic investigators may not have the experience or interest in translational studies, this model allows interested investigators to build the evidence necessary to justify further development and to attract additional investment from industry partners or venture capitalists.

Although academic support provides a helpful boost to projects with validation and early screening needs, it does not fill some of the critical knowledge gaps that academics often have, because very few possess deep expertise in the overall drug development process. They may not know the appropriate assays and industry standards required for a robust dataset that attracts the right partner, and they may not have the expertise to build a solid business plan for future development. As such, some investigators may struggle to push through to the next stage without additional support. Thus, funders must pay careful attention to ensure that the investigator is set up for success in both the current project and in the next steps.

ACADEMIC SUPPORT | ALZHEIMER'S DRUG DISCOVERY FOUNDATION

The Drug Discovery program of the Alzheimer's Drug Discovery Foundation aims to bridge the translational funding gap between early-stage discovery and clinical development with a specific focus on Alzheimer's disease. The program funds projects that advance lead molecules to the clinical selection stage or those that build out preclinical evidence for repurposed or repositioned drugs in animal models.

MODEL 2: SUPPORTER

While many nonprofits offer direct financial support to help move assets through the drug development pipeline, many roadblocks extend beyond research that requires a different type of assistance. For example, new therapeutic programs often need assistance with business development and project management. Therefore, some nonprofits offer this type of help, which we have deemed the "supporter" role, to fill these critical gaps by acting as a support system for researchers. To accomplish this role, the supporter nonprofits regularly act as educators, mediators, or matchmakers, or some combination of all three:

Educator

Academic investigators are well versed in discovery, but many do not have the expertise required for drug development or business management. Nonprofits can serve as educators by providing training on topics including business development, legal agreements, and FDA submission requirements.

Matchmaker

Finding the right partners is critical to success in the drug development process. Nonprofits can facilitate interactions among research investigators, partners, and funders at various stages of the development process and can take an active role in developing the team required to move a therapeutic forward.

Mediator

Communication between academic labs and industry is often challenging because of competing priorities. Nonprofits can serve as the facilitator in collaborative efforts, acting as a neutral third party in the arrangements. In this role, they can assist in streamlining the process and can ensure that each side understands the terms of the agreement.

This model requires the active engagement of the nonprofit to invest time and energy in developing, maintaining, and managing a variety of experts either in-house or in its network to support investigators. Generally, this model requires less capital because it provides limited infrastructure or funding to the investigator. However, in fields where capital is insufficient to perform translational experiments, the supporter role may not be effective; rather, a model to introduce capital into the field may be more appropriate.

SUPPORTER | HARRINGTON DISCOVERY INSTITUTE

Harrington Discovery Institute (HDI) focuses on providing funding and support to areas of unmet medical need through a disease-agnostic, institution-agnostic, and modality-agnostic approach. One of its programs grants two years of funding, education, and a team of mentors to physicians and scientists to develop a therapeutic. The high-touch management and mentorship is the defining factor of the program and has led to a number of successes. The venture firm BioMotiv, which is part of the HDI umbrella, is poised to help successful projects spin out companies and provide seed funding.

MODEL 3: INCUBATOR

When relevant labs or start-ups are highly concentrated in a region, nonprofits may determine that physical consolidation of research and support services is the best method of engagement. To do so, nonprofits can build an incubator to act as both a service firm and an investor to support early-stage start-up companies typically led by academic investigators. An incubator's goals are to fast-track business development by providing the start-up capital and resources and to accelerate scientific process, thus reducing uncertainty in early stages of investment and decreasing the overall time to market. To accomplish these goals, successful incubators often provide the lab space and core facilities with limited overhead, as well as mentorship or business courses to fill in knowledge gaps. In addition, many incubators limit the amount of time a new company can use their services to pressure the occupant to learn, act, and deliver quickly.

Although incubators provide an important service, the number of start-ups they can house at one time is limited. Investment decisions are typically made using a portfolio approach to maximize operational and investment returns while minimizing risk—similar in concept to that of a venture capital firm. Thus, to keep an active, sustainable ecosystem within the incubator, a critical mass of projects must be ready for incubation within the research pipeline. In addition, this model is limited to geographic hubs, which can be challenging for investigators bound to their universities or institutions.

