New Financing and Business Models to Accelerate the Development of Novel Therapeutics

by

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Submitted to the Institute for Data, Systems, and Society in partial fulfillment of the requirements for the degree of

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Abstract

Many obstacles contribute to the uncertainty and risk associated with early drug development, leading to the "valley of death" in which promising drug candidates experience difficulties in reaching the market. These challenges have serious consequences for patient populations facing significant unmet medical needs. In this paper, we highlight three models that offer innovative financing mechanisms or new business models for early stage biopharmaceutical assets. Specifically, we evaluate and profile examples of venture philanthropy and academic-industry partnerships as sources of financial capital for early stage assets. In addition, we identify a "one-disease" business model in biotechnology that can mitigate risk and accelerate the translation of biomedical research into novel therapeutics. The three examples highlight the potential for creative mission-driven models to speed up drug development and provide capital in the earliest, and often riskiest, stages of drug development. These models are collaborative and leverage the expertise of the various stakeholders in the process, including patient advocates, private sector drug developers, and academic researchers.

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## Contents

1 Introduction .................................. 15
   1.1 Motivation .................................. 15
   1.2 Challenges of Drug Development ......... 16
   1.3 Drug Development Financing ............... 16
   1.4 Policy Approaches ......................... 17
   1.5 Thesis Overview ............................ 19

2 Methodology .................................. 21
   2.1 Case Study Methodology ................... 21
   2.2 Case Selection ............................. 21
   2.3 Interviews .................................. 22
   2.4 Data Collection and Synthesis .......... 22

3 One-Disease Business Models: Solid Biosciences 23
   3.1 Introduction ............................... 23
   3.2 Background ................................ 25
      3.2.1 Duchenne Muscular Dystrophy ....... 26
   3.3 Company History ........................... 26
   3.4 Company Funding and Operations ....... 28
      3.4.1 Company Management ................ 29
   3.5 The Solid Portfolio ....................... 30
      3.5.1 Corrective Therapies and Solid GT .. 31
      3.5.2 Disease Modifying Therapies ........ 32
      3.5.3 Assistive Devices .................... 32
3.5.4 Disease Understanding .................................................. 33
3.6 Analysis of Business Model ............................................. 33
  3.6.1 Keys to Success .......................................................... 35
  3.6.2 Patient Perspective ....................................................... 36
3.7 Challenges and Future Plans ............................................ 36
3.8 Conclusion ........................................................................ 38

4 Academic-Industry Partnerships: Stanford SPARK Program 41
  4.1 Introduction .................................................................... 41
  4.2 Translational Medicine Background ................................. 43
  4.3 The Origin and Mission of SPARK ................................. 46
  4.4 How SPARK Operates .................................................... 47
    4.4.1 Management ............................................................. 48
    4.4.2 The Advisors ........................................................... 48
    4.4.3 Funding .................................................................. 49
    4.4.4 SPARK and the Office of Technology Licensing ........... 51
    4.4.5 On SPARK’s Culture ................................................... 51
  4.5 Project Selection ............................................................. 52
  4.6 Program Results and Benefits ........................................ 54
    4.6.1 Implications for Stanford ........................................... 55
    4.6.2 Keys to Success ........................................................ 57
  4.7 Challenges and Future Plans ............................................ 58
    4.7.1 Financing ................................................................. 58
    4.7.2 Institutional Support .................................................. 58
    4.7.3 Measuring Success .................................................... 59
    4.7.4 Growing the Program ................................................ 60
5 Venture Philanthropy: Cystic Fibrosis Foundation

5.1 Introduction ............................................ 63
5.2 Overview of Cystic Fibrosis ............................... 66
5.3 History of the Cystic Fibrosis Foundation ............... 67
5.4 The CFF’s Venture Philanthropy Model .................... 68
  5.4.1 Agreement Structure ................................ 68
  5.4.2 Emphasis on Providing Clinical Expertise ............ 70
  5.4.3 Portfolio Approach .................................. 70
  5.4.4 Patient-Centered Focus ............................... 72
  5.4.5 Measuring Impact .................................... 73
5.5 The CFF and Vertex Collaboration ........................ 74
  5.5.1 Decision to Collaborate ................................ 74
  5.5.2 Development of Kalydeco .............................. 75
  5.5.3 CFF Support .......................................... 77
5.6 The Royalty Sale Strategy .................................. 77
  5.6.1 Agreement Structure .................................. 79
  5.6.2 CFFT Rationale for Monetization ...................... 79
  5.6.3 Royalty Pharma Rationale for Investment ............... 79
5.7 Lessons Learned ........................................... 80
  5.7.1 Best Practices ........................................ 81
  5.7.2 Another Example: Profile of the SMA Foundation ..... 83
5.8 Looking Ahead ............................................. 84
6 Conclusion

A Profiles of Selected SPARK Projects

A.1 Project Profile 1: Licensing to an Existing Company ........................................ 93
A.2 Project Profile 2: Entering a Clinical Trial ....................................................... 95
A.3 Project Profile 3: Technical Failure ................................................................. 97

B CFF Case Study Supplementary Materials

B.1 CFF Therapy Pipeline ......................................................................................... 99
B.2 Scope of the Ionis-SMA Foundation Collaboration ............................................ 100

C Bios of Interviewees

B.1 Solid .................................................................................................................. 103
B.2 SPARK .............................................................................................................. 106
B.3 CFF ................................................................................................................... 111

D Additional Acknowledgements and Notes ........................................................... 117
List of Figures

3-1 Solid’s Key Company Milestones .................................................. 27
3-2 Solid’s Company Structure .......................................................... 29
3-3 Solid’s Disease Modifying Therapy Approach .............................. 32
3-4 Solid’s complementary approaches under a one-condition focus .... 34
4-1 SPARK fills the gap between academic discovery and industry ....... 45
4-2 SPARK has generated significant follow-on grants, 2007–2015 ......... 50
4-3 (A) Distribution of SPARK projects by clinical indication.
    (B) A majority (65%) of SPARK projects address child or maternal health (39%),
        orphan diseases (34%), or global health (21%) ............................ 53
4-4 Distribution of graduated SPARK project outcomes ..................... 54
5-1 Median Predicted Survival Age of People with CF over Time .......... 66
5-2 Distribution of CFFT Portfolio as of February 2017 ....................... 71
5-3 CFFT’s Funding for Research Grants v.s. Therapeutics Development Program Awards from 2010 to 2015 ................................. 72
5-4 Abridged Timeline of Kalydeco Development .............................. 76
5-5 CFF Public Support Funding ....................................................... 86
B-1 CFTR-Targeting Pipeline as of February 2017 .............................. 99
List of Tables

4-1 Breakdown of “failed” SPARK faculty projects (N = 28) .......................... 60

5-1 CFFT Royalty Revenues and Sales ..................................................... 73
Chapter 1

Introduction

1.1 Motivation

In the past few decades, the pace of life sciences basic research progress has led to incredible advances with promising implications for the practice of medicine [1]. Universities are advancing basic science discoveries that can be translated into exciting new technologies and therapies for patients. The decreasing cost of and increasing potential of genome sequencing along with new technologies, such as CRISPR gene editing, and significant improvements to gene therapies, have the potential to deliver cures that correct the root cause of debilitating and fatal diseases.

However, many barriers exist that stymie biomedical research from being developed into new drugs or products reaching patients. Despite an overall increase in total NIH funding for biomedical research over the past few decades, the number of drug approvals has not risen accordingly [2]. Further, biopharmaceutical companies are pressured to make decisions about which programs in their portfolio to pursue and develop into therapeutics. With limited capital and resources, biotechnology firms make decisions that will maximize their likelihood of success and financial outcomes. This thesis seeks to address the obstacles to translational medicine, with a focus on early projects that fail to progress due to lack of funding and de-risking expertise. In evaluating various innovations and new models, we particularly highlight applications of best practices in financial engineering that can help accelerate medical discoveries and drug development.

The profiled examples include academic-industry partnerships, new biotechnology business models, and financing through the use of venture philanthropy. These models can help bridge gaps between stakeholders, facilitate an exchange in expertise, and provide strategic funds at key milestones in drug development. Two of the three examples we highlight focus on models addressing rare diseases, which are those defined by the FDA as affecting less than 200,000 individuals in the U.S [3].
1.2 Challenges of Drug Development

Drug development is a laborious and risky process, with the majority of potential preclinical candidates never receiving FDA approval. In order for a drug to be approved in the U.S., an asset must undergo three phases of a clinical trial to meet the FDA’s standard of safety and efficacy.

Development of an asset to approval often takes more than ten years [1], requiring significant capital and work from discovery to FDA approval. In recent years, the number of FDA approvals of new therapeutics has been on the order of low to mid 20’s [4]. At the same time, the costs of drug development have been rising over time, with estimates citing over $2 billion to take an asset to approval [5].

According to Hay [6], the likelihood of approval for a new drug from phase 1 is about 10-15%. This does not take into account the steps required for an asset to become a clinical stage asset or to enter phase 1 trials. Hay’s analysis calculates probabilities of transition between phases of a clinical trial and ultimate approval. While the transition probabilities individually range from 30% to nearly 86%, in aggregate, the likelihood of approval from a phase 1 stage compounds the various transitions, thus resulting in a significantly lower probability.

1.3 Drug Development Financing

In recent years, studies suggest that pharmaceutical research and development productivity is low [4] and as a result, large companies are conducting less of the earliest stages, and often riskiest, of drug development [7]. The gap is being addressed by biotechnology companies, who are taking on the early stage research and development burden. Once the assets are sufficiently de-risked, pharmaceutical companies have been acquiring biotechnology companies to fill their pipeline, resulting in increased merger and acquisition activity in the industry [7].

The pharmaceutical industry is facing challenges now that the blockbuster era is over and perceived “low-hanging fruit” of drug development are gone [8]. While there are significant unmet medical needs to be addressed, companies must make decisions to maximize commercial
return. As a result, incremental improvements in therapies are sometimes pursued over
breakthrough therapies for unmet, but perhaps less lucrative, needs.

Early stage companies must seek investment or partner with large pharmaceutical
companies in order to carry out the necessary development steps, including clinical trials, to
reach the market. Many venture capital investors are focusing on clinical-stage assets [1], leaving
a gap for the earliest stage drug development projects. Within the context of increasing
innovations and capabilities stemming from biomedical research, the trend is discouraging for
early stage firms seeking investments. Academia, on the other hand, tends to do earlier stages of
target identification [7] rather than validation, which is a key step for translation and is often
conducted by early stage companies.

The valley of death has particularly been a problem for categories of diseases such as rare
conditions and global health. The intuition is that biopharmaceutical companies are hesitant to
allocate significant resources and time to develop drugs with unattractive commercial upside.
Developing a drug for rare diseases, for a population of a few thousand, may take as long and be
as costly as developing a drug for millions of patients. Further, because of the small patient size
and lack of clinical development precedent in many rare and orphan disease categories,
biotechnology firms will face challenges of being a first entrant into the space in addition to
having to design and recruit clinical trials to accommodate so few patients.

1.4 Policy Approaches

The patient community for rare diseases, by necessity, has been particularly well-
mobilized and active. Disease-focused non-profits have been active in fundraising but also with
lobbying and advocacy efforts. Many engage with legislators in Washington D.C. and advocate
for policies that increase funding for biomedical research, incentivize R&D in drug development,
and improve FDA approval processes, among many issues. While one part of the drug
development ecosystem, medical non-profits have been effective in supporting and influencing
key legislation to support their mission. Some of the significant legislation include the FDA’s
priority review program and the Orphan Drug Act of 1983. More recently, the FDASIA
legislation and 21st Century Cures Act, were passed with the goal of speeding up the rate of drug
development and subsequent approvals. The passage of the Orphan Drug Act of 1983 has been
successful in approving hundreds of new rare and orphan drugs [9]. The legislation has made rare disease drug development commercially attractive and the indications in this category are now one of the most active among drug developers [7].

The NIH also attempts to address translational medicine. Within the organization, they have established National Center for Advancing Translational Science (NCATS), focused on translating science into products. The initiative, founded in 2012, has worked on various projects and programs in order to accelerate drug development, particularly for unmet needs and areas where the private sector is not active.

The focus of our research is on the development of novel therapeutics for unmet medical need rather than therapeutics that provide incremental improvements. In particular, our work has focused on unmet needs posed by the numerous rare diseases without any available treatments. In aggregate, the category presents significant medical need and impacts nearly 30 million individuals in the U.S. Of the known 7000+ diseases in this category, only 500 have any treatments at all [9].

In addition, we find that there are several aspects of the rare and orphan category that are amenable to accelerated drug development and adoption of new financing and business innovations. As discussed earlier, one reason is that the rare disease patient community is incredibly well-mobilized. Historically, because of the small community and private sector neglect, the rare and orphan advocacy groups have been forced to be innovative in the ways that they extend their resources to make and sustain impact. Accordingly, they have been able to leverage significant disease expertise and access to the larger patient community, which offers advantages for drug development firms. From a technical perspective, many rare and orphan diseases are caused by mutations to a single gene, which may provide a clearer drug development pathway. Finally, regulatory incentives have paved the way for lucrative commercial opportunities for firms that are able to bring orphan drugs to the market. For all of these reasons, we find that the business model and financing innovations highlighted in this thesis could particularly be well-suited for rare diseases.
1.5 Thesis Overview

While translational medicine faces many obstacles, the key motivation of our research was the issue of the valley of death in early stage biotech. This problem is caused by a number of reasons including lack of financing or high risk of taking on early stage projects. As discussed in earlier sections, this is mainly problematic in that it adds a bottleneck to the translational process for potentially promising therapies. The core research question we hoped to address was whether financial engineering and new business models can help allay this problem. In tandem with financial and business innovations, these models can establish partnerships and expertise that facilitate faster progress in drug development. Our research aims to explore whether new solutions can accelerate the pace of translational medicine. In particular, we expect that these models can cover gaps in early stage financing and de-risk drug development.

To achieve our aims, we conduct literature reviews on drug development and employ the methodology of developing case studies to conduct deep dives into specific innovations in financing or de-risking of early stage therapeutics, with an emphasis on rare diseases. De-risking early stage therapeutics is especially significant in that it can lower the bar for subsequent investments and de-risk an asset for investors.

We profiled three cases to illustrate new financing vehicles and business models: Stanford’s SPARK program, biotechnology company Solid Biosciences, and the Cystic Fibrosis Foundation’s venture philanthropy work. The three cases represent various members of the drug development community, including a university, a drug development company, and a disease-focused non-profit. All three cases also represent early adopters of the innovations of focus. In SPARK, we profile a novel university-industry partnership that provides strategic advice and financing of basic science projects with translational potential. Solid Biosciences is a firm solely focused on Duchenne muscular dystrophy with a strategic application of one of the key principles of financial engineering, diversification or a portfolio approach. The Cystic Fibrosis Foundation case highlights the use of venture philanthropy as a financial vehicle for funding early stage biotechnology.

We found that few studies in the literature systematically study and analyze these case examples from a management lens, and we aimed to fill the gap. In particular, we wanted to analyze key aspects of the operations, the impact of these examples, key drivers of success, and
recommendations for the greater drug development community. Further, we saw the opportunity to add our perspective as researchers approaching the cases from a financial and business point of view. We ultimately hope that these case studies can be didactic examples for others to adopt or learn from. These case studies contribute to the larger literature of translational medicine research by highlighting efforts of novel models that de-risk drug development and provide access to capital at the earliest stages.
Chapter 2

Methodology

2.1 Case Study Methodology

The primary methodology used in this research was the development of case studies. The format lent itself well for deep analyses of specific innovations and examples that we aimed to highlight. Further, a case study’s final product was amenable to our goals of readily reaching our target audience of various stakeholders in the drug development community.

Eisenhardt [10] states that a case study allows you to “understand the dynamics” within one specific example or setting. Analyzing both qualitative and quantitative aspects of a case, we aimed to construct an understanding of an organization’s key drivers and characteristics. The research strategy allows a rigorous analysis of relatively new innovations, for which a larger sample may not yet be available for alternative research methodologies.

The format is particularly useful for a deep dive into a single phenomenon or innovation. Case studies are often used in the social sciences for an in-depth analysis of a practice within its “natural context” [11]. Such a format may be more appropriate for analysis of a management or business phenomenon over a controlled experimental study.