INCUBATOR | LAUNCHBIO

True nonprofit incubators are difficult to maintain. LaunchBio has bridged this gap by partnering with BioInnovation Labs LLC to provide a network of co-working spaces designed and run by entrepreneurs, While BioInnovation Labs maintains the physical space, LaunchBio provides the connections to the larger entrepreneurial support community, shortening the time for a founder to start and grow a company. Their spaces are located across the nation's leading life science hubs, including Boston, San Diego, San Francisco, and Raleigh-Durham.

MODEL 4: CONTRACT RESEARCH ORGANIZATION

The preclinical stage is considered one of the most laborious, with many perspective therapeutics failing because of scientific problems or unforeseen regulatory hurdles. Furthermore, these experiments are often cost-prohibitive to most academic labs or emerging companies. Many nonprofits bridge this gap by giving grants to academics or companies to utilize a CRO to perform these critical experiments, particularly for target validation, expansion of hits, and translational studies. In addition, some nonprofits are CROs themselves, performing these contracted services at a reduced rate.

Although all CROs provide support in the form of research services as part of a contract, a preclinical CRO specifically provides the expertise and skill required to develop a pharmaceutical product from the discovery stage to a lead compound. These experiments are done in an unbiased manner with industry-grade standards yielding robust and reliable datasets. In addition, CROs are often familiar with the best practices and government regulations necessary to successfully develop a drug. Overall, CROs are valuable because they can alleviate some of the potential regulatory hurdles and de-risk the asset for future investors.

Although preclinical CROs can provide an excellent service to the sponsoring organizations, many challenges can disrupt progress, including short timelines, non-standard experiments, and custom reports. Additionally, because use of CROs is a more a de-centralized approach compared to in-house R&D, strong project management by the academic investigator and/or the nonprofit is required for a successful program.

CRO | CHORDOMA FOUNDATION

The Drug Screening Program of the Chordoma Foundation (CF) was initiated after a gap in resources for chordoma researches was identified. At the time, there was only one federally funded chordoma lab, and there were very few models to test therapeutics. To fill this gap, CF generated cell lines and xenograft models of chordoma and made these tools available to investigators through the Drug Screening Program. This grant provides funding to perform preclinical validation experiments on repositioned or repurposed drugs in cell and tissue transplant models of disease through a partnership with a CRO.

MODEL 5: IN-HOUSE RESEARCH AND DEVELOPMENT

Nonprofits have historically supported drug development by providing funding to other organizations, usually through grants to academic investigators. However, a growing number of nonprofits see the utility in controlling the R&D process in house to maximize their oversight and overcome traditional roadblocks that occur in the Valley of Death. This level of ownership allows nonprofits to use proceeds from successful therapeutics to fund future promising projects.

Most in-house R&D programs engage in target discovery through Phase I or Phase II clinical trials, because Phase III trials are generally cost-prohibitive. They provide a full suite of support throughout the most critical points in the Valley of Death, with both a full range of scientific and industry expertise and a dedicated business development and administrative team. In addition, they provide all of the physical infrastructure to conduct experiments, such as laboratory space, equipment, and reagents.

The end-to-end support for both scientific and business development provided by this model is attractive and beneficial; however, the start-up phase is more challenging. A large amount of capital is required to build the infrastructure and attract experienced staff necessary to conduct the work. As such, there is a long lead time to initiate such a program. An additional challenge is maintaining the program once it is off the ground. A model for long-term sustainability through active fundraising is often required, similar to that mentioned in the for-profit support section.

IN-H0USE R&D | DRUG DISCOVERY INSTITUTE

Drug Discovery Institute (DDI) is an in-house drug discovery program of Alzheimer's Research UK that is embedded within three universities in the United Kingdom. The goal is to validate targets found in academic labs and to generate novel chemical matter that is attractive to partners. DDI recognized that academic investigators are skilled at identifying targets and understanding disease mechanism, but they often lack the know-how to turn hits into validated, attractive leads. DDI fills this knowledge gap by providing the expertise in program design and the in-house scientific staff to conduct the experiments. Additionally, it provides an on-ramp to partnership with industry to move a drug to the next stages.

MODEL 6: FOR-PROFIT SUPPORT

Based on our research, we found that nonprofit support for early-stage drug development within for-profit companies is a growing phenomenon. This phenomenon may be driven in part by the comparatively higher failure rates in the earlier stages and the longer time horizons for returns, which are more acceptable to a nonprofit. Meanwhile, traditional investors are engaging later in the drug development process. The chance of failure decreases from approximately 80 percent for preclinical studies to 35 percent for Phase I clinical trials with an average

development time of 17 years.[5,6,7] Nonprofits can bridge this gap and provide the needed seed capital by promising young companies to gather the data necessary to attract other funders or support the creation of a new drug development program within an established company.

As with any investment, several key considerations should be addressed before working with a for-profit group.

Demonstrated need for funding by nonprofits

The for-profit company should provide a clear statement of need. This statement should also indicate why it could not attract funding from traditional sources, such as industry or venture capital.

Experienced, balanced teams with a full range of skills

The drug development process is challenging and requires several skill sets, including business acumen, scientific knowledge, and technical expertise. A team missing any of these primary components is a precarious investment because it opens the door for operational failure in an already risky therapeutic space.

Established busines plan or strategy

Companies need to demonstrate that their business plan supports their therapeutic development program. The plan should include regulatory considerations, an IP summary, market analysis, milestones, scientific and financial goals, and a commercialization plan.

FOR-PROFIT SUPPORT | CUREDUCHENNE VENTURES

CureDuchenne was founded by a parent of a patient and initially funded academic science efforts. However, the team quickly became frustrated with the pace of science within the university setting and decided to work with biotech and industry. It initiated a new branch of the nonprofit focused on funding emerging biotechs in return for equity. An early funded project was so successful that it was able to fund five new projects. Then, it officially launched CureDuchenne Ventures, the venture philanthropy arm of the nonprofit, which has invested in a number of projects leading to successful exits.

5 Drug Discovery World, "Fall 2014 Report," https://www.ddw-online.com/2014/p274237-ddw-fall-2014.html.

6 BIO, Biomedtracker, and Amplion, "Clinical Development Success Rates 2006-2015," https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf. .html.

7 James Gilbert, Preston Henske, and Ashish Singh, "Rebuilding Big Pharma's Business Model," In Vivo Medicine and Business Report 21, no. 10 (2003), https://www.bain.com/contentassets/040b2c20d74b4a42b262d0b0a3067a9b/rebuilding_big_pharma.pdf.

A CONSOLIDATED MODEL

Where Do These Activities Help?