2.2 Case Selection

We chose a selection of cases to highlight innovations in financing and business models of translational medicine. The cases that we analyze in this thesis are well-recognized examples and considered distinctive in the larger drug development community. We sought examples of models that could help us evaluate our hypothesis that financial engineering and new business models could accelerate progression of promising biomedical research into therapeutics with patient impact. Cases were selected based on an organization’s position as an early adopter of an innovative model and the relative uniqueness of the model in the industry. We also selected cases
that we thought could be applicable and useful for other stakeholders to implement or adopt. We profiled cases with the explicit permission of the profiled organization or company.

2.3 Interviews

After selecting cases, we identified a research plan, goals, and an outline for the final case study product. Then, we mapped out the various stakeholders that were relevant to achieving a balanced and thorough view of the example. Subsequently, we developed interview questions for the selected type of stakeholders.

The questions we constructed generally aimed to understand the following components of a case example: the background and history, the motivations, the decision-making, operations and structure of an organization, challenges and future plans, and keys to success.

2.4 Data Collection and Synthesis

Whenever possible, we collected data that would help achieve our goals of understanding case examples and the various financial and business innovations relevant to the examples. For instance, we often had access to some data related to an organization’s investment portfolio or research and development pipeline. When relevant and illustrative to our argument, we include the data in the case study.

While the MIT Laboratory for Financial Engineering research team synthesized the final output and generated independent insights, we provided interviewees opportunities to review the written material to correct inaccuracies and provide feedback.
Chapter 3

One-Disease Business Model: Solid Biosciences

Abstract

Duchenne muscular dystrophy (DMD) is a rare genetic disorder affecting thousands of individuals, mainly young males, worldwide. Currently, the disease has no cure, and is fatal in all cases. Advances in our understanding of the disease and innovations in basic science have recently allowed biotechnology companies to pursue promising treatment candidates for the disease, but so far, only one drug with limited application has achieved FDA approval. In this case study, we profile the work of an early-stage life sciences company, Solid Biosciences, founded by a father of a young boy with DMD. In particular, we discuss Solid’s one-disease focus and its strategy to treat the disease with a diversified portfolio of approaches. The company is currently building a product pipeline consisting of genetic interventions, small molecules and biologics, and assistive devices, each aimed at addressing a different aspect of DMD. We highlight the potential for Solid’s business model and portfolio to achieve breakthrough treatments for the DMD patient community.

3.1 Introduction

Drug development is a risky and costly endeavor, requiring more than 10 years and $2.5 billion for a single successful candidate to reach the market [5]. The process is capital-intensive, each milestone on a drug candidate’s timeline requiring millions of dollars for such items as discovery, animal model studies, clinical trials, regulatory filings, and marketing and sales. As a result, biopharma companies have generally focused on developing assets for lucrative and usually large markets [12]. In recent years, however, policy incentives and strong opportunities for commercialization have driven biopharma companies to increase research and development
for rare and orphan diseases [13], which affect smaller populations, but present significant unmet medical needs.

Historically, orphan and rare diseases, defined by the FDA as diseases with fewer than two hundred thousand cases in the U.S., have largely been neglected, since drug developers have had little incentive to develop treatments for so few patients. Currently, 7,000 of these rare diseases affect a total of 30 million individuals in the U.S. [14]. In 1983, congressional legislation created the FDA’s Orphan Drug Designation, which gives incentives to orphan drug developers to develop treatments for rare diseases. Despite this progress, developers of drugs for rare diseases (now including big pharma and biotechnology companies) still face significant scientific and financial risks, and many rare diseases still present significant unmet needs. Among the diseases still without a proven and effective U.S.-approved treatment is Duchenne muscular dystrophy (DMD), a fatal and rare genetic disease with an incidence of approximately 1 in 5,000 males, primarily among young boys, worldwide [15].

In recent years, the FDA has announced the possibility of accelerated approval for DMD drug candidates. This is an attempt to create incentives and stimulate development of therapies for the DMD patient population. The extended DMD community has been waiting for a treatment for decades [16]. Recently, there has been an increase in momentum in DMD drug development, with a handful of companies actively developing treatments for DMD patients. The persistent involvement and advocacy of the DMD patient community underscores the urgent need for a successful treatment.

This need is still unmet. In the past year, the FDA has rejected initially promising drug candidates from PTC and BioMarin, candidates that had been championed by the DMD patient community. In a recent victory for the community, however, Sarepta, another company working on DMD drug development, has gained accelerated approval from the FDA for its drug, eteplirsen, which targets approximately 13% of DMD patients. Nevertheless, the company must continue to run studies to show the safety and efficacy of the drug, and the approval may be subject to withdrawal based on further findings.

In this case study, we discuss the work of one life sciences company, DMD-focused Solid Biosciences, founded by the parents of a young boy with DMD. This young company has achieved several promising early successes. We highlight its unique business model and its potential to achieve further breakthroughs in developing long-awaited DMD treatments.
Specifically, we emphasize Solid Biosciences’ one-disease focus and modality-agnostic approach to developing drug candidates for DMD. We analyze the potential of this model to mitigate the challenges associated with drug development and successfully bring to market treatments for patients with rare diseases.

3.2 Background

Rare and orphan diseases are defined by the FDA as those that affect fewer than 200,000 individuals in the United States. Starting in 1983, congressional legislation has created policy mechanisms to accelerate innovation and development for rare diseases with target populations too small to financially justify large research and development programs. Through this legislation, the Orphan Drug Designation was created, which provides seven years of market exclusivity for the first developer to achieve approval for a candidate. Since the legislation was enacted, more than 500 orphan drugs have been approved [9], compared to just 10 between 1973 and 1983 [3]. Companies that have developed these drugs have done quite well during the exclusivity period [13], offering an attractive investment for investors and the biopharma companies that develop the drugs. While some of the candidates that fall under this category are novel, others are part of partially developed asset programs that had been previously shut down, or are candidates initially developed for other indications.

Despite the success of the Orphan Drug Designation, there are still many untapped opportunities in drug development, particularly for rare and orphan diseases. Declining research and development activity in the pharmaceutical industry has resulted in many promising early-stage candidates that fail to advance to the clinic for further study, let alone to patients. Because of the significant cost and time required for drug development, investors are more likely to fund later-stage assets that have achieved proof of concept, or those assets that have the potential to become blockbuster drugs. Meanwhile, mergers and acquisitions in the pharmaceutical industry have become increasingly common, and large biopharma and biotech companies often acquire the early work of smaller biotech companies that do the early development and “de-risking” of assets. With pharmaceutical companies losing significant value due to stagnant R&D productivity [17] and investors averse to early-stage assets, there is a significant lost opportunity in the development of potential therapies for patients. However, recent trends show that the
pharmaceutical industry is experiencing economically favorable returns with orphan drugs [13] and, as a result, unaddressed rare and orphan indications offer a potentially lucrative area for future drug development.

3.2.1 Duchenne Muscular Dystrophy

Duchenne muscular dystrophy is a severely debilitating muscle disease caused by a genetic mutation on the X chromosome, resulting in the lack of dystrophin, a protein that is critical for establishing muscle stability [18]. Currently, there is only one approved treatment for a small subset of DMD patients and no cure in the United States for this rare disease, which disproportionately affects young boys (and in rare cases, girls). The current standard of care involves palliative options and the use of steroids, which result in significant side effects in children. Despite its classification, DMD is one of the more prevalent “rare” diseases in the U.S., and places a significant disease burden on families, communities, and the healthcare system. The disease is fatal in all boys, most requiring wheelchairs by age [12] and dying due to heart failure or respiratory difficulties in their twenties [18]. It is estimated that approximately 10,000-15,000 boys suffer from DMD in the U.S., translating to a national economic burden of nearly $500-800 million annually [19].

3.3 Company History

Solid Biosciences is a private life sciences company based in the Kendall Square biotech hub in Cambridge, Massachusetts. The company was founded by Ilan Ganot, Gilad Hayeem, and Andrey Zarur soon after Ganot’s son was diagnosed with DMD in 2012. The company’s name, Solid, is the English translation of his son’s Hebrew name, Eytani.

As a parent, Ganot was frustrated with the lack of progress in DMD drug development, but as Solid’s future CEO, he also saw a commercial opportunity for a new company that would address this unmet medical need. Ganot initially considered other vehicles to make a contribution to DMD research and development. Prior to founding Solid, Ganot had been an investment banker with JPMorgan Chase, and had years of experience in corporate finance and structuring.
deals. The early Solid team considered a range of options for making a contribution to DMD research and development, from creating a nonprofit organization to establishing an investment firm, before ultimately deciding that a hands-on drug development company would maximize its impact on the DMD population. With that, Solid's current business model was born.

Soon after founding Solid, Ganot discovered that many pharmaceutical companies and academic institutions had promising early-stage investigational candidates for DMD that had stalled in development. Ganot and his first hire, Joel Schneider, a former graduate student in DMD research, now a director of Solid's research and development program, reviewed the landscape of DMD assets for potential breakthrough applications, including gene therapy. The company ultimately decided to in-license intellectual property for a gene therapy candidate for DMD. Soon after, Ganot convened a conference with many of the major DMD researchers working on gene therapy in the U.S., leading to some of Solid's first academic partnerships.

Since its founding in 2013, Solid has established itself as a center of excellence for DMD research and drug development. It currently operates four platforms: Assistive Devices, currently developing the Solid Suit, a DMD assistive device; Disease Modifying Therapies, for biologic and small molecule assets that address the multiple secondary disorders that result from DMD; Disease Understanding, which strives to use biomarkers to improve diagnostes and the understanding of the impact of therapy; and Corrective Therapies, which includes its gene therapy platform under the company's subsidiary, Solid GT.
Based on its proposed business plan and its articulation of an unmet need in DMD, Solid Biosciences was able to raise $17 million in its Series A fundraising in 2013. A critical early backer of Solid was JPMorgan, Ganot’s employer at the time he learned of Eytani’s diagnosis. JPMorgan invested $5 million into the Series A round for Solid, and it currently holds a seat on Solid’s board of directors. In addition, Gilad Hayeem, one of the company’s cofounders, and current board member Matthew Arnold, each invested in the round. The two are currently the biggest individual shareholders of the company.

The backing of JPMorgan was critical in Solid’s early stages. It was an uncharacteristic step for the financial services firm, which does not typically participate in one-off venture investing, let alone in an employee venture. However, JPMorgan was preparing for the IPO of a biotech company also working on DMD, and thus understood the business opportunity and its unmet medical need. Furthermore, Ganot’s story had percolated within the company and received internal support, including from JPMorgan’s CEO, Jamie Dimon. The investment did not fall neatly inside JPMorgan’s existing lines—not in the bank’s charitable investing unit, its impact investing department, or its private investments. Nevertheless, the firm’s senior executives believed investing in the cause was the right thing to do, and rallied behind Ganot and his family. Over the course of nine months, the details were ironed out and due diligence was completed, allowing JPMorgan to lead the first financing round.

One key early decision at Solid was to dive deep into gene therapy for DMD. Solid GT, a Solid Biosciences subsidiary, was formed, and in December 2014, a Series A round was completed. This complemented Solid Bioscience’s $5 million of investment with an additional $5 million of capital, which was invested in return for equity ownership of Solid GT by three prominent U.K.-based DMD charities: DMD Research Fund, DMD Children’s Trust, and Joining Jack. This partnership with DMD-focused organizations was instrumental in providing a promising start for Solid GT. Each organization, in addition to its capital, was able to provide expertise, leadership, and a keen sense of urgency.

In November 2015, Solid GT closed a $42.5 million Series B round, led by the investment fund Perceptive Advisors, which focuses on healthcare, and by the biotechnology company Biogen, to continue development of its Corrective Therapies platform. Unlike Solid
Biosciences’ first round of fundraising, the management team was able to raise money for Solid GT based on the progress of its scientific work, specifically, the promising preclinical data for its lead gene therapy candidate, SGT-001. Executives from Biogen and Perceptive Advisors have since joined the Solid GT Board of Directors.

3.4.1 Company Management

Solid Biosciences is an operating company, now with more than 25 employees, which oversees four platforms, Disease Modifying Therapies, Assistive Devices, Disease Understanding, and Corrective Therapies, the latter of which is held within Solid GT, a formal subsidiary of the Company. The platforms encompass Solid’s work in small molecules and biologics, assistive devices, biomarkers, and genetic interventions, respectively. The company operates under its CEO and management team, with active and regular participation by its board members. Ganot, the CEO, runs the day-to-day operations of the company. Gilad Hayeem, currently a Solid board member and its president, also runs the investment management firm Waverly Capital, based in New York City. Andrey Zarur currently serves as the chairman of the Solid Biosciences board. Business decisions and activities are initiated by the management team, and are reviewed by the management boards. Currently, there is a dedicated Board of Directors and Scientific Advisory Board for Solid’s subsidiary, Solid GT, in addition to the Board of Directors for the umbrella company, Solid Biosciences.

Figure 3-2: Solid’s Company Structure
3.5 The Solid Portfolio

Solid’s complete focus on understanding DMD gives it a unique edge when considering potential asset acquisitions and licenses. The management team naturally looks at groundbreaking science, commercial potential, and the likelihood of clinical success. However, the most important factor for Solid is that the science must have the potential to be translated into a therapy for DMD patients. A central tenet of Solid’s strategy is that if Solid focuses on the science with the most potential in DMD, financial reward will follow. In addition, because Solid is modality- and technology-agnostic, it is not tied down to any particular class of asset or scientific approach. This method has allowed the company to make quick shutdown decisions when data was unpromising or not indicative of future clinical success.

In general, when evaluating potential assets, Solid leverages its scientific expertise in DMD to pursue peer-reviewed research initiated and conducted by leading DMD researchers in the field. In addition to its business analysis of an asset (including the potential target market), the Solid team favors assets that have shown promise in animal models, or better still, that have promising human data. Because animal models are not perfectly indicative of an asset’s performance in humans, poor data from animal studies is not necessarily a deal breaker, if the scientific advisory and management team feels that there is potential efficacy for DMD patients.

Solid is able to make holistic decisions about assets. Key to this process is the expertise of the advisors, clinicians, and experts on Solid’s advisory board, who help to reduce risk when the management team is considering potential assets and making important decisions. Solid’s focus on a single disease has attracted a strong community of scientific and clinical experts, which provides Solid with a key strategic advantage in developing its portfolio of candidates.

Solid’s strength is its ability to focus its asset review on DMD alone. Because it knows the space and competitive landscape so well, Solid is able to avoid redundancy. While the company still actively researches and pursues potential in-licensing opportunities, Solid is now on the receiving end of licensing offers from other researchers and companies who are familiar with its work and focus on DMD.

Solid outsources research and development, helping to manage offsite labs, largely at academic research centers. Solid not only funds these labs, but also strategizes and thinks through scientific decisions with them, bringing its DMD expertise to the table. In alignment
with its strategy of being modality-agnostic, Solid has a portfolio ranging from genetic intervention and secondary disorder management to Solid Suit, an exoskeleton device for children with DMD to wear. As of 2016, Solid's assets are all in the preclinical stage, and represent a diverse range of potential solutions for DMD patients.

3.5.1 Corrective Therapies and Solid GT

Through its Corrective Therapies platform, Solid is pursuing therapeutic approaches that address the underlying cause of the disease to benefit as many DMD patients as possible. The company's biggest bet in this effort is the application of gene therapy to replace the defective gene responsible for DMD. Gene therapy was first shown to work in patients with melanoma in 1990 [20], but it still has not been approved in the U.S. In 2016, the European Medicines Agency (EMA) approved its second gene therapy, used for the treatment of a rare metabolic disorder, ADA-SCID, for the European market [21]. While gene therapy is still in its infancy, with challenges ranging from gene delivery in patients to manufacturing and production, Solid Biosciences sees recent advances in methods in the biotechnology industry as bringing about the "third wave" of gene therapy efforts.

Solid Bioscience's subsidiary, Solid GT, has made progress in Corrective Therapies for DMD. Thus far, it has been involved in successful preclinical animal studies of its lead gene therapy candidate, SGT-001. The data from these studies has helped Solid GT raise approximately $50 million for additional development, and the company plans to initiate clinical trials for SGT-001 in 2017. Significant challenges still remain for gene therapy. Challenges specific to DMD gene therapy include the systematic delivery of the gene to all affected muscles, as well as significant hurdles in manufacturing and immunological response to the therapy. Furthermore, there is the challenge that gene therapy, if successful for DMD patients, would only prevent further damage, but will not be able to address muscle degeneration that has already occurred.
3.5.2 Disease Modifying Therapies

In addition to its Corrective Therapies platform, Solid is building a pipeline of small molecule and biologic assets, which have the potential to address the secondary disorders that result from DMD (see Figure 3-3). Most of the assets, which must show utility in DMD, are or will be in-licensed from other organizations, or developed in partnership with other organizations. For example, in 2016 Solid established a collaboration with Strykagen to investigate Galectin-1, a preclinical biologic candidate that has the potential to improve muscle regeneration and repair through multiple biologic pathways.