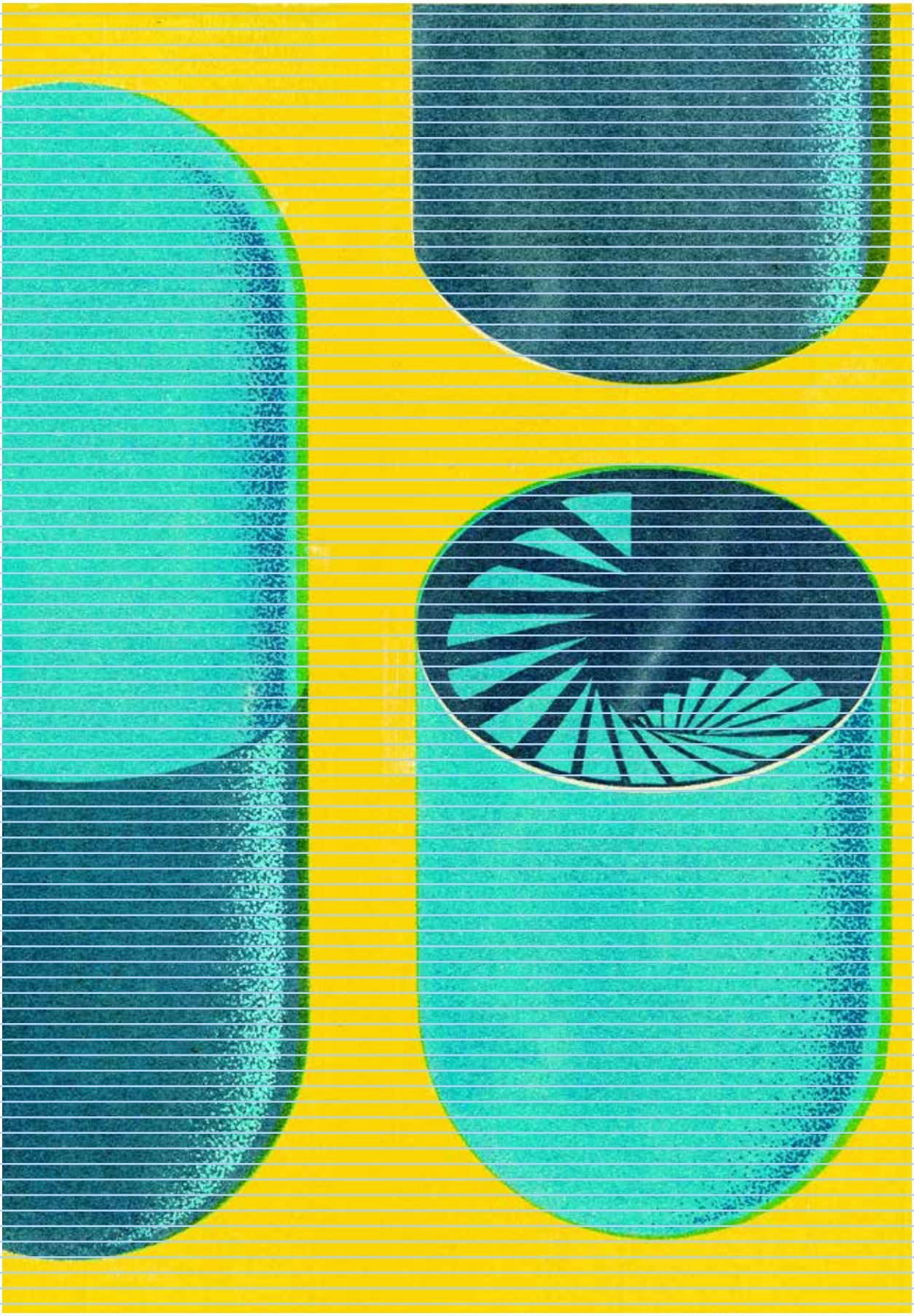
Our catalog of activities illustrates the numerous ways that nonprofits can support the drug development process, their specific limitations, and how they meet needs within the drug development process. The following diagram provides a consolidated view of how each activity addresses the identified barriers (Figure 3).

At first glance, it is clear that some nonprofit activities fill in more gaps than others. However, this does not indicate their relative effectiveness. In some cases, addressing one issue may be sufficient to address the needs of a field. For example, as shown in the diagram, a CRO model can provide the capital to perform the necessary preclinical studies in the presence of expert medical chemists, which can de-risk a therapeutic for future investment. Alternatively, a supporter may not provide capital or medicinal chemistry expertise, but can instead prepare an investigator to present a solid business plan with clear project milestones to potential investors and make the necessary connections between these two groups. Thus, each activity provides a valuable service to the drug development community—and ultimately to the patient communities in need of effective therapeutics.

Figure 3: Overcoming Gaps in Drug Development

How does each of the nonprofit activities address the gaps in the drug development process?

IDENTIFIED GAP	MODEL: Academic Support	Supporter	Incubator	CRO	In-House R&D	For-Profit Support
Insufficient Funding for Validation and Translational Studies	✓		✓	✓	✓	✓
Few Medicinal Chemists Integrated into Academia				✓	✓	
Lack of Drug Development Expertise and Access to Resources		✓	✓		✓	
No Consensus on Intellectual Property Management		✓	✓		✓	
Limited Knowledge of Business Strategy and Development		✓	✓		✓	✓
Difficulty Identifying the Right Partners at the Right Stage		✓	✓		✓	✓



PUTTING THE PIECES TOGETHER

A Decision Tree

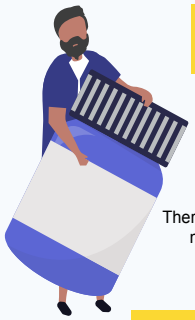
This paper aims to provide nonprofits with a catalog of mechanisms and a decision tree to determine the best model to adopt to support drug development—there is no “one-size-fits-all” approach (Figure 4). Begin the decision tree by examining the robustness of the therapeutic pipeline in your relevant biomedical field, because this provides information on the overall likelihood of success.

These questions and considerations are meant to guide decision-making for nonprofits to best support their field in the manner that aligns most with their internal capabilities and interests and to provide a launching pad for new therapeutics to reach patients.

Figure 4: Decision Tree

Which model is right for my organization?

DRUG DEVELOPMENT IS TOUGH, BUT NONPROFITS CAN MAKE A REAL DIFFERENCE IN THE PROCESS. HOWEVER, WITH ALL OF THE POTENTIAL DIRECTIONS, WHAT EXACTLY SHOULD YOUR ORGANIZATION DO? USE THIS GUIDE TO HELP IDENTIFY THE RIGHT PATH FOR YOUR ORGANIZATION'S EFFORTS TO ACCELERATE THE ROAD TO A CURE.



IS THE THERAPEUTIC PIPELINE ROBUST?

YES
There are a number of diverse drugs moving through development

NO
Only a few therapeutics are in development and/or they lack diversity

ACADEMIC SUPPORT
Build basic knowledge to bolster the future pipeline

IS THE FIELD ESTABLISHED?

VERY
Plenty of publications and academic programs are thriving

NOT YET
Not many papers or academic programs exist

HOW MUCH INFRASTRUCTURE DO YOU WANT TO CREATE?

Build away!

Let's keep it minimal

IN-HOUSE R&D
Take the lead in growing the field and the pipeline

SUPPORTER
Shepherd the field forward with aid and expertise

HOW ACTIVELY INVOLVED WOULD YOU LIKE TO BE?

ACTIVE
High degree of internal support

INTERMEDIATE
Involved, but not the lead

MINIMAL
Mostly hands-off

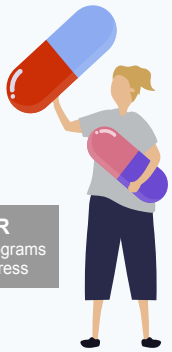
IS THERE GEOGRAPHIC DENSITY?

FOR PROFIT
Fund innovative for-profit programs to derisk and seed

CRO
Fund outsourcing of critical experiments

YES

NO



HOW MUCH INFRASTRUCTURE DO YOU WANT TO BUILD?

Build away!

Let's keep it minimal

INCUBATOR
House emerging programs to jump start progress

IN-HOUSE R&D
Take the lead in growing the field and the pipeline

SUPPORTER
Shepherd the field forward with aid and expertise

IS THE THERAPEUTIC PIPELINE ROBUST?

In a field where many diverse drugs are moving through the pipeline, nonprofits should focus on ways to help the progression of these therapeutics by providing additional capital or scientific and business support services. However, if the field has few therapeutics within the pipeline, or the pipeline focuses on only one or two targets, then investing in the academic discovery process is more likely to lead to long-term growth in the field. Next, we ask the organizations of fields with robust pipelines whether their field is established, with publications released at regular intervals and several academic programs working on this topic. Those in less established fields may choose to assume a more involved role within their community to increase the number of studies, investigators, or therapeutic programs. These nonprofits can either build new infrastructure and roll out an in-house R&D program or create less formal infrastructure and become the educators, matchmakers, and/or mediators for academics in the field, acting as supporters.

IS THE FIELD WELL ESTABLISHED?

Nonprofits from established fields have additional questions to address, the first of which is how actively involved they would like to be in drug development efforts. For example, if a nonprofit does not have a large internal staff or cannot follow a hands-on approach, developing a CRO program allows the nonprofit to support critical experiments with the right expertise and infrastructure without the internal investment. Interestingly, some organizations are developing tools to act as a matchmaker between nonprofits and CROs to accelerate the process of finding the right organization, such as the Alzheimer's Drug Discovery Foundation ACCESS program. However, if the internal staff is mid-sized and well versed in the field but does not have the bandwidth to provide day-to-day management or oversight, investing in for-profit companies is a viable option to make an impact within the field. Nonprofits with a large staff and the capacity to provide a high degree of internal support can assume a more hands-on approach through three potential avenues.