![Symptoms Management Diagram](image_url)

Figure 3-3: Solid’s Disease Modifying Therapy Approach

3.5.3 Assistive Devices

Solid Biosciences’ assistive device platform focuses on devices that may help patients perform everyday activities with greater ease. The platform currently encompasses the company’s activities in developing an exoskeleton suit for children with DMD, called the Solid Suit. Solid added the suit to its portfolio after recognizing that patients were physically limited in ways that could be alleviated through an innovation like the Solid Suit. Unlike the other candidates in its portfolio, which address the biochemical causes of DMD, the Solid Suit addresses a previously unmet need discovered through its close interactions with the patient.
community. In fact, Parent Project Muscular Dystrophy, a leading U.S.-based patient advocacy group, founded by a mother of two sons with DMD, is one of the noteworthy partners in the development of the Solid Suit, providing unparalleled information, connections, and access to patients and opinions that continue to influence the development effort.

3.5.4 Disease Understanding

Solid’s Disease Understanding platform focuses on research and development to identify new potential biomarkers for measuring the progression of DMD. At present, many existing DMD clinical trials use expensive and invasive muscle biopsies to measure the dystrophin protein levels in affected patients. Alternatively, studies may employ gross motor function tests. However, these assessments do not necessarily provide biochemical information about the impact of a DMD therapy on the human body. Solid is looking to supplement current tests by examining potential DMD biomarkers in serum or urine to identify additional relevant clinical endpoints. While there is a growing amount research to identify DMD biomarkers [22], no effective serum and urine biomarkers have been validated for DMD clinical trials. The company hopes that its work will lead to an improved understanding of DMD’s disease progression and provide synergistic opportunities for enhanced clinical trials with their existing pipeline.

3.6 Analysis of Business Model

Solid Biosciences identifies itself as a disease-focused company that pursues multiple approaches with the potential to benefit DMD patients. As a “one-condition” company, Solid balances its singular focus with diversification in its research and development strategy. Its focus on a single disease gives the company a competitive advantage, and establishes it as a center of excellence for DMD, allowing it to gain significant business and scientific expertise in therapeutic development. Equally, Solid achieves strategic diversification in two ways: by targeting various points along the pathological cascade experienced by DMD patients, and by pursuing varied approaches to the treatment of DMD. It is able to achieve portfolio diversification by targeting distinct yet complementary approaches, while simultaneously
pursuing methods to better understand and measure the underlying biology of the disease. In addition, a diversified approach is consistent with Solid’s modality-agnostic strategy, not tying itself to any particular cure or technology platform.

A common model in the biopharmaceutical industry is to apply a compound or modality to as many different indications as possible. Solid takes the opposite approach, and applies as many viable modalities as possible to one disease. Solid’s strategy, in essence, is to take many well-selected “shots on goal,” all of which are complementary, and where one success does not take away from the possibility of success in other areas. While the DMD-causing gene mutation, and its subsequent pathology, have been well characterized, the reasons for the mutation are still unknown. While some mutations are hereditary, a significant portion occurs spontaneously [18]. Because of the heterogeneity in its disease biology, DMD, like many diseases, manifests and expresses itself in different ways in different patients. Furthermore, the mutation and the accompanying lack of the dystrophin protein result in numerous associated disorders that offer several targets for further research and development. As a result, Solid’s assets may be useful to address the various phenotypes and associated challenges of DMD patients.

Beyond the strategic approach of its portfolio, Solid’s one-disease model allows it to be efficient, nimble, and focused. Because it can convene the top scientific experts, key patient groups, and top talent, Solid is able to leverage this expertise to mitigate the many scientific and financial challenges associated with drug development.
3.6.1 Keys to Success

Like other biotech companies with responsibilities to its investors, Solid Biosciences defines success through its valuation, which is driven by scientific progress and reaching its milestones. As the parent of a son with DMD, Ilan Ganot is a strong parental advocate within the DMD community. His direct ties and personal understanding of the medical and human experiences of DMD patients enable the company to identify and tackle significant problems in the treatment of DMD. At the same time, as the CEO of a company focused on DMD, Ganot and his team must manage potential conflicts of interest. Solid has implemented measures to ensure its objectivity by creating a governance system to check and review management decisions. As a result of mitigating this risk, Ganot’s personal ties and motivation serve as assets when meeting with existing and potential investors, rather than potential conflicts.

Furthermore, the company has been able to assemble an impressive board and advisory committee of DMD experts, who not only provide credibility for its work, but also advise its management decisions. Solid has been successful in convening experts and encouraging collaborative work between them. Having the top DMD experts on its board to advise Solid provides it a significant advantage over biotech companies that may apply a technology platform more diffusely across several diseases.

Finally, an undeniable key to Solid’s success is Ganot’s single-minded determination to find a treatment for DMD, not only for his son, but for all patients with DMD. Under Ganot’s leadership, Solid is solely and genuinely focused on improving the lives of patients with DMD. This single-minded determination is reflected in the mission of the company, as well as its business strategy. Solid is successful because it focuses on the problem first, and then looks for the best solutions and approaches to solve it. To help operationalize this effort, Solid’s team consists of people who believe in its mission to treat DMD patients with the best therapies as quickly as possible, and are committed to developing a treatment for the DMD community.

Before Solid’s Series B fundraising, a number of pharmaceutical giants offered to partner with Solid and potentially buy it, based on the company’s promising SGT-001 gene therapy results. Solid turned down the offers in order to maintain its control of the development of its gene therapy platform. Selling an asset and leaving its future in the hands of another company does not align with Solid’s mission. Ganot had already observed that larger pharmaceutical companies
often choose not to pursue development of early-stage assets, whether due to risk, limited resources, or more attractive options in their vast portfolios.

3.6.2 Patient Perspective

An instrumental key to Solid’s success is its support from DMD patients, families and advocacy groups, which together comprise an extremely close-knit community. This support is not merely financial. For years, this community has joined forces to advocate for more research and progress in DMD drug development; and for years, it faced a series of disappointing updates, or worse, a lack of interest in this rare disease. Today, however, the drug development landscape is quite different, with many companies seeking to develop therapies for rare diseases, motivated not only by an unmet medical need, but also the promise of a significant return on investment.

For Solid Biosciences, the involvement of DMD patients and their parents is critical. Keeping the patient’s perspective in mind during development allows Solid to understand the true pain points of patients and the clinical effects of the current standard of care. Many of Solid’s employees maintain close ties with the patient community. The company’s employees regularly attend DMD patient conferences, and Annie Ganot, Eytani’s mother, heads Solid’s patient advocacy efforts, helping the company establish strong relationships with the DMD community globally. Furthermore, leaders of major DMD patient organizations have backed Solid by funding and advising its research and development activities. Examples include Parent Project Muscular Dystrophy, which invested in the Solid Suit and has collaborated with the company on other activities; DMD Research Fund; DMD Children’s Trust; Joining Jack, which co-founded Solid GT; and a number of additional partnerships with DMD groups worldwide. Solid’s one-condition focus has been instrumental in developing these partnerships with DMD patient organizations, which recognize Solid’s dedication and commitment to the same disease.

3.7 Challenges and Future Plans

Since 2013, Solid has achieved significant milestones and built a pipeline of promising assets with the potential to treat DMD patients. However, drug development is a risky and costly
endeavor for any company, and Solid Biosciences is no exception. Moreover, Ganot is a first-time CEO and a newcomer to drug development. As it stands, Solid relies heavily on partnerships with third-party companies, labs, and manufacturers for its work. In addition, like many biotech companies, Solid will need to rely on partners for its manufacturing and distribution capabilities. Because Solid’s mission is to reach the global DMD patient population, partnerships are considered the primary means to achieve this goal.

One criticism of the company is: with so many approaches, is Solid really able to focus its activities to achieve success? Solid, like other early biotech companies, has limited resources, and it must decide how to allocate funds across its portfolio. If it pursues too many assets and approaches, it risks limiting success in any given approach. From Solid’s perspective as a drug developer and patient advocate, however, it identifies the work that it finds most promising for DMD patients and attempts to bring it closer to market. As it grows and progresses, Solid will have to address increasing development costs as its assets enter the clinical stage. Furthermore, because of Ganot’s personal ties to the disease, Solid will need to continue to maintain its objectivity in its business decisions to select and shut down assets that no longer hold sufficient promise.

In order for Solid to bring a therapy to patients, it will also need to overcome the challenges of clinical development in human studies, which require significant time, personnel, creativity, and funds. So far, none of its candidates have yet entered the clinical stage, which will be a large milestone for the company. These studies cost millions of dollars, and Solid will need to raise the funds to design, initiate, and complete them. In particular, gene therapy, Solid’s biggest undertaking, will incur significant costs and resources in clinical trials.

Solid is also working to nurture further therapeutic innovation by training the next generation of leading researchers and scientists in DMD. It has established the Solid Fellows program, which trains postdoctoral researchers at universities currently active in DMD research, and it is setting up partnerships with universities to lay a foundation for continued and future DMD research. Part of Solid’s vision is to invest in academic research that could potentially lead to next-generation therapeutics for DMD patients. So far, the company has invested money in more than 15 academic research labs to continue and support DMD research.
3.8 Conclusion

The stakes for DMD drug development are extremely high. Hundreds of boys and young men die every year from this rare disease, yet drug development for it has been riddled with failure. Several companies have filed DMD candidate drugs for approval with the FDA, but only one has achieved this goal. News of a rejected candidate is a setback for the entire DMD community of patients and families, including Ganot and his family. While Solid does not yet have a candidate in clinical trials, the team has been vigilantly watching these developments. These recent FDA decisions have provided Solid Biosciences with important knowledge about the approval process, and have helped the company better understand the agency’s position on matters such as dystrophin expression, the need for sufficient endpoints, and the high threshold for FDA approval.

In this case study, we have highlighted Solid Biosciences’ business model. Solid Biosciences’ one-disease focus on DMD has enabled it to achieve significant milestones relatively quickly and efficiently, and have made it a center of excellence for research, attracting patient groups, researchers, advisors, and investors to join its mission. Solid’s expertise in DMD enables it to diversify its projects and approaches strategically. Still, Solid faces several hurdles ahead as it enters the clinical stage, where any candidate’s chances of success are low [5].

As interest in developing therapies for rare and orphan diseases increases in the biopharma industry, it is fruitful to consider business models that could result in faster cures with lowered risk. A diversified, one-condition approach has the potential to be a model for other biotech companies to emulate in rare disease drug development. Furthermore, investors may find this model of development to be more attractive than traditional models in which a single technology platform is applied to multiple and varied indications.

Beyond creative business models, however, drug development for rare diseases like DMD could be helped by external systemic changes that incentivize or accelerate development. While beyond the scope of this discussion, policy changes are a critical area for further inquiry to speed up innovation for rare diseases. The Orphan Drug Designation has already been successful in attracting drug developers to study long-neglected diseases. Additional policies that accelerate the approval process, or modify the thresholds for approval, may be able to help bring drugs to the millions of U.S. patients with rare diseases but limited or no treatment options.
For decades, the DMD patient advocacy community has been waiting and pushing for treatments for DMD. Every month or year that a treatment is delayed, thousands of children further deteriorate. Ilan Ganot’s son, Eytani, is now six years old, and is increasingly showing symptoms of DMD. However, there is hope in the patient community that a cure or an effective treatment is achievable. More than ever, the scientific community’s understanding of DMD and its biology is of increasing use in drug development. Technological and scientific advances have allowed companies like Solid Biosciences, which employ strategic business models to minimize their risk while maximizing their chance of success, to take innovative approaches to drug development, toward the ultimate goal of achieving the long-desired breakthrough treatments for the DMD patient community.
Chapter 4

Academic – Industry Partnerships: Stanford SPARK Program

Abstract

Translating academic medical research into new therapies is an important challenge for the biopharmaceutical industry and investment communities, which have historically favored later-stage assets with lower risk and clearer commercial value. The Stanford SPARK program is an innovative model for addressing this challenge. The program was created to help educate students and faculty about how to take academic research from bench to bedside. Now in its tenth year, the program has experienced significant success, moving dozens of projects into the clinic and licensing many more. Every year, the program funds and provides mentorship for approximately a dozen SPARK “scholars,” with a focus on impacting patients’ lives, regardless of economic factors. The SPARK team and the SPARK scholars share the belief that academia has an important role to play in new medical discoveries, and this common conviction accounts for a significant portion of the program’s success. By reviewing the detailed structure, function, and operation of SPARK, we hope to provide a template for other universities interested in de-risking and facilitating the translation of biomedical research.

4.1 Introduction

In this case study, we profile the structure and impact of the SPARK Translational Research Program at Stanford University School of Medicine, a partnership between academics, industry executives, and experts dedicated to overcoming the hurdles of translating academic discoveries into drugs and diagnostics that address unmet clinical needs. Its underlying philosophy is that academia has an important role to play in decreasing the time and cost of
development of new therapeutics and diagnostics to benefit society. By studying this innovative partnership between academia and individual experts in industry, we aim to provide a template for other universities and academic medical centers interested in launching their own translational medicine accelerators.

Developing a new medical therapy is an arduous and complex process, with the risk of failure at every step. The pharmaceutical industry undertakes investments that are considerably riskier than those in other high-technology sectors because of a multitude of factors, including the high cost of drug development, the complexity of human biology, and the uncertainty of meeting the regulatory requirements of the United States Food and Drug Administration (FDA). The cost to yield a single FDA-approved drug today is over $2.5 billion [5], compared to $128 million in 1975 [23]. This increase in cost reflects the various technical, regulatory, and economic challenges facing the industry’s R&D pipelines, and has led to a decrease in pharmaceutical R&D investment in recent years [24].

The regulatory environment for new medical drugs is especially complex because of the multiple stakeholders involved. The approval and use of a drug depends on the decisions made by the relevant regulatory authorities, such as the FDA in the United States, the European Medicines Agency (EMA, previously EMEA) in Europe, and the Pharmaceuticals and Medical Device Agency in Japan. These authorities, in turn, are governed by specific laws. Patients also have an important function in the success of new drug development via their participation in the clinical trials process. For-profit pharmaceutical companies dominate the development of drugs and are the principal participants in their promotional activities, sales, and lobbying. Lastly, academia—defined here to include nonprofit universities and scientific research institutions—is another major stakeholder, one that can play an important role in affecting the progress of medical research because of its breadth of scientific knowledge and resources.

The interactions between academia, the pharmaceutical industry, and regulatory authorities are of paramount importance for ensuring the quality, efficacy, and safety of drugs in clinical and commercial use. Some interactions have proven to be unproductive or inappropriate, with economic interests sometimes prevailing over the rights of patients [25]. However, many other interactions have led to an effective streamlining of the drug development process. New
models, such as that of SPARK, can facilitate partnerships among stakeholders and accelerate the commercialization of biomedical research.

4.2 Translational Medicine Background

The past few decades have brought tremendous breakthroughs in the fundamental knowledge necessary for understanding, preventing, diagnosing and treating many diseases—breakthroughs such as human genome sequencing, immunotherapies, and gene therapies. However, the process of translating new discoveries into products severely lags behind the pace of discovery [1], and there remains a long list of diseases for which there are no cures or reliable treatment options.

Many basic discoveries barely start the journey down the drug development pipeline. Promising projects often get lost in translation because they lack the funding, incentives, technical expertise, and resources to advance. The ever-widening gap in funding and support needed to move basic science down the path toward therapies has been termed the “valley of death.” According to the National Institutes of Health (NIH), 80 to 90 percent of biomedical research projects never progress to human trials [26].

Translational medicine is a growing field, focused on addressing this gap between medical discovery and commercialization [27]. Within the last decade, the NIH has made translational research a priority, forming the National Center for Advancing Translational Sciences (NCATS), and launching the Clinical and Translational Science Award (CTSA) program in 2006. Academic centers, foundations, disease-related organizations, individual hospitals, and health systems have also established translational research programs, and at least three journals are devoted to furthering this field: Science Translational Medicine, the Journal of Translational Medicine, and New Horizons in Translational Medicine.

Historically, translational research has two distinct definitions, depending on where in the drug development process it occurs. These two definitions have been described by the Institute of Medicine’s Clinical Research Roundtable as the two “translational blocks” in the clinical research enterprise, labeled as T1 and T2 [28]. For many, translational research refers to the
"bench-to-bedside" enterprise of harnessing knowledge gained from basic science to produce new drugs, devices, and treatment options for patients, i.e., research at the interface of basic science and clinical medicine. For this first translational block, T1, the endpoint is a promising new treatment that can be used clinically or commercially, or in other words, "brought to market." Other stakeholders, such as the health services researchers and the public health investigators whose studies focus on health as the primary outcome, work in T2. For them, translational research refers to the proper adoption of new treatment strategies into general clinical practice. Translational research by this definition is only successful if new treatments and knowledge actually reach the patients or populations for whom they are intended, and are implemented correctly [29].

Before entering the market, a drug must pass through multiple stages of research, culminating in clinical trials to demonstrate both safety and efficacy in the intended patient population. The drug development process starts in the so-called “preclinical” phase, which includes the search for chemical compounds with potential medicinal value and testing the candidate compounds for properties such as chemical stability, solubility, target selectivity, and potency, before advancing to studies of efficacy, pharmacokinetics, and toxicity in animals such as mice. Should a compound demonstrate sufficient promise in the preclinical phase, it will proceed to testing in human subjects in phase I (first tests of human safety), phase II (preliminary efficacy and dose finding), and phase III (definitive safety and efficacy), depending on the results at each phase. Upon successful completion of these trials, the drug developer can submit a new drug application (NDA) to the FDA for review and marketing approval.

The majority of early-stage drug discovery occurs outside of pharmaceutical companies, taking place in academic institutions, as evinced by the fact that only 12% of active preclinical assets currently reside in large pharmaceutical companies [30]. Investors are reluctant to bear the full cost of entering the valley of death due to the high risk and historically low return on investment for early-stage R&D, which discourages large pharmaceutical companies from pursuing more innovation internally.

The valley of death has created a more risk-averse attitude in the pharmaceutical industry, in contrast to the culture of academia where risk-taking is often rewarded by promotion and recognition. For this reason, scientists from both industry and academic communities can benefit
from collaborating to develop novel therapeutics. Because of the dearth of private-sector funding for the valley of death, charitable institutions and government funding bodies play a large role in early-stage drug discovery. For example, at the twenty most research-focused medical schools, an average of 80% to 85% of total research dollars comes from federal research grants [31]. Several noteworthy public-private collaborations in funding academic research have also arisen to address this funding gap. For instance, the Broad Institute in Cambridge, Massachusetts, is a partnership between the Massachusetts Institute of Technology, Harvard University and its hospitals, and the Whitehead Institute for Biomedical Research is funded by charitable donations, the Novartis Diabetes Initiative, and the RNAi consortium [32]. Such partnerships are still early in their life cycle, and will require continued effort to become an efficient method of bringing new medicines to market. In addition, the growing complexity of collaborations with academia may have significant consequences for the sharing of royalties once a product reaches the market.

Open collaboration and new business models, such as joint ventures between pharmaceutical companies and other external entities, can increase the productivity of biomedical research. The large role of academic institutions in commercial drug development calls for a better funding mechanism to reward academic contributions and a more efficient collaboration between industry and academia. While this process is complicated by the fact that academic and commercial interests are not always aligned, this evolving drug discovery model can be useful in mitigating risks and increasing productivity by sharing resources and ideas. SPARK provides one such example.

Figure 4-1: SPARK fills the gap between academic discovery and industry.
4.3 The Origin and Mission of SPARK

The SPARK program was founded in 2006 by Professor Daria Mochly-Rosen, who came up with the idea while serving as Senior Associate Dean for Research in the Dean’s Office of Stanford University School of Medicine. Two years before her appointment, she had taken a leave of absence from Stanford to found her own company, KAI Pharmaceuticals, which was subsequently acquired by Amgen in 2011. From her experience with KAI, Daria found that bridging the translational research gap was extremely challenging and not necessarily an intuitive process for academics. Recognizing the need for education and funding to help her academic colleagues translate their research into therapies, Dr. Mochly-Rosen created SPARK with critical early backing from the Dean’s Office of the School of Medicine, which allocated the funds to launch the program and continues to provide financial support. Additionally, Dr. Mochly-Rosen recruited Dr. Kevin Grimes, an academic internist with drug development experience, to join her as co-director of the program. Both hold faculty appointments at the Stanford University School of Medicine in the Department of Chemical and Systems Biology.

Now in its tenth year, SPARK offers training, support, and mentorship to academic researchers to support basic research with potential medical applications. Founded on the idea that academia has a social responsibility to accelerate the progression of basic science into translational medicine, SPARK’s stated goal is “to move five to ten new discoveries each year from the lab to the clinic and/or to commercial drug and diagnostic development [33].” Every year, SPARK selects a class of 10 to 15 projects that remain in the program for a two-year cycle.

Initially, some faculty members were concerned about what role, if any, a university should play in supporting translational medicine. However, with SPARK’s record of success, and its strong educational focus, these concerns have largely dissipated. Within Stanford, and likewise within the greater community of investors and industry, it is largely seen that SPARK has had a growing, positive impact on tackling the barriers impeding the advance of promising early-stage biomedical research. Although SPARK started out in a small conference room in the Dean’s Office, SPARK meetings have now grown to include over a hundred individuals, necessitating a lecture hall.
4.4 How SPARK Operates

The SPARK program is centered on its researchers. Selected project leaders, called SPARK “scholars,” receive approximately $50,000 annually for two years in addition to extensive educational mentoring from SPARK advisors. These scholars are required to attend interactive weekly Wednesday meetings, which include lectures from industry experts and project updates that occur on alternate weeks. While the funding from the program is limited to the selected SPARK scholars, any member of the university is welcome to attend these meetings and engage in educational sessions. Currently, about 100 individuals, including scholars, members of the Stanford community, and members of the SPARK advisor network, attend regularly.

Throughout a scholar’s SPARK tenure, funding is distributed as project milestones are met. Scholars’ requests for funds must be linked to the accomplishment of specific milestones. These funds are held centrally and released for expenses appropriate to the approved tasks. Once a milestone is achieved, additional funds may be requested for the next stage of development. The principal investigators are kept accountable to the program by attending and presenting progress updates at the Wednesday meetings. Any unused funds revert back to the general pool of funds, which is managed centrally by SPARK. Access to Stanford’s infrastructure, facilities, and resources helps to maximize the use of the $50,000. One key to SPARK’s success is its ability to tap into the medical school’s resources, providing basic researchers with access to clinicians in order to better understand the clinical implications of biomedical research.

While the funding is an important reason to apply to SPARK, a key to the success of the program is undoubtedly the advice provided by the volunteer industry expert advisor network, both at the Wednesday meetings and in smaller focused meetings with the investigators. This intangible benefit significantly aids scholars in achieving the next milestone for a translational project. For instance, one scholar capitalized on SPARK’s expert advisor network to help him find the right licensing partner for a patent that he had filed with the university a few years prior. To alleviate concerns about the disclosure of updates regarding scholars’ milestones and assets at the Wednesday meetings, SPARK mandates confidentiality agreements for all attendees and has worked to create a culture of trust and sharing within the program.
A key element of the SPARK training is to teach investigators to think using a translational approach. The scholars are trained to identify the unmet clinical need of the patient and to understand the problem in tandem with product development. In other words, they are trained to keep “the end in mind” as they embark on the drug development process. Scholars are encouraged to take a meticulous approach to drug development project management and to plan for specific milestones that will move their product through its development. SPARK uses tools such as target product profiles and project timelines to help teams plan and identify key milestones, necessary endpoints, and critical decision points.

4.4.1 Management

The SPARK program, currently led by Drs. Mochly-Rosen and Grimes, operates with a management team of five individuals, which oversees communications with project teams, runs its weekly meetings, oversees SPARK funds, and otherwise manages operations. While the majority of the funds for SPARK comes from the Dean’s Office, the program operates independently within Stanford University and is managed solely by the SPARK team. Significantly, much of SPARK’s success and credibility among Stanford’s faculty comes from the fact that the program is led and managed by well-respected Stanford faculty colleagues. Currently, Dr. Mochly-Rosen spends one day a week on SPARK, while Dr. Grimes is full-time, in addition to time spent practicing at the clinic.

4.4.2 The Advisors

One of the most important keys to SPARK’s success is the strength, expertise, and engagement of its advisor network. These advisors volunteer their time to work with SPARK projects, attend the weekly meetings, and participate in evaluating potential projects. They have no ownership or rights to any inventions or intellectual property from the program, and they work with SPARK strictly on a volunteer basis. As of 2016, SPARK has over 100 advisors with significant entrepreneurial or industry experience in drug development. These advisors generally
have a specific area of expertise. On occasion, they are organized into working groups, focused on areas such as medicinal chemistry, biologics, financing and venture capital, business development, and clinical trial design. Furthermore, because of their deep drug development background, these advisors often bring specific therapeutic expertise in areas ranging from pulmonary hypertension to infectious diseases of developing countries. Advisors remain engaged because of their interest in the core science behind the projects and the opportunity to remain part of such a strong network of industry experts. Working with a mission-driven program dedicated to translational medicine offers an opportunity to help bring impactful products to market, which may not have been the primary focus of the advisors’ former for-profit industry employers.

The SPARK structure includes several advisors per area of expertise, thus providing SPARK scholars with a number of perspectives on any given topic. For example, if scholars have a knowledge gap about the business model required by a potential investor, SPARK’s venture capital advisors can help bridge that gap. This advice is given in the vibrant and active Wednesday night meetings, during special “focused” groups, and in one-on-one meetings. A critical component to success is the public nature of much of this advising, where multiple opinions are offered without the need to reach a consensus. This open exchange is an opportunity for the advisors to comment based on their experience, and to balance their advice based on the feedback from other experienced experts.

New advisors often join the program after hearing about the program from an existing member of the SPARK community. Any conflicts of interest are managed by confidentiality agreements and regular check-ins by the SPARK team. As SPARK advisors are not compensated in any way for their time, mentoring is an opportunity for these advisors to have an additional impact on drug development in a low-risk environment. These advisors are typically matched to SPARK scholars via SPARK management, but matches can also be initiated directly by either party.

4.4.3 Funding

The SPARK program is funded primarily through the Dean’s Office within the School of Medicine, with additional support from non-profit organizations and the NIH. SPARK receives
no revenue from its projects. Since 2006, about $7.1 million has been spent, covering staff salaries, scholars’ research expenses, and other program expenses. Additional funding for the program comes from the Children’s Health Research Institute, which goes towards research projects with a pediatrics focus. It is a key element of the program to operate on funds that are not tied to commercial incentives. The program has always turned down funds from for-profit companies to avoid creating perceptions of conflict of interest.

Additionally, although the SPARK project selection process focuses on unmet medical needs, the SPARK program generates significant follow-on grants and funding to support further research for Stanford. Thus far, SPARK has generated nearly $38.7 million in additional grant funding, about 4.95 times the amount provided by the Dean’s office over the same period (see Figure 4-2). Since follow-on grants were generally received in the second year of SPARK participation, this multiple was calculated using a discount rate of 5% and a funding interval of two years.

**SPARK Follow-On Grant Funding**

![Bar chart showing SPARK project total investment and additional funding generated.](image)

Figure 4-2: SPARK has generated significant follow-on grants, 2007–2015.
4.4.4 SPARK and the Office of Technology Licensing

Patents are necessary ingredients for drug development in industry, since they offer exclusive rights for commercialization for the life of the patent. Without patents, investors and industry have little incentive to invest in further development or commercialization. In general, however, academic institutions initially own the intellectual property rights for discoveries made at the university. At Stanford, the Office of Technology Licensing (OTL) manages the patent process and licensing negotiations for discoveries made at the university. SPARK works in tandem with OTL to match projects with potential licensees. After a company expresses initial interest, the process is handed over to OTL to handle the negotiations and terms.

SPARK works collaboratively with OTL to increase the licensing opportunities for SPARK's biomedical projects, and the relationship is mutually beneficial. SPARK de-risks its projects by vetting them with industry experts and advancing them to a more mature stage of development, thereby making them more attractive candidates for OTL to license. At the same time, SPARK depends on the expertise and resources of the office to negotiate licenses, find licensing partners, and file patents.

4.4.5 On SPARK’s Culture

One critical element of the SPARK program’s success is its unique culture. Despite the challenges and frustrations of the drug development process, the program has maintained its aspirational mission and optimistic spirit. Its weekly Wednesday meetings offer a collaborative environment where peers are accountable to the program and to one another by sharing their progress and offering mutual feedback. Questions, challenges, and comments are encouraged between presentations. SPARK has succeeded in creating a culture of sharing information, while setting in place safeguards to protect sensitive information from leaving weekly meetings. The program succeeds because it is able to harness the altruistic spirit of faculty, industry advisors, and others who see translational research as a means to help patients.
4.5 Project Selection

A significant factor contributing to the SPARK program’s accomplishments is the rigorous project selection process, conducted by a handpicked committee each fall. The committee typically consists of the SPARK management team, two to three Stanford faculty members, and a dozen SPARK advisors. The three primary criteria for successful applications are that the project addresses an unmet clinical need, uses a novel approach, and has the potential for the SPARK program to improve its licensing and/or clinical trial prospects over the two-year cycle. Notably, commercial potential is not a factor in the selection process.

In the early years of the program, the majority of proposals came from the OTL’s portfolio of unlicensed discoveries from the previous year (narrowed to biologics, drugs, and diagnostics). SPARK now typically reviews around 200 potential projects a year, with approximately 150 from the OTL’s portfolio of unlicensed discoveries and 50 to 70 through an open application process. The application itself is not overly extensive—approximately two pages long—to lower the barrier for academics and potential scholars to apply. This two-page application includes a description of the proposed product, underlying technology, clinical indication, current standard of care and unmet need, translational objectives that can be achieved with the funding, and a broad development plan.

The review committee picks the top twenty finalists, who make their pitches over four nights using a standard presentation format. Following the presentations, the SPARK team and advisors discuss and vote for the top 10-12 projects to make up the annual SPARK scholars cohort. Although not as common, off-cycle opportunities occur when particularly promising projects are pitched to SPARK. These projects join the program as seed projects and are given a smaller amount of funding, usually ranging from $10,000 to $15,000, compared to $50,000 for the annual cohort. Over the last few years, the selection process has become more competitive, with the application pool consisting of stronger proposals, both in terms of the underlying science and the initial stage of progress.

SPARK selects projects to target a variety of therapeutic areas. These drugs can be novel or repurposed with a new dose or a new method of administration. Although drug repurposing has a smaller economic impact, SPARK typically has several repurposing projects in its portfolio.
because drug repurposing provides an opportunity to have an impact on patient care quickly. It is important to note that certain projects can fall into more than one project area. For example, 30% of projects address orphan diseases, and 32% are related to child or maternal health issues. A distribution of project areas is shown in Figure 4-3, and for concreteness, three specific SPARK projects are profiled in Appendix A.

![Pie chart showing distribution of SPARK projects by clinical indication.

Figure 4-3: (A) Distribution of SPARK projects by clinical indication.

(B) A majority (65%) of SPARK projects address child or maternal health (39%), orphan diseases (34%), or global health (21%).
4.6 Program Results and Benefits

SPARK’s mission has three elements. Its first purpose is to help academics overcome the obstacles involved in moving their early discoveries from bench to bedside. Second, SPARK educates faculty, postdoctoral fellows, and graduate and medical students about the translational research process and the path to clinical application, so that the future development of promising discoveries becomes second nature to the institution, and future members of the workforce are better prepared for careers in industry. Finally, SPARK is meant to develop more cost-effective and innovative approaches to drug development.

The SPARK program has a unique and rigorous success metric. A project is deemed successful only if it enters a clinical trial, is licensed or transferred to an existing biopharmaceutical company, or leads to the founding of a new startup. Projects successful by SPARK metrics often meet more than one of the three listed criteria. In the 10 years since SPARK was founded, 74 projects have graduated from the program. Of these, 24 were licensed to startup companies, eight were licensed to existing companies, four have been transferred to industry without licenses and 31 are in clinical trials (10 without licenses). Together, this amounts to a success rate of 62% (see Figure 4-4).