HOW ACTIVELY INVOLVED DO YOU WANT TO BE?

For nonprofits looking to actively manage drug development efforts in areas with a high geographic density of scientific programs in relevant fields, establishing an incubator could be effective. Because an incubator requires a critical mass of emerging projects, this activity should be limited to areas with many universities and/or programs churning out potential assets to ensure a sustainable future. However, nonprofits that want to play an active role, but do not necessarily operate in a field or location with a high geographic density of discoveries, can achieve equal impact with both the in-house R&D and supporter models. However, the choice between the two will depend on the amount of internal infrastructure the organization is able and willing to build.

COMPLETING THE PUZZLE

Determining the Best Funding Mechanism

Nonprofits are increasingly employing principles first described in the financial world, using different mechanisms to distribute capital or resources to best match their activities or desired outcomes. In the complex world of nonprofit drug development activities, choosing the right funding mechanism can be imperative to success. The intersection of both the desire to accelerate progress and the need to create a sustainable program helps to drive the decision-making process. Below, we outline and illustrate the funding mechanisms most suitable for each activity (Figure 5).

Figure 5: Funding Mechanisms in Drug Development
How should nonprofits fund their activities in the drug development process?

MECHANISM	MODEL: Academic Support	Supporter	Incubator	CRO	In-House R&D	For-Profit Support
Gifts	✓	✓		✓		✓
Venture Philanthropy	✓	✓	✓	✓		✓
Self-Funded				✓	✓	

ACADEMIC SUPPORT

Grants or gifts are the most common mechanism for funding academic drug development efforts, providing the most flexibility for the investigator to design the experiment and to interact with additional partners. Although possible, venture philanthropy investments often require more formalized contracts and interactions with technology transfer offices at the originating academic institutions.

SUPPORTER

Both grants and venture philanthropy investments are common within the supporter role because the resources provided are vital to the drug development process and can lead to a successful partnership or funding opportunity.

INCUBATOR

Incubators nearly exclusively operate through venture philanthropy, because it is difficult to sustain such an expensive program without a return on investment. However, examples of nonprofits partnering with for-profit incubators to create a hybrid model do exist.

CRO

All three funding mechanisms are utilized to support this activity. Grants and venture philanthropy investments are appropriate to use as a funding mechanism when outsourcing critical preclinical activities to a CRO. Alternatively, a nonprofit CRO is, by definition, self-funded.

IN-HOUSE R&D

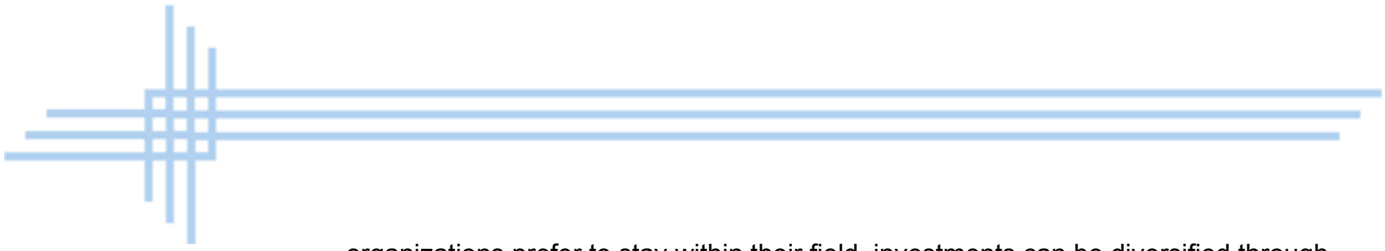
Because these programs are internal to the nonprofit itself, the funding mechanism is exclusively through self-funding.