![Distribution of graduated SPARK project outcomes](image)

Figure 4-4: Distribution of graduated SPARK project outcomes.
These metrics are based solely on what is under the control of the SPARK program: moving projects forward to clinical trials or into commercial entities. SPARK’s metric for success is similar to the metric used by Eli Lilly and Company in Chorus, their small, operationally independent (but housed within the company) clinical development organization [34]. However, SPARK’s metric is quite different from that of industry investors, who would not consider a project successful until it generates a financial return. By maintaining its established metrics, SPARK can accurately compare its successes and impact from year to year, which is critical to financing since the program must reapply for funding annually. SPARK’s success metric may differ from industry norms, but it aligns well with the program’s goals. One venture capitalist familiar with the SPARK program admits that although the SPARK team may be altruistic to a fault, the program does a good job of exposing scholars to the translational development process and preparing them for the next step: investor meetings. In addition, scholars with strong projects develop the necessary skills and professional exposure to succeed in investor and industry meetings beyond the SPARK program, as a result of their interactions with the SPARK staff and their industry mentors.

4.6.1 Implications for Stanford

The homegrown nature of SPARK has been a source of strength for the program. Founder Daria Mochly-Rosen’s first exposure to biotechnology was during the KAI Pharmaceuticals development process; she had never before worked in the field. Through this experience, Dr. Mochly-Rosen identified inefficiencies in the development process and gaps in her knowledge. She founded the SPARK program to address those needs for future Stanford researchers and entrepreneurs. As a result, the history and structure of the SPARK program are conducive to a tight-knit, Stanford-affiliated network. The Stanford network provides the SPARK program with a constant flow of interest, as many scholars and mentors hear about the program via word of mouth. In return, the SPARK program provides the Stanford community with increased integration and communication across schools. For example, basic scientific research laboratories can collaborate with physician-based laboratories through SPARK to gain a clinical perspective that they would ordinarily lack.
A crucial facet of SPARK’s Stanford network is its group of industry advisors. Advisors continue to participate in the program because they have seen SPARK’s success and are interested in seeing its future progress. They may want to network with prospective translational medicine entrepreneurs or may simply be curious about the next big ideas in science or business. Stanford faculty and students who are part of the program meet with industry mentors every Wednesday evening, an opportunity to strengthen their professional networks and make cross-disciplinary connections. Some advisors are SPARK graduates who benefitted from the program and want to impart their knowledge and lessons learned to aspiring translational scientists and entrepreneurs. In addition, former SPARK scholars cite its extensive educational content and their interest in continuing to learn about the industry as key reasons for staying involved in the program.

For academics, including physician-scientists, SPARK provides a structure for scholars to pursue lines of research with translational potential. SPARK scholars are often motivated by the hope that their efforts will have a substantial impact on healthcare and patient outcomes. These scholars also benefit from the network of advisors and mentors with significant professional experience and contacts. Because the program is on campus and the learning is communal, participants retain and internalize new knowledge and tools that they can apply to their current and future research projects. Students and fellows in the program who seek industry positions after SPARK have received job leads, recommendations, and career advice. They credit SPARK with helping them learn about industry positions and career paths, as well as providing helpful connections and job recommendations.

Finally, Stanford University benefits from the SPARK program, which has become a recruiting tool for attracting talent and a source of pride. One recent graduate specifically stated that SPARK was an important factor in his decision to join Stanford’s Chemical and Systems Biology department. Outside the Stanford campus, SPARK has influenced other colleges and universities to launch versions of the program on their campuses.
4.6.2 *Keys to Success*

The keys to SPARK’s success are the strength of its structure and its network of advisors. The combination of Stanford-affiliated researchers and industry advisors leads to a distinctive and necessary diversity of interests and experiences. Because industry advisors come from a variety of backgrounds, ranging from chemistry to pharmacology to regulation to investments, SPARK scholars gain exposure to experts in fields far beyond their own, rare for translational researchers outside of the SPARK program. Past SPARK scholars say that the industry advisors give SPARK an advantage over similar programs. Other programs are composed solely of academics, thus missing relevant industry experience, while those programs that have a single or few advisors lose the checks and balances provided by multiple advisors. Importantly, these advisors receive no financial compensation. Industry advisors and mentors must participate for the right reasons for the program to be successful, and cannot be driven by financial motivations such as salary or an equity stake in new companies.

Although SPARK co-directors Drs. Mochly-Rosen and Grimes consider the industry advisors the most important component in providing variation in background and perspective to the program, SPARK scholars and advisors alike credit the core SPARK team as the main driver of program success. The program has gained much momentum and credibility because Dr. Mochly-Rosen is well respected by her peers, both as an academic and a successful biotech entrepreneur with KAI Pharmaceuticals. The credentials of Drs. Mochly-Rosen and Grimes were essential to the ramp-up of the program; they had proven their leadership and capability for teamwork as a duo via their successful development of KAI Pharmaceuticals. The SPARK program has been successful since its creation because it has stayed true to its founding motivation and mission, creating a strong network of industry mentors under the guidance of an experienced, knowledgeable, and incredibly passionate management team.
4.7 Challenges and Future Plans

4.7.1 Financing

One major challenge for SPARK is to procure sustainable funding for the program. Currently, the program relies heavily on institutional funds, mainly from the medical school’s Dean’s Office, as well as grants from nonprofit and government agencies. The program takes no equity stake in the projects, and receives no royalties from its projects’ revenue or license deals. The program does not intend to profit from the commercial success of its projects, as doing so would not align with SPARK’s core educational and social mission. As it currently stands, the program needs $2 to $2.5 million a year in funding. Ironically, according to the Dean’s Office, many donors find this too small of an investment. On the other hand, if the program sustained itself through the commercial success of its scholar projects, there is a risk of SPARK inaccurately appearing to be a commercial venture. Going forward, ways that SPARK might finance itself include a long-term endowment or an annual allocation in Stanford’s budget.

4.7.2 Institutional Support

Another key consideration is that SPARK’s longevity relies on the continued partnership and support from the Stanford University School of Medicine. In addition to funding support, the program currently receives significant advice and technical support from university resources and facilities. Programs such as SPARK need institutional buy-in, especially in the alignment of the broader university with their key values, namely, the mission to educate and accelerate the translation of biomedical research. For such a partnership to thrive, institutions cannot expect substantial revenues or rewards—although universities do benefit from increased success in commercializing intellectual property. Institutions will have to recognize the importance of the less tangible benefits of a SPARK program, such as the creation of a strong institutional memory and infrastructure to support innovation and the translation of biomedical research.

In addition, Stanford University benefits from the successes and engagement of former SPARK scholars who find industry positions with the help of SPARK, and continue to remain
involved in SPARK. The larger medical school community benefits from SPARK's weekly sessions and extensive educational content. As SPARK's legacy and recognition increases, the program itself has the possibility to become an important driver in drawing graduate students and faculty talent. Already, several former scholars have stated that the existence of a program like SPARK attracted them to pursue research at Stanford.

4.7.3 Measuring Success

Drug development and the translation of research is a lengthy endeavor, hence the long-term impact of SPARK is still unclear. In the near decade since its launch, the program has learned many things about the challenges of drug development, some of them unique to academia. Projects are generally successful when physician-scientists are able to identify a strong medical need, and when they are based on strong science. Furthermore, a clear or identifiable pathway to patients is critical for development.

Although SPARK's current success metric matches the contemporary landscape and its goals, in moving forward, SPARK will need to pinpoint the right metrics and implement the necessary processes to track the direct impact of its projects. Similarly, SPARK would benefit by measuring the impact of the indirect benefits of the program to the university, such as education and increased job placements in industry.

As discussed earlier, a graduated SPARK project is deemed successful in three ways: if it enters a clinical trial, if it is licensed to an existing company, or if it leads to the founding a new startup. An analysis of unsuccessful or "failed" projects, on the other hand, sheds light on the complexity of biomedical research in an academic setting. In addition to the typical ways in which translational research fails (e.g., lack of funding or failed proof of concept), SPARK and other venues for academic research must take into consideration the academic researchers' other commitments.

A failure analysis of past SPARK faculty projects (Table 4-1) shows the diverse ways in which projects do not move forward. The most common way is a "failure to execute," which accounts for 36% of all SPARK faculty project failures. In these cases, the SPARK scholars
became disengaged from their project, had inadequate primary investigator engagement or personal conflicts, or ignored advisor input and misused funds. As expected, a significant proportion of projects failed for scientific or technical reasons such as inability to develop an acceptable drug candidate or to demonstrate benefit in preclinical models. Yet another reason for failure was the inability of several promising projects to obtain commercial funding as scholars moved beyond the SPARK program. Although SPARK is useful in making connections with some industry investors, not all projects are the best fit for certain investors, and the SPARK team and its scholars do not always have the time to pitch their ideas to other investors. Projects may also encounter technical problems using animal or human models, or fail in the clinic due to a lack of participating patients. In addition, project continuity can be a challenge when faculty, postdocs, or graduate students move to new institutions. In one case, a SPARK drug development project was anticipated by industry efforts and therefore discontinued.

<table>
<thead>
<tr>
<th>Reason for Failure</th>
<th>Number of Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of team to execute</td>
<td>10</td>
</tr>
<tr>
<td>Failed to advance to development candidate</td>
<td>9</td>
</tr>
<tr>
<td>Failed preclinical proof of concept</td>
<td>3</td>
</tr>
<tr>
<td>Unable to obtain commercial funding</td>
<td>3</td>
</tr>
<tr>
<td>Researcher left institution</td>
<td>2</td>
</tr>
<tr>
<td>Scooped by Industry</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>28</strong></td>
</tr>
</tbody>
</table>

Table 4-1: Breakdown of “failed” SPARK faculty projects (N = 28).

4.7.4 Growing the Program

As SPARK continues to achieve success at Stanford, the program must decide how to grow. There has been rising interest in the program, reflected in the increasing number of participants at weekly meetings and stronger application pools. One approach would be to expand the program by supporting more projects, not necessarily allocating more funds per
project. At the same time, however, funding too many projects may make SPARK too big and too difficult to manage. Too much growth could take away from SPARK’s success, much of which depends on its intimacy, culture, and the strength of its advisor network. Another approach would be to increase the extent and duration of support, helping the projects progress further in the drug development process.

4.7.5 Replicating the Program

While SPARK has made a significant progress in bridging the valley of death, its scope is currently limited to Stanford. Programs like SPARK, across the U.S. and abroad, promise to play a larger role in changing the systemic problem of early-stage translational efforts. While some may argue that SPARK is uniquely positioned to succeed, given the strength of Stanford University’s resources and its Silicon Valley location, the founders of the program envision SPARK-like programs at universities throughout the U.S. and the world.

While it is true that SPARK and Stanford University are located in a hub of biomedical research and venture formation, SPARK-like programs have already been started in the U.S. and in 24 universities in eight countries outside the U.S. [35]. These replication efforts will depend on an institution’s ability to obtain local backing from the academic and biopharma communities, to create a strong advisor network, to collaborate with technology licensing offices, and to maintain a strong biomedical research program. These ingredients are not always available. For instance, one non-U.S. university’s attempt to replicate SPARK came to a halt because the institution had no office of technology licensing or structure to manage the institution’s intellectual property.

4.8 Conclusion

SPARK has achieved remarkable success thus far. To expand SPARK’s impact, the program’s founders would like to support projects further into the development cycle. Some projects need more funding to reach a value inflection point; for example, an antibody
therapeutic cannot move forward without humanization of the antibody, an endeavor that costs much more than the typical SPARK investment of $50,000 to $100,000. However, as described earlier, expanding the program at Stanford will require significantly more funding than the program currently deploys.

For SPARK to be an attractive model for other institutions, the program will need to further articulate the metrics of its success and collect data from past and current scholars so that it can be measured and analyzed. These detailed analyses will help the program understand what makes a project successful. Similarly, an understanding of project failures can provide valuable information for future projects. Of course, many benefits from SPARK cannot be easily quantified, such as educational and professional enrichment. One challenge SPARK faces is to meaningfully capture the impact of the program, including the total grants received, the prestige of the program, the impact on university recruiting, and the future successes of graduated SPARK scholars. To conduct a strategic measurement and analysis of this impact, SPARK will need to expand its current team.

Finally, stakeholders across the board, including the Dean’s Office of the Stanford University School of Medicine, agree that SPARK has the potential to initiate a critical conversation about the need for systemic change in translational medicine. Such a conversation would not only reduce the barriers to drug development and increase the efficiency of the entire biopharma industry but could get more life-saving therapies into the hands of doctors and patients sooner rather than later.
Chapter 5

Venture Philanthropy: Cystic Fibrosis Foundation

Abstract

Advances in biomedical research have created significant opportunities to bring to market a new generation of therapeutics. However, early-stage assets often face a dearth of funding, as they have a high risk of failure and significant development costs. This has historically been a problem for rare diseases, where market sizes are too small to justify costly development.

Venture philanthropy (VP), a model in which nonprofits make investments to advance their programmatic work, potentially achieving returns that can be reinvested in their mission, can help address these funding challenges in biotech, offering an alternative to traditional funding sources like venture capital or the public markets. Despite its potential for nonprofits to add professional expertise that may help de-risk drug development, VP is still not widely employed among disease-focused nonprofits. In this paper, we highlight the model of the Cystic Fibrosis Foundation (CFF), widely considered to be the leading organization deploying VP in biotech.

The support of the CFF and its nonprofit drug discovery and development affiliate, Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), made possible the development of Kalydeco, the first disease-modifying therapy approved to treat cystic fibrosis. In 2014, CFFT sold its rights to Vertex CF royalty streams for $3.3 billion, providing it with an opportunity to supercharge its mission to cure cystic fibrosis. We evaluate the CFF example with an emphasis on its agreement structures and strategy, explore the challenges that nonprofits may have adopting this strategy, and provide recommendations for future financing using this model.

5.1 Introduction

Drug development is a risky and costly endeavor. According to frequently cited estimates, the process can require over a decade and $2 billion for a single successful therapy to
reach the market [5]. Due to the risks and costs associated with this process, candidates with lucrative markets or later-stage assets that have already generated promising data are typically favored. In fact, many early-stage assets are unable to receive the funds they need to progress in the drug development cycle, a phenomenon known within the industry as the “valley of death.” Historically, orphan products, defined by the Orphan Drug Act of 1983 as therapies to address diseases with fewer than two hundred thousand cases in the U.S., have been especially vulnerable to the “valley of death,” since drug developers had little financial incentive to develop treatments for so few patients. However, the Orphan Drug Act created policy mechanisms to incentivize manufacturers to develop orphan drugs. As a result, the number of treatments for rare diseases has grown significantly, with over 500 approved products on the market since the passage of this legislation [9]. Furthermore, with the increase in drug pricing, companies developing orphan products now expect relatively high financial returns on their R&D investment. Nevertheless, people with rare diseases continue to face significant unmet clinical needs, as 7,000 rare diseases still have no approved treatment [36].

Venture philanthropy (VP) in biotechnology was borne out of the need to provide incentives such as upfront funding and reduced risk to drug developers in order for them to focus on unmet clinical needs. VP can be defined and implemented several different ways, ranging from nonprofit venture-capital-type investment to entrepreneurial and strategic nonprofit activities. VP has been employed by organizations such as the Bill and Melinda Gates Foundation as well as a number of other disease-focused nonprofit organizations. Increasingly, more nonprofit organizations are exploring VP and other forms of impact investing to achieve their aims in previously neglected areas of medicine, including rare diseases and global health.

The Cystic Fibrosis Foundation (CFF) is the world’s leading non-profit organization in the search for a cure for cystic fibrosis (CF). It is considered a pioneer in employing VP for orphan drug development. As part of its strategy, the foundation funds promising CF research within academic laboratories and biotechnology/pharmaceutical companies. This strategy originated from the need for the CFF to incentivize biotechnology companies to engage in CF drug development after decades of advances in basic science. One of the early funding agreements of the CFF’s nonprofit drug development affiliate, Cystic Fibrosis Foundation Therapeutics Inc. (CFFT), was an effort with a for-profit company to discover compounds that might correct the core genetic defect in people with CF. This work ultimately led to the
identification and development of Kalydeco, the first FDA-approved treatment for CF that addressed the underlying cause of the disease. Over a period of twelve years, the CFF committed $150 million to CF programs in development at Vertex Pharmaceuticals, a Boston-based biotech. The agreement included royalties on future sales of successful CF drugs resulting from that support. This agreement benefited the CF community tremendously: in 2012, Vertex’s Kalydeco, which was initially approved for about 4% of people with CF, was quickly followed by a combination drug called Orkambi, which extended treatment to around 50% of people with CF, transforming the lives of a substantial number of people with the disease [37].

In 2014, CFFT sold the rights to its remaining Vertex royalties to an outside investment firm, New York City-based Royalty Pharma, for $3.3 billion in cash. The news sparked praise in the biotech community, but concern from critics worried about the future of the CFF’s patient-driven mission. On one hand, CFFT generated enough capital to fund dozens of new investments into more promising CF treatments, including potential one-time cures via gene therapy and gene editing. Critics, however, argued that the CFF was being rewarded at the expense of patients and payers, who would have to face a $300K/year price tag for Kalydeco [38].

CFFT’s use of contracted research in the development of Kalydeco has been well analyzed previously [39-40]. This paper focuses instead on the CFF’s overall strategy, its decision-making process, and the structural elements of the CFFT’s agreements and transactions, especially with respect to Royalty Pharma. We discuss the roles and incentives of the various stakeholders involved, and highlight the keys to CFF’s success and the implications for best practices in VP. As funding from the National Institute of Health (NIH) and other agencies for early-stage compounds and basic science continues to decline, we expect that the role of nonprofits will grow in importance, not only in providing much-needed capital, but also in offering disease-specific expertise and insights from the patient community to accelerate and de-risk drug development. We highlight and analyze the CFF’s VP model with the goal of providing a framework for increasing nonprofit participation in drug development.
5.2 Overview of Cystic Fibrosis

Cystic fibrosis (CF) is a hereditary condition caused by one of more than 1,700 known mutations to the CFTR gene. The CFTR defect causes mucus blockages in the lung and airways, often leading to significant bacterial infection and difficulty in breathing, and results in severe lung disease, although it affects multiple organ systems [37]. Worldwide, it affects nearly 70,000 individuals. Other drugs approved for CF and funded by the CFF before Kalydeco, like Pulmozyme and TOBI, addressed the symptoms but not the underlying cause of the disease; the disease was always fatal, with patients typically dying young due to lung failure. Although there is still no cure, the outlook for people with CF has improved dramatically over the past several decades (see Figure 5-1), due in large part to the work of the CFF. As of 2015, the median age of survival is 41.7 years, according to the CFF’s patient registry of nearly 29,000 U.S. patients [41]. In addition to new therapeutic options such as Kalydeco and Orkambi, CF patients also take a regimen of medications and supplements to manage mucus build-up, infections, digestive problems, and other symptoms. Prior to Kalydeco, the cost of treating a person with CF in the US with mild lung impairment was estimated to be around $40,000 annually [42].

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Figure 5-1: Median Predicted Survival Age of People with CF over Time. (Source: CFF.org)
5.3 History of the Cystic Fibrosis Foundation

The CFF, currently based in Bethesda, Maryland, was founded in 1955 by parents of children with CF. When the foundation was first established, there were no approved treatments for CF, no research being conducted on the disease, and no hope for parents whose children received a CF diagnosis. Because of the Foundation’s investments into research and care, the median age of survival for people with CF has been extended by decades. This donor-funded organization oversees extensive patient registry; provides funding for and accredits 120 care centers specializing in CF treatment; and established, and is the primary source of funding for, the Therapeutics Development Network, the largest CF clinical trials network in the world. Over the years, the CFF has led advances in the scientific understanding of the disease, including discovering the gene that causes CF, as well as most of the therapeutics for CF. The mission of the organization is “to cure cystic fibrosis and to provide all people with the disease the opportunity to lead full, productive lives by funding research and drug development, promoting individualized treatment and ensuring access to high-quality, specialized care.”

The success of the organization is undoubtedly tied to the CF community, which tirelessly fundraised for the cause, and its visionary leadership. In particular, Dr. Robert Beall, Ph.D. was critical in shaping the evolution and strategy of the Foundation. Beall was associated with the organization for over 30 years before retiring, the last 21 years as its president and CEO. Beall was a pioneer in redefining the activities of a medical charity. He, along with former Chief Operating Officer C. Richard Mattingly, successfully raised more dollars per patient than any other disease-focused organization in history, and was particularly known for taking an entrepreneurial and outcomes-oriented approach to his leadership, setting up the organization to achieve key milestones including gene discovery, a clinical trials network, a robust research and development program, and venture philanthropy. In 2015, the Foundation made a successful transition of leadership to its current president, Dr. Preston Campbell, MD formerly the CFF’s executive vice president of medical affairs. During Campbell’s 17-year tenure in that role, he oversaw research and medical activities that ultimately led to the discovery of disease-modifying therapies and other importance advances in CF treatment and care. Under Campbell’s leadership, the CFF is expanding its role to serve patients and further accelerate drug development to realize its mission of curing CF.
5.4 The CFF’s Venture Philanthropy Model

Before the term “venture philanthropy” became popular in the field, the CFF used donations and royalties to accelerate the development of therapeutics for CF. One of the earliest cases is its funding of the inhaled antibiotic, TOBI, which was approved to help reduce lung infections in people with CF. In the late 1990s, frustrated by the lack of industry attention to CF therapeutic development despite significant advances in scientific understanding of the disease, the CFF Board of Trustees challenged the organization to take on more risk and further engage the private sector. The CFF established Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), its nonprofit drug discovery arm, to facilitate these drug development contracts. The sale of TOBI royalties and a grant from the Bill and Melinda Gates Foundation for an additional $20 million enabled CFFT to fund its initial $40 million agreement with Aurora Biosciences, which was later acquired by Vertex. Since then, CFFT has diversified its efforts across many therapeutic programs, including therapies that target both the symptoms and the underlying cause of the disease. Over the years, CFFT has had a hand in nearly all the products approved for CF. The pipeline of CF therapies with the potential to address the root CFTR protein dysfunction alone includes over 15 programs as of early 2017 (see Figure B-1 in Appendix B). While many of the programs it has funded have been unsuccessful, as is often the case in drug development, some have led to new treatments, significantly advancing the Foundation’s mission and enabling additional investments into research and care. Below, we describe some of the key characteristics of its model.

5.4.1 Agreement Structure

Kenneth Schaner, CFF’s general counsel since 1983 and founding partner of the law firm Schaner and Lubitz, has been the lead in structuring VP agreements for the organization. Because the CFF pioneered this model for nonprofit funding of drug development, it “set the market,” creating the baseline structure that is now used by other disease-focused organizations. In total, Schaner has been involved in over 400 VP agreements, 80 to 100 of which have been with the CFF. He has also worked with 50 to 60 other disease-focused nonprofit clients.
One of the first features that CFFT negotiates in its agreements is milestone- or activities-based payment. This aligns the incentives among stakeholders, and ensures that progress is being made on an asset for the benefit of patients, which is the central purpose of the Foundation’s involvement. Another key element of the agreements that has evolved is the interruption license, which allows CFFT to take ownership of an asset if the company decides to halt development or goes bankrupt. In its history, CFFT has only invoked the interruption license a handful of times. One example is Altus Pharmaceuticals. When Altus was unable to continue with its trials, the Foundation took back the product candidate to be able to control the re-licensing and future development of the product.

When structuring an agreement, CFFT’s goal is to lower the bar for a biotechnology company to engage in CF research. CFFT aims to strike a balance that will create an incentive for a company to invest in research, but also, when possible, provide some upside for the CF community if there is commercial success. For a biotechnology company, financing obtained from a disease-focused nonprofit provides two key advantages: significant expertise in the disease and low cost of generally non-dilutive capital. In other words, the capital provided by disease-based nonprofits is usually non-dilutive, and is often less encumbering than traditional venture capital. The attractive financing from a nonprofit allows a biotechnology company the opportunity to pursue riskier programs. Rather than take an equity stake in the company, CFFT takes a royalty interest on any future revenues of a product—this distinction is critical, as CFFT’s interest is in furthering the development of new treatments for CF, not in seeing a specific company succeed or achieving a financial return.

In some cases, the return is capped, others not. The underlying strategy when constructing an agreement is to reduce the upfront and near-term payments from biotechnology companies in order to make it less difficult for the biotechnology collaborators to engage in CF research and development to benefit the CF population. The trade-off is limited control on the part of the CFFT during development, and no ability to set prices or to influence commercial plans.
5.4.2 Emphasis on Providing Clinical Expertise

The CFF brings extensive non-financial resources and expertise during the drug development process, which further creates incentives for companies to prioritize development programs for CF. These resources include scientists on staff who can help interpret clinical data and improve study design, extensive clinical trials, and care center networks.

Most importantly, the CFF accumulates invaluable data that can significantly de-risk the development process, particularly in the early stages where the risk of technical and scientific failure is high. In the development of Kalydeco and Orkambi, the organization facilitated access to decades of data from the CF patient registry, which effectively comprised a natural history of the disease. Remarkably, the registry includes nearly all people with CF in the U.S., a testament to the CFF’s deep commitment to people with CF and their clinicians and caregivers. Individuals involved in the approval process cite the registry as critical to the speedy FDA approval of Kalydeco. Dr. Bob Beall estimates that Kalydeco was brought to market approximately two years earlier than expected thanks to the expertise and financing provided by CFF.

Depending on its stake in a particular program, the CFF may attend periodic research meetings, or participate on a scientific advisory committee to provide insight, as was the case in the early days of the Vertex collaboration.

5.4.3 Portfolio Approach

Since the success in identifying the CFTR protein as a therapeutic target, the organization has continued its efforts to develop products that target the protein, but it has also pursued a portfolio approach in its R&D investments to ensure it is well-positioned for success in helping all people with CF. As of late 2016, CFFT has funded a portfolio of nearly 40 programs, ranging from preclinical assets to approved drugs. These programs are diversified across five major categories of targets, and within each category, it has diversified further by funding multiple approaches. The distribution of its current portfolio can be seen in Figure 5-2.

In recent years, CFFT has been able to increase significantly its funding of research across the various categories of therapies in the CF pipeline (see Figure 5-3). The funds are categorized into Therapeutics Development Program Awards, which are focused on drug
development, and basic medical research. In 2012, CFFT allocated research funds of $87 million across 17 grants. In 2016, the total amount of research funding was $181 million across 500 medical awards. Going forward, the CFF is optimistic about the potential of gene therapy and gene editing for CF, investing $12 million in 2016 alone, and allocating over 40 awards to advance research in this field.

![Distribution of CFFT Portfolio](image)

Figure 5-2: Distribution of CFFT Portfolio as of February 2017
5.4.4 Patient -Centered Focus

At the core of the CFF model is an unwavering focus on the needs of people with CF. Internally, this is achieved by having clear criteria that support efficient decision-making. With a single metric of success, the potential of a program to benefit people with CF, the organization is able to conduct due diligence and make its decisions quickly. Currently, the CFFT board must approve investments over $3 million, but CFFT’s management can approve smaller grants or awards.

This mission-focused decision-making process permeates the CFF board, which is composed of CF patients and parents as well as business leaders and members of academia. Many disease-focused nonprofits have boards composed of members of academia who are thought leaders and experts on the disease, but who may be more risk-averse and conservative in their approach to commercial agreements. In contrast, the CFF cites its diverse board as critical to its ability to make timely strategic decisions that align with the mission of the organization. In fact, the deliberation for both its collaboration with Vertex and the sale of its royalty was relatively brief because both strategies so clearly stood to advance the CFF’s mission.
A by-product of the CFF's successful VP model are funds to act on its mission. Any funds stemming from royalty sales (see Table 5-1) are reinvested in R&D, the continued expansion and enhancement of the CF care network; programs to support people with CF, such as mental health, lung transplant initiatives; and other elements of the mission in general.

<table>
<thead>
<tr>
<th>CFF Product Revenues ($M)</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royalty Revenue and Sales of Licenses</td>
<td>54</td>
<td>0.12</td>
<td>156</td>
<td>257</td>
<td>3,280</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 5-1: CFFT Royalty Revenues and Sales (Source: CFF Financial Statements)

5.4.5 Measuring Impact

The CFF measures the performance of its VP efforts by the therapies that have been brought to market and their resulting impact on people with CF. By that standard, its programs have been extraordinarily successful. The CFF’s involvement not only made Kalydeco and Orkambi possible, but they estimate that Kalydeco was brought to market two years earlier than expected, thanks to the expertise and financing the Foundation provided. Patients are now expected to live into their 40s and beyond, compared to single digits when the CFF was founded.

Of nearly a hundred agreements, only a handful have resulted in financial return to the CFF, including TOBI, Kalydeco, a CF medical device, and a small number of others. Over its history, the CFF, via CFFT, has invested about $500 million in total into its VP agreements.
5.5 The CFF and Vertex Collaboration

The path that led to the development of Kalydeco was built on decades of basic research performed by scientists and academics, many supported by the CFF. In the earliest stages of this research, scientists discovered that CF was connected to the impeded movement of chloride ions into and out of cells. The CFF-funded research led to the discovery of the gene responsible for the disease in 1989 [43]. Once the CFTR gene and its associated defective protein were identified, the scientific community was enthusiastic about the possibility of targeting the protein, and started screening potential compounds that could correct the root cause. However, it took research groups in academia two to three days to screen a single individual compound. The CFF realized that this pace was not adequate for the urgent needs of people with CF, and started to look at high-throughput screening as a tool to identify compounds at scale. This ultimately led to an agreement with a San Diego-based biotech company, Aurora Biosciences, to leverage the company’s advanced screening capabilities in 2000.

Vertex Pharmaceuticals later acquired Aurora Biosciences in 2001. The acquisition of Aurora and its high-throughput screening capabilities was thought to be highly synergistic with Vertex’s expertise in rational drug design. Aurora’s early CF work was not necessarily a draw for Vertex, but not a deterrent either. Interestingly, while Vertex is now known for its expertise and success in CF, at the time of the Aurora acquisition, CF was not an area of focus for them. In fact, Vertex’s development programs were known primarily for targeting hepatitis C.

5.5.1 Decision to Collaborate

Upon completing the Aurora acquisition, Vertex had to determine whether to continue the collaboration with CFFT. Two key drivers motivated its decision to continue the collaboration: (1) the CFF’s mission-driven financial support, which meant that the CFF could provide funding and tolerate risk that Vertex preferred to avoid, especially during the high-risk early-stage development period; and (2) the CFF had significant disease and scientific expertise.

Despite these reasons to pursue CF, Vertex had concerns about the disease focus, such as CF taking away resources from Vertex’s hepatitis C franchise, the small market size of CF, the inherent technical risk that needed to be mitigated, and the additional financial resources that
would be required fully commercialize the CF research. Vertex had virtually no background in CF, and since there had been no prior successful clinical development programs for the underlying cause of CF, they were wary of the high risk involved in venturing into CF (Vertex’s decision is explored in depth in a 2007 Harvard Business School Case [44]). The hepatitis C program was of significant help, however, allowing Vertex to become a commercial entity, and its CF program benefited from this success. There were also significant champions of the CF program within Vertex’s leadership. The CFF collaborations were an opportunity to work with a neglected but incredibly passionate and engaged patient community to develop a transformative therapy for an unmet need. From the commercial perspective, Vertex had to justify CF’s small patient population, but it saw potential for sales beyond the U.S. As a rare disease, cystic fibrosis also qualified for market incentives under the Orphan Drug Act, including support for clinical trial costs, tax breaks for certain expenses, Prescription Drug User Fee Act (PDUFA) waivers, as well as favorable EU Orphan Drug policies. Later, as the development of Kalydeco began, Vertex came to believe the science behind Kalydeco would lead to FDA approval, and the prospect of a second approval—ultimately, the combination drug, Orkambi—motivated the company to continue its collaboration with the CFF.