FOR-PROFIT DEVELOPMENT

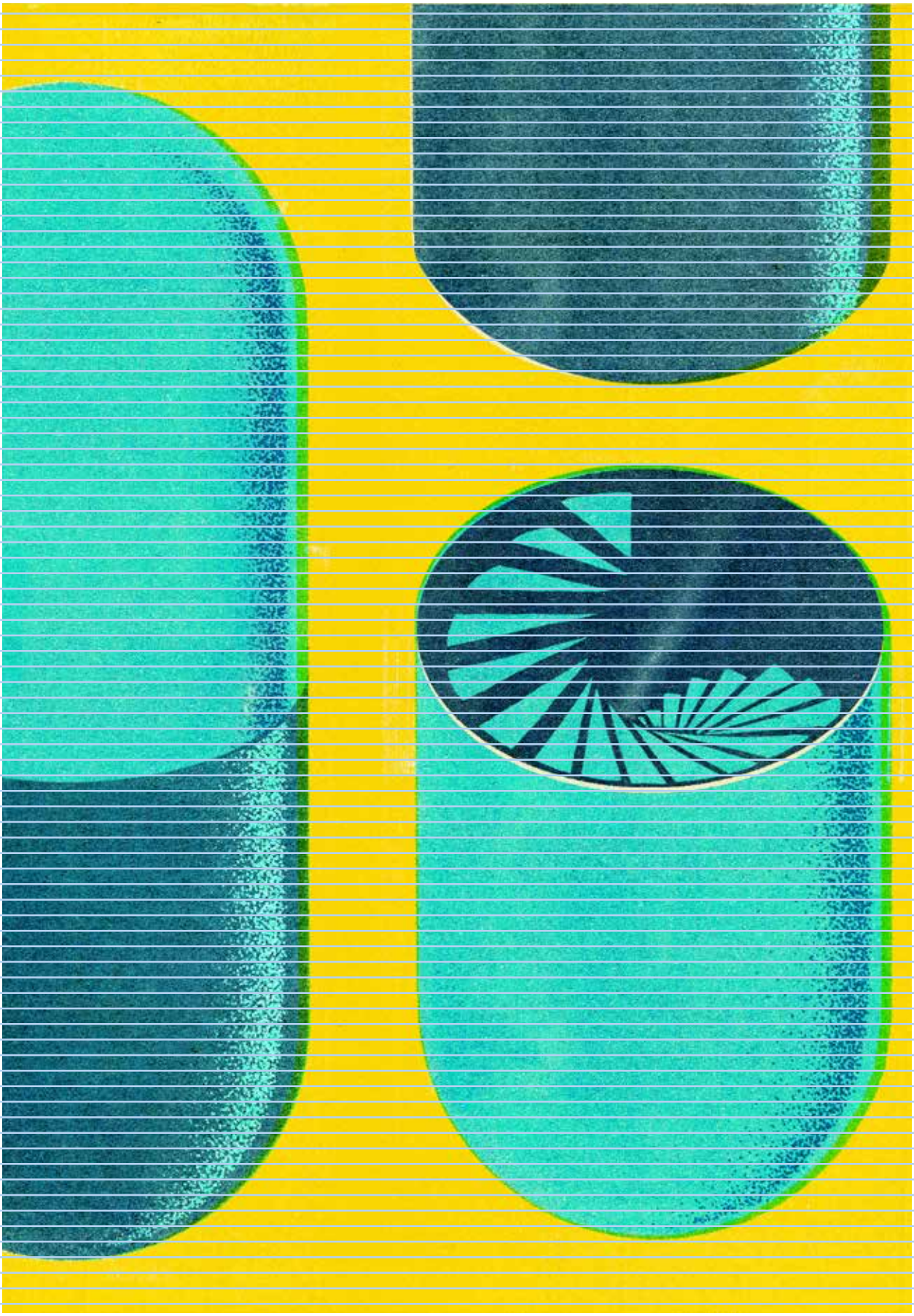
The majority of financial support of for-profit companies is provided through venture philanthropy because the intellectual property is often more defined; however, grants can be awarded if the nonprofit is interested in providing capital with no strings attached.

A venture philanthropy approach allows nonprofits to generate a financial return, which can be recycled back into the organization. However, a comparatively larger investment is typically required for this approach, because projects are more expensive in these validation stages.

Many successful nonprofits have followed a portfolio approach to for-profit investments to mitigate the overall risk of these investments. Although there are limitations to the breadth of the portfolio, because many disease-focused



organizations prefer to stay within their field, investments can be diversified through different targets, mechanisms of action, or drug modality. As maintaining a portfolio of for-profit investments requires significant capital, most nonprofit organizations have found that this approach requires either robust fundraising efforts or an endowment.



CHAMPIONS OF DRUG DEVELOPMENT

Through our analysis, we encountered numerous innovative ways in which nonprofits fund and participate in preclinical drug development to advance therapeutics through the Valley of Death. They fund academic inquiries, CRO outsourcing, and for-profit development efforts. They act as incubators and supporters of academic entrepreneurs to create the network, resources, and education needed for success. Some nonprofits maintain their own drug development hubs. Nonprofits combine these activities with three broad financial mechanisms: gifts/grants, venture philanthropy investments, and self-funding, which can be applied to provide unencumbered support, de-risk a promising asset, or take on an internal program that others are overlooking.

Nonprofits are tackling some of the greatest problems in R&D and are achieving great success, bringing new therapeutics into the pipeline and allowing more robust, rigorous preclinical science to take place. Nonprofits are setting the groundwork for expanding efforts into the clinical space and can do so by applying the same careful and tactical approaches to the evolving problems and reaching the finish line. We are excited to see the advancement of biomedical research that is due to nonprofit efforts, the development of new treatments and cures long awaited by patients, and ultimately new nonprofit players embarking on therapeutic development to create hope and progress for their communities.

ABOUT THE AUTHORS

Cara Altimus is a director at the Milken Institute Center for Strategic Philanthropy. Utilizing her expertise in neuroscience, Dr. Altimus advises individual philanthropists and foundations on the state of research for various disease areas to help them identify opportunities for giving. Altimus has more than a decade of experience in neuroscience research, including neurological devices, psychiatric illness, learning and memory, as well as sleep and circadian rhythms. Most recently, Altimus worked at the Food and Drug Administration leading the Neural Interfaces Laboratory, which evaluates the safety and effectiveness of electrical stimulation methods in the brain. She serves as an advisor to the Ontario Brain Institute, and the NIH SPARC program, as well as the chair for the Trainee Advisory Committee for the Society for Neuroscience. Previously, she spent a year as an AAAS Science and Technology Policy Fellow developing a neuroscience research portfolio at the Department of Justice. Altimus holds a bachelor's degree in genetics from the University of Georgia and a doctorate in biology from Johns Hopkins University.

Kirstie Keller is a senior associate at the Milken Institute Center for Strategic Philanthropy biomedical science team. Dr. Keller comes to the Institute with over ten years of biomedical research and consulting experience in fields ranging from cancer cell metabolism and bacterial pathogenesis to strategic planning and organizational design. At the Milken Institute, she has led work on the Alzheimer's Disease Giving Smarter Program, the Nonprofit Drug Development portfolio, and the strategic planning efforts of the Breast Cancer Research Foundation. Keller received her BSc in biology from Gonzaga University and her doctoral degree in biology from Johns Hopkins University, where she studied cancer cell metabolism and developed a novel method for identifying protein-metabolite interactions. Additionally, she completed a post-doctoral fellowship at the Johns Hopkins School of Medicine studying the regulation of a unique protease found in pathogenic bacteria.

LaTese Briggs is the senior director of strategy and programs at the Milken Institute Center for Strategic Philanthropy. She has more than 15 years of experience in biomedical research and philanthropy. Dr. Briggs leads initiatives focused on maximizing return on philanthropic investment by creatively leveraging innovations used to address one social issue and translating them to others, executing on best practices, and developing key performance indicators. Briggs previously served as a pharmaceutical market analyst for Decision Resources, a Boston-based research and consulting firm serving the biopharmaceutical industry. In this capacity, she provided expert analytics on the state of research and clinical development, including research challenges, market drivers, and unmet patient needs in the infectious disease space. She is trained as a biochemist, having completed her doctoral studies at the University of Maryland Baltimore County and then postdoctoral training at Harvard University/ Broad Institute focusing on chemical biology and early drug discovery. She has authored several scientific articles and received a number of honors, including being named a Bill & Melinda Gates Millennium Scholar.

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