5.5.2 Development of Kalydeco

There are two primary classes of drug therapeutics that address the CFTR protein defect: potentiators and correctors. Depending on the specific mutation, the CFTR protein defect that causes CF limits the CFTR protein moving to the cell surface, which is addressed by correctors, or it disrupts the activity of CFTR protein at the cell surface, which is addressed by potentiators. Vertex initially debated which CFTR mutations to target, seeking to maximize the number of patients that could be reached with an attainable CFTR-targeting therapeutic. The CFF played a significant role in this decision by providing critical expertise regarding the various mutations and associated patient impact. While the F508del mutation affects nearly 90% of the CF population, Vertex decided to focus on the G551D mutation, which affects about 4% of the population, because the company believed it would be able to bring the medicine to people with CF more quickly: this mutation could be addressed with only a potentiator, whereas the other mutation would require both a potentiator and a corrector. Furthermore, this mutation affects the
second-largest CF population after the F508del mutation, ensuring there would be a sufficient number of patients to participate in a development program. (The timeline of major Kalydeco milestones is displayed in Figure 5-4)

Vertex also saw an eventual pathway to reach more patients after succeeding with this initial target. The phase 2 results for Kalydeco were a particularly significant turning point, when both Vertex and the CFF realized that targeting the CFTR protein was going to be a successful strategy for a future CF treatment. Furthermore, it was becoming clearer that a combination therapeutic of Kalydeco plus a corrector candidate might address the nearly 50% of people with CF who have two copies of the F508del mutation. (This combination was ultimately approved and is marketed under the brand name Orkambi.)

It became evident early on that Kalydeco was able to make marked improvements in the lung function of people with CF. The drug benefited not only from the incentives of the Orphan Drug Act, since CF qualified for orphan disease designation, but also from the FDASIA Act, which gave Kalydeco a “breakthrough” designation for CF individuals with certain mutations and priority review within the FDA approval process. Kalydeco was ultimately approved in 2012 for individuals aged 6 years and older who had the G551D mutation in the CFTR gene. The FDA approval of Kalydeco took 100 days, an accelerated timeline credited to the drug’s strong safety and efficacy signals.

Figure 5-4: Abridged Timeline of Kalydeco Development
5.5.3 CFF Support

Once the collaboration was running, the CFF provided expertise and engagement from its highest levels. Drs. Beall and Campbell were involved in the relationship early on, and the Foundation followed the development program’s progress through quarterly steering committee meetings, where updates were provided around clinical planning, trial design, profiles of assets, and progress on dollars spent. These meetings involved clinical planning during drug development, clinical trial design, profiles of assets, progress on dollars spent, and updates on new progress and data. This successful collaboration led to a number of follow-up agreements between the two stakeholders. The biggest one-time agreement was in 2011, when the Foundation committed $75 million as part of a 5-year collaboration centered on VX 661 and second-generational correctors developed up to 2016. Payments from CFFT would be made to support specific Vertex activities. In total, CFFT provided nearly $150 million in support of the Vertex collaboration. While Vertex would still need to invest its own financial resources into its CF research and development, the CFF funding played a significant role in the overall success of the program. Despite the size of the investment, CFFT’s funding only provided a portion of the total cost of developing Kalydeco, albeit the portion with the highest risk.

5.6 The Royalty Sale Strategy

Time is the most important commodity for the CFF, as it is seeking to treat and cure a progressive disease. It is important to re-emphasize that the CFF is not an investment firm, but a nonprofit organization with a mission and mandate to extend and improve the lives of people with CF. In contrast with investment firms, it is not a priority for the CFF to take longer-term risk simply for a better financial return.

With that in mind, from 2012 to 2014, the CFF engaged in discussions with Royalty Pharma about selling its royalty in Kalydeco and other future Vertex CF products. Royalty Pharma is a private investment firm founded in 1996 which manages a portfolio of approximately $17 billion. It is the largest dedicated healthcare investment firm in the world, and it is by far the largest firm focused on healthcare royalties [45]. It primarily focuses on approved products, but it has more recently partnered with companies to fund late-stage clinical trials in
exchange for milestone and/or royalties if the trials are successful and lead to regulatory approval. The firm is led by Pablo Legorreta, who sought to develop creative methods for financing biotech, and started the firm to test the hypothesis of whether monetizing pharmaceutical product revenues would be a viable investment model. The firm’s mission is to provide an alternative private funding model that can make the research and development process for drug development more efficient and productive.

One of Royalty Pharma’s competitive advantages is its tax-efficient, evergreen-like structure, allowing it to operate as a permanent business rather than the more conventional private equity or venture capital model of raising funds serially. In addition, Royalty Pharma owns a diversified portfolio of royalties on many of the world’s leading biopharmaceutical products, marketed by the world’s top pharma companies, which produces long-duration, predictable, and uncorrelated cash flow. Royalty Pharma’s structure and diversified portfolio has enabled it to achieve an investment-grade debt rating from the three leading rating agencies (Standard and Poor’s, Moody’s, and Fitch), as well as access to over $7 billion of debt at the low cost of Libor plus 1.75% to 2.25%. This low-cost funding platform allows Royalty Pharma to make highly competitive proposals to academic institutions and foundations that are selling royalties.

Royalty Pharma’s structure and diversified portfolio is also attractive to university endowments, institutional investors, and other sophisticated long-term investors, who make up the majority of Royalty Pharma’s equity investors. In fact, in several transactions with academic royalty owners, Royalty Pharma has offered the seller of the royalty a portion of its equity as part of the transaction. This has enabled the academic owner of the royalty to convert a concentrated royalty with a finite life in a single product into cash plus an equity interest in a permanent vehicle that owns and reinvests in a long-duration diversified portfolio of royalties.

Prior to 2012, Royalty Pharma had not worked actively with nonprofit patient advocacy groups, primarily because there are so few involved in investing in therapeutics. One of Royalty Pharma’s first interactions with the CFF was in a transaction involving the antibiotic TOBI, one of the first therapies developed through funding by CFFT. In 1997, Royalty Pharma acquired a royalty interest on TOBI owned by its inventor, Dr. Arnold Smith, a pediatrician and researcher associated with Seattle Children’s Hospital. During the TOBI due diligence process, the Royalty Pharma team became familiar with the market opportunity for CF products. While TOBI was a
major breakthrough in alleviating the symptoms of infection for people with CF, Royalty Pharma knew that there was still a significant unmet need facing this patient population.

5.6.1 Agreement Structure

CFFT had already monetized a portion of its royalties to a Canadian pension fund in two separate transactions for about $400 million.

Royalty Pharma proposed purchasing the entire asset for an upfront payment of $3.3 billion in cash, in addition to Royalty Pharma sharing with CFFT a portion of the royalties on sales in excess of a very high threshold. This structure allowed CFFT to substantially de-risk its largest asset and remove its ownership and potential conflict of interest.

5.6.2 CFFT Rationale for Monetization

In the CFF’s case, it found that the Vertex royalty streams were over 80% of its total assets. Royalty Pharma, with its large and diversified royalty portfolio, did not face the same issue of risk concentration. By selling these royalties to Royalty Pharma, the CFF was able to meet multiple objectives: to obtain upfront proceeds that could be reinvested into the pipeline of future CF therapies and its mission and, perhaps most importantly as a nonprofit organization, to remove the perception of ongoing conflicts of interest. A complete monetization of the royalty would mean that the Foundation would no longer receive royalties from Vertex on sales of Kalydeco, Orkambi, and some future Vertex combinations, thereby freeing the Foundation from any perception that it had an interest in the success of Vertex or its CF products. For strategic guidance, the CFFT called on the services of Morgan Stanley and L.E.K. to help advise it in the royalty sale, and it has engaged legal counsel since the start of its VP strategy.

5.6.3 Royalty Pharma Rationale for Investment

In its preparation for the CFFT negotiations, Royalty Pharma had examined the Vertex pipeline beyond Kalydeco, and was excited about the possibility of the combination drug later called Orkambi, as well as combinations in earlier stages of development. This was critical to its
investment decision, since Kalydeco only treats about 4% of people with CF, while Orkambi reaches up to 50%, and future combinations could reach up to 90% of the patient population. Future candidates that would fall under the royalty agreement included a combination of Kalydeco and VX 661, a corrector in development as of 2014, as well as certain other second-generation correctors in the Vertex pipeline. Royalty Pharma saw CFFT’s royalty stake from the Vertex collaboration as attractive for two primary reasons. The first was its potential to achieve attractive long-term financial returns. The second was Royalty Pharma’s desire to be the future partner of choice for patient advocacy nonprofits. The firm saw increased engagement with patient advocacy nonprofits as an attractive way to advance its mission of making drug discovery more efficient.

5.7 Lessons Learned

Like the CFF, a handful of other disease-focused nonprofit organizations have also been involved in VP, or more broadly, in entrepreneurial engagement with biotechnology companies. Some examples of such groups include the Spinal Muscular Atrophy (SMA) Foundation, the Michael J. Fox Foundation, and the Leukemia & Lymphoma Society. In recent years, as traditional sources for biotech funding have shifted to prioritize later-stage investments [40], nonprofits have increasingly funded early-stage drug development. They are particularly well suited for this stage, which requires lower amounts of financing than later stages, where the risk is higher, and in which the private sector is less interested. Whereas institutional investors must balance risk with their financial incentives, nonprofits have a higher appetite for risk because they are mission-focused, and not driven by financial incentives.

FasterCures, a nonprofit think tank dedicated to accelerating medical research, has seen an increase in the number of organizations employing creative funding solutions in recent years, many of which are emulating the CFF model. It has assembled a network of nonprofits, including the CFF, to allow groups to connect, to encourage more activities, and to provide a forum to share and grow. This initiative, known as The Research Acceleration and Innovation Network (TRAIN), has been growing in membership, and is attracting increasing public attention. FasterCures sees a “new generation of philanthropy” in which nonprofits provide not
just funding, but also strategic engagement in the drug development process. TRAIN thinks strategically about what patient organizations can bring to the table besides capital, and how they might attain leverage. These include the oversight of management and basic science, funding registries and clinical networks, and other activities.

In a FasterCures survey of 250 disease-specific nonprofits conducted in 2014, about 60% of respondents have governance policies that permit funding to for-profit biotechnology companies. Of those nonprofits that fund biotechnology companies, the majority (74%) fund at levels less than $1 million. While they may not fund biotech drug development directly, the vast majority of the nonprofits (96%) are developing research tools that can enable and de-risk later stage development within the biotech sector, such as animal models and patient registries, and building critical expertise to be a strategic collaborator in the drug development ecosystem [46]. Many nonprofits in the FasterCures survey pool are focused on rare diseases, representing neglected patient populations that face high unmet medical needs. A rare disease community that has had success in leveraging the capabilities of nonprofits is Duchenne muscular dystrophy (DMD), a fatal rare disease known for a particularly strong and mobilized patient network. DMD-focused organizations have been involved in financially supporting drugs such as Sarepta Therapeutics’ eteplirsen, which received FDA approval in 2016. The SMA Foundation is another example of a nonprofit that has supported an asset, which later became the first treatment approved for spinal muscular atrophy (see the SMA Profile in section 5.7.2).

Following the example of the CFF, other nonprofits are starting to explore the role of VP as they seek to make progress more quickly. The example of Kalydeco has given organizations significant hope to achieve their goals of providing approved therapies for their patients. By participating in funding biotechnology activities, nonprofits have the opportunity to influence drug development activities, and subsequently further their mission to develop life-changing treatments for their communities.

### 5.7.1 Best Practices

The CFF example offers several insights regarding best practices for nonprofit employment of VP. First, nonprofits require strong leadership and vision to take on risky entrepreneurial activities. Second, it is critical that they understand the constraints and objectives
of drug developers. Specifically, they need to understand a drug developer's cost of capital, especially in the earliest stages of development, which is where funding from nonprofits is most attractive. Rather than structuring agreements like typical venture capital deals, the CFF model suggests that nonprofits should focus on lowering the barriers for drug developers to work in the nonprofits' disease area.

According to FasterCures, organizations that are embracing this new approach to philanthropy share some common characteristics. First, they are pursuing a novel or breakthrough therapeutic for their disease. Second, they have in-house scientific expertise, or access to significant scientific expertise, to carry out the due diligence required when financing or supporting a drug development program. Third, the organizations are centralized and ready to mobilize quickly when making decisions. Fourth, one of the most significant characteristics of these organizations is their relationship with patients. Insights from individuals living with a disease are a source of expertise not typically available to drug developers but can significantly de-risk clinical trials and development decisions. Organizations can learn from the CFF example where the input from people with CF was immensely powerful. Finally, divesting at the earliest opportunity is a key strategic decision that helps mitigate conflicts of interest in the future, as patient organizations may wish to avoid an ongoing financial interest in a commercial product they funded and which their patient community will use.

Despite the growing interest in entrepreneurial approaches among nonprofits, challenges remain. It is clear is that the CFF's VP activities stand out among disease-focused nonprofits. The number and size of investments it has made are atypical, and it is able to make these financial commitments due to its larger size and decades-long organizational history, which have facilitated the required funding, community support, and institutional infrastructure. Other organizations rarely have the initial capital required to invest and sustain a “many shots on goal” strategy like the CFF. Even without significant capital, however, nonprofits can do more to leverage their value with their disease expertise and patient access. Their expertise can help companies reach the market more quickly. Further, organizations need significant buy-in from their boards to participate in risky endeavors and manage conflicts of interest with their mission and nonprofit status. In addition, they must have the capacity, both in terms of scientific and business expertise, to conduct proper due diligence. Finally, and perhaps most important, nonprofits must communicate the value of collaborating with the private sector to their patients.
and the broader stakeholder community, who are often financial contributors to the organization’s work. Organizations that participate in VP or other entrepreneurial activities face the challenge of managing actual and perceived conflicts of interest, particularly with regard to drug profits.

5.7.2 Another Example: Profile of the SMA Foundation

When the SMA (spinal muscular atrophy) Foundation first started, it faced a number of challenges. There was little public awareness of SMA, a rare genetic disorder, limited understanding of the disease or its research programs, poor clinical treatment for patients, and few available funds. At the NIH, about $1-3 million was spent on SMA annually, compared to $50 million for a comparable disease like ALS. The little work being done in SMA was fragmented, and the tools for R&D in this disease were limited and in a poor state.

Under the leadership of President Loren Eng, the SMA Foundation developed a two-fold strategy: 1) to fund the development of necessary tools, such as cell lines and biomarkers, and the clinical infrastructure to facilitate R&D in SMA, and 2) to repurpose drugs from other indications to SMA. One of its approaches was to fund work at academic institutions, and then license it from the universities to share the results widely. If biotech companies were successful using these tools, the SMA Foundation would share in the upside.

As one of its strategic approaches, the SMA Foundation started to engage with biotech companies. The initial engagements were via grants to fund research programs and to create incentives for them to work on SMA. Later, its philosophy evolved, and it generally sought to recoup its investment if the companies were successful. In a few cases, if the SMA Foundation investment were sufficiently large, it would require a multiple of what it put in. Again, this would only occur if the companies were successful, which reduced the cost of capital for biotechnology companies. The underlying idea was to incentivize companies to work in the historically neglected area of SMA without expensive stipulations. However, if there was an upside, the organization wanted to recoup its costs in order to be able to support ongoing R&D as well as programs for patients and clinical care.

The SMA Foundation’s key takeaway from the use of these partnerships is that they are tools to achieve the ultimate goal of accelerating drug development in SMA. The goal is not to
make the best deal, and the SMA Foundation is happy to leave money on the table as long as it is able to drive cures for SMA with its partners. Any upside that the foundation shares is less useful for the sustainability of the organization, but may be more useful for future investments in R&D programs. Founded by parents of a child with SMA, the SMA Foundation is not focused on its own longevity and sustainability, but rather, the fastest path to a cure. Biotech and pharmaceutical partners of the SMA Foundation have since learned that beyond funds, the Foundation has an incredible intangible resource of expertise and scientific understanding that it can provide.

Given the funding environment, the future will involve more nonprofits funding drug development. Drug companies have their pick of indications to work on, and foundations need to invest money to have their voices heard, and to create incentives for them to look at unmet needs and neglected areas. Foundations have to lower barriers and the cost of capital for biotechnology companies (more so than Big Pharma) to get involved. A key to success for the SMA Foundation was working closely with experienced lawyers and getting the right strategic guidance. The efforts for the SMA Foundation paid off in late 2016. The Foundation helped fund Adrian Krainer’s research at Cold Spring Harbor Laboratories, which resulted in a technology that was licensed to Ionis (formerly Isis) Pharmaceuticals. The Foundation was engaged throughout the development process by facilitating important introductions, providing resources, and giving access to SMA clinical expertise (a more extensive description of their involvement can be found in the Appendix). Ionis later partnered the SMA program with Biogen. In December of 2016, this became the first FDA-approved SMA drug. The drug price will be $750,000/year in the first year, $375,000 a year thereafter for the life of the patient.

5.8 Looking Ahead

The CFF has an ambitious goal of achieving a cure for its patients in the coming decades, based on the current status of promising new technologies such as gene editing. The foundation is modeling its future capital needs for this target date. The sale of its royalties from Vertex and the strategic management of these assets give it leeway to plan for the next two decades. The
organization is establishing an investment office to manage its investments to maximize the benefit of the resources in future years allocated towards this mission.

However, the CFF will encounter a number of challenges as it seeks to sustain its VP approach in its mission to develop a cure for cystic fibrosis for all patients. Like all organizations in a period of transformation, CFF is focused on maintaining its culture and sense of mission following the approvals of Kalydeco and Orkambi, and the subsequent monetization of their royalties. For decades, the Foundation has been a poster child for effective grassroots mobilization, and the CF community has been highly engaged in fundraising at the local level. Yet since Kalydeco’s approval, the CFF has experienced a 3-4% decline in fundraising totals annually (see Figure 5-5). At the same time, its models indicate that there could be a gap where it may run out of funds while pursuing its a one-time cure. As such, the Foundation must proactively convey the message of the remaining unmet needs faced by people with CF: while disease-modifying drugs represent a significant therapeutic breakthrough, only about 50% of people with CF potentially benefit from currently approved modular therapies. Much additional work remains to be done to develop disease-modifying treatments for all people with CF, to better address symptoms and infections, and to discover a one-time cure for the disease.

The CFF is also actively working to ensure that people with CF have access to needed treatments and care. The cost of modulators is one of the potential barriers to treatment. In 2017, Orkambi, for example, has a list price of $259,000/year and Kalydeco has a list price of $300,000/year. Most patients will not have to cover this entire cost because of insurance or charitable organizations, and Vertex currently offers financial assistant programs in cases of economic hardship [38]. Any barrier to care can pose significant health problems for people living with CF, and the Foundation is hopeful that accelerating research and development of additional drugs for CF will create a more competitive environment that will ultimately drive prices down. In the meantime, the CFF is working to ensure all people with CF who could benefit from these drugs are able to access them in a timely manner. The Foundation regularly engages with public and private insurers and connects them with clinical experts so their coverage decisions support the delivery of high-quality CF care. The foundation has also established CF COMPASS, a free service that helps patients navigate financial, legal, insurance, and other issues.
The CFF will also have to evolve and execute a strategy for managing its recently acquired funds through monetization. With its sudden influx of cash, it faces important asset-allocation and portfolio management decisions. It will have opportunities to continue to expand the diversity of its existing portfolio of investments, and consider riskier but potentially groundbreaking therapies for the treatment of CF. For example, the CFF is pursing CRISPR gene editing as a potential strategy for a one-time cure, and has funded CF research programs underway at biotechnology companies that are pioneering this approach, such as Editas.

The CFF faces a major challenge in public perception in the reconciliation of its status as a nonprofit and its funding of research at for-profit entities. As VP becomes more commonly used, and there are more successes, there will be increased public scrutiny regarding potential conflicts of interest with commercially successful VP investments and the role of nonprofits in financing private-sector drug development. In particular, the CFF has been involved in nearly all CF products that have come to market or are in the pipeline. As a result, it is directly involved in creating competition. By virtue of its many agreements, it can increase the rivalry of one approach to treating CF versus another. This influence poses an additional conflict of interest that the CFF must manage closely.

CFF Funds from Public Support

![CFF Funds from Public Support](image)

Figure 5-5: CFF Public Support Funding
In addition to a cure, there remains more work ahead for CF treatments. There are still segments of the CF population with no treatment for the underlying cause of the disease. The Vertex program has more candidates in the pipeline, and a goal of treating all CF patients. Additional second-generation correctors, including Vertex candidate VX 661, are progressing in the pipeline, and there is even a potential triple combination therapy on the horizon. In early 2017, Vertex released positive phase 3 clinical data for VX 661, and is expected to file a new drug application for the candidate shortly. Vertex’s future triple-combination therapies could potentially be indicated for up to 90% of the CF patient population [47].

The CFF also continues to expand its clinical care and research capabilities. It has developed a clinical trials network, initially with 6 to 8 sites, which now has over 80 locations. In 2016, there were 56 clinical trials in the network supported by the organization, compared to 28 in 2012. The Foundation also opened a CF research lab in Boston, a leading hub of biotechnology innovation and collaboration. In 2016, the Foundation increased its support of the CF care model by over 44%, investing almost $43 million to sustain and improve care delivery through the nationwide network of more than 120 accredited CF care centers.

The CFF will also remain involved in policy discussions to mitigate the access challenges that can come with successful drug approvals. While it has no ability to set the price with the manufacturer, the CFF is interested in new models of nonprofit and private-sector collaboration that can develop pricing that ensures people with CF can access needed treatments and care. The CFF is also involved in other policy areas, advocating for clinical trial innovations, more funding for the FDA and NIH, and health insurance that is adequate, affordable, and available.

Since its founding in 1955, the CFF has made remarkable strides on behalf of people with CF, including the development of groundbreaking treatments for people with CF, who previously had no effective therapeutic option. The CFF’s model to incentivize biotechnology companies to work in CF remains effective; in the early days, the CFF sought out biotechnology companies, but few responded seriously to its inquiries. In 2016 alone, however, 140 companies have approached the Foundation to discuss potential collaborations.

While the CFF example is an inspiring model for other nonprofits, a robust VP ecosystem in biotechnology does not exist. In addition to formulating a VP strategy, organizations must also overcome significant obstacles. The initial capital required to pursue advances in basic science, establish patient registries and other enabling resources, and provide funding for drug discovery
and development process is a large barrier, and many organizations do not have the fundraising capacity that the CFF was able to build over its decades-long history. Furthermore, some nonprofits may have missions that do not necessarily involve curing a disease. The CFF’s mission is specific to curing CF, which lends itself to supporting drug development. Other organizations may choose to support more academic research. In fact, most organizations have to balance the tensions of supporting basic science versus translational work. For many unmet medical needs, nonprofits may not have the option of supporting translational science if the foundational understanding of the disease has not yet been elucidated. The CFF spent decades advancing basic science that led to a comprehensive understanding of the biology of CF, which led to the identification of the gene and potential therapeutic targets. Without this scientific groundwork, it would not have been able to make the transition to supporting translational projects. For the CFF currently, the balance between basic and translational research is increasingly moving towards the translational.

Most nonprofits seek to maximize their impact, and they have the potential to fill funding gaps and provide important expertise to accelerate drug development for their patients. In spite of the many challenges to adopting VP, there is a growing interest among nonprofits for entrepreneurial engagement in drug development. While the CFF model is just one example, we expect that nonprofits will learn much from this example as they develop their own strategies.
Chapter 6

Conclusion

The biotechnology industry is poised for significant medical advances over the next few decades. The development of breakthrough and curative therapies based on these advances can help address unmet clinical needs. This work highlights three examples of innovative models that can help provide additional financing for early stage drug development and lead to promising new therapeutics. Notably, these examples involve mission-driven organizations aiming to accelerate the development of novel treatments for unserved patient needs. In the three case studies, applications of strategies such as diversification, non-dilutive funding, and drug development expertise were utilized to help mitigate the uncertainty and risks associated with translational medicine.

Our case analyses also suggest that there are intangible benefits to working with a mission-oriented organization. Whether it’s clinical development expertise, scientific knowledge, patient access, or a strong mission-driven focus, the intangible benefits aid the drug development process by de-risking the achievement of milestones and facilitating faster progress towards those goals. This, in turn, translates to tangible financial benefit, whether it’s increased investment, increased probability of commercial success, or faster timeline of development (and thus longer patent life during commercialization). However, while the interviewed stakeholders acknowledge the importance of mission and the intangible benefits that mission-driven organizations can provide, these benefits can be hard to quantify and may at times, even be undervalued by other stakeholders. The Stanford SPARK program is completely mission-oriented and focused on unmet medical needs rather than commercial potential. They are able to benefit heavily from the experiences and input of industry advisors, who altruistically join SPARK to participate in its mission to translate biomedical discoveries in order to achieve patient impact. The Cystic Fibrosis Foundation, as a disease-focused non-profit, is entirely mission-driven and focused on delivering treatments and cures for their patient community. In this case example, the organization’s scientific and patient expertise helped de-risk and accelerate translation of CF treatments. Stakeholders emphasized the collaborative nature of the
venture philanthropy partnership in accelerating the development of Kalydeco. In the Solid Biosciences case, the company’s founding and mission was indelibly marked by the CEO’s personal story. As such, the company’s leadership has a very tangible understanding of time, which helps the company make decisions to move forward the development of treatments. While we highlight the intangible benefits of a mission-oriented partner or stakeholder, we recommend further studies and research to better identify, quantify, and disseminate the value of scientific and patient expertise as well as the value of a partnership that is driven by and influenced by a strong sense of patient advocacy and mission.

Further, in all three cases, we see examples of non-traditional roles for stakeholders of the drug development community. The Cystic Fibrosis Foundation, in essence, took on the role of acting as a source of capital for drug development. This doesn’t come without challenges, as there are many cultural barriers to overcome in order for organizations to adopt new practices. SPARK is taking a big step to create institutional knowledge for translational medicine, which may not always be the primary priority of a research university. In addition, they are acting as a university incubator of sorts, providing seed funding for promising early stage biomedical research.

Our lens, that of a financial engineering research group, sought to emphasize and analyze elements in these cases that either utilized financial innovations or where financial engineering could be useful. For instances, in the three cases, we observed that the portfolio approach has many applications across drug development, whether in investment strategy or in the projects that are selected, funded, and pursued.

While the cases are certainly illustrative of the potential of new financing and business models in early stage drug development, these are only three examples. Furthermore, these examples represent early adopters in the field. In the case of the Stanford SPARK program and the Cystic Fibrosis Foundation, these institutions benefit from access to resources not widely available to peer organizations. One of the challenges with the case study methodology hard is that the examples are not perfectly replicable and can’t be generalized across the industry [11]. In addition, the examples are analyzed anecdotally. Still, despite these limitations, there are many lessons learned and takeaways that can be applicable to other stakeholders in the industry. Challenges to implementation include cultural barriers for new roles or change in standard industry practices. However, both mission and financial motivations demand faster medical
discoveries and translation of science into products, which can help influence organizations to explore and engage in new practices.

Beyond business models, new innovations in drug development itself can help accelerate translation of biomedical research. While we didn’t emphasize such models in this thesis, we see the potential for innovations in areas such as clinical trial design to bridge gaps in translation in tandem with these business and financing models. For example, adaptive clinical trials are a growing innovation that leverage ongoing learning to improve clinical trial design. In addition, policy mechanisms can help accelerate translational medicine. In fact, regulations such as the Orphan Drug Act have already been successful in incentivizing rare disease drug development and NIH’s NCATS has been set up to spearhead initiatives focused on translation. Beyond specific policy mechanisms, continued federal funding for biomedical research is necessary in order to provide a funnel for translational medicine projects that can lead to novel therapeutics.

The case analyses provide frameworks and insights for further adoption of these new models in industry and for additional research. Further research can be conducted to explore the value of new business models and financing vehicles in the drug development process. Additional research should particularly emphasize measuring and quantifying the results and impact of new biotechnology business models and partnerships. We profile three examples here as case studies, but we recommend that additional methodologies be employed to better understand the growing influence of such models and the consequences for therapeutics development.
Appendix A

Profiles of Selected SPARK Projects

A.1 Project Profile 1: Licensing to an Existing Company

Project: Repurposed β1-Adrenergic Receptor Agonist to Treat Alzheimer’s Disease  
Scholar: Mehrdad Shamloo, PhD  
Years: 2014–Present (as of August 2016)

Unmet Medical Need

Alzheimer’s disease (AD) is characterized by loss of neurons and synapses [48] and pathological hallmarks such as amyloid plaques and neurofibrillary tangles [49]. Current available treatments offer relatively small symptomatic relief [50] and aim only at improving the cognitive and behavioral symptoms without reversing the progressive synaptic dysfunction or neuropathology associated with the disorder. The lack of effective AD therapy might be attributable to our incomplete knowledge of underlying mechanisms and of the relationship between molecular, cellular, and behavioral symptoms. Thus, it is particularly urgent to identify new therapeutic targets that would not only rescue the cognitive symptoms of AD but also delay or block the development of neuropathological abnormalities that are responsible for loss of function and behavioral symptoms.

Project Background

Dr. Shamloo’s project involves repurposing small molecules and developing new derivatives to improve memory in AD patients. Studying the noradrenergic system’s role in neurocognitive diseases, Shamloo found that cognitive deficits observed in the Ts65Dn mouse model of Down syndrome were associated with an age-dependent loss of norepinephrine-containing neurons in the locus coeruleus and with an upregulation of β1-ADR expression in the dentate gyrus [51]. Moreover, he showed that acute activation of β1-ADR with the partial
agonist xamoterol rescues the cognitive deficits observed in mice [51, 52]. Considering the similar pathophysiology between Down syndrome and AD, he aimed to determine whether similar observations could be made in a mouse model of AD. Researchers first performed a battery of behavioral and cognitive tests in the Thy1-APPLond/Swe+ mouse model of AD and observed impairments in various cognitive functions [53]. They then ran preliminary studies with an acute sub-cutaneous injection of 3mg/kg of xamoterol. Results showed that this acute activation of β1-ADR rescues working memory and social recognition deficits observed in Thy1-APPLond/Swe+ mice.

SPARK Impact

Dr. Mehrdad Shamloo is an associate professor of Neurosurgery at Stanford University and runs a research laboratory focused on neurodegenerative diseases. He is a two-time SPARK scholar and an active member of the SPARK community. He received SPARK funds to carry out pharmacokinetic and behavioral studies of chronic treatment in a mouse model of AD. These studies showed improvement of cognitive behaviors at doses relevant to human safety data. SPARK support was able to help Shamloo and his team develop the candidate to a stage at which it could be licensed to a company to further develop it as therapeutic treatment.

Progress to Date

Xamoterol was patented for AD treatment. Since 2014, the patent has been licensed to Cortice Biosciences, a clinical-stage drug development company developing novel therapies for oncologic and neurologic indications with urgent unmet medical need. Cortice Biosciences is conducting the clinical studies to evaluate this molecule in AD.
A.2 Project Profile 2: Entering a Clinical Trial

Project: Pharmacologic Inhibition of Hyaluronan Synthesis for Type 1 Diabetes Prevention and Treatment  
Scholar: Paul Bollyky, MD, DPhil  
Years: 2014–Present (as of August 2016)

Unmet Medical Need

Type 1 diabetes (T1D) is characterized by progressive, immune cell-mediated destruction of pancreatic beta cells. Individuals with T1D are critically dependent on lifelong insulin injections and at higher risk of diabetic complications, including blindness, heart disease, and stroke.

Project Background

Bollyky recently reported [54] that autoimmune insulitis in T1D was associated with islet-specific deposition of hyaluronan (HA), an extracellular matrix polysaccharide thought to contribute to chronic inflammation in a variety of settings [55, 56, 57]. Using human T1D tissue samples from cadaveric organ donors obtained through the Juvenile Diabetes Research Foundation (JDRF) Network for Pancreatic Organ Donors with Diabetes (nPOD) program, Bollyky discovered that HA deposits were present in islets from donors with recent-onset T1D but not in those with longstanding T1D or type 2 diabetes or non-diabetic controls. However, it was unclear from previous studies whether HA deposition preceded or merely followed autoimmune insulitis or whether HA contributed to diabetes pathogenesis [58].

Using mouse models of T1D, Bollyky tested the hypotheses that HA is fundamentally required for progression of autoimmune insulitis and that pharmacologic inhibition of HA synthesis may prevent progression of autoimmune diabetes. Results showed that inhibition of HA synthesis stopped local autoimmunity and increased beta cell viability. Since individuals who develop T1D develop islet autoantibodies well before disease onset, they can be started on
preventive therapy before the disease progresses [58]. Bollyky has shown similar benefits in animal models of other autoimmune diseases.

**SPARK Impact**

SPARK has been integral in the success of this project to date. SPARK funded dosing and pharmacokinetics studies, and provided materials for a clinical trial. Through the SPARK-funded research, Bollyky has learned that the drug effect is very dose-dependent, a key fact that indicates that human dosing effects may differ from those in mice and other non-human models. Additionally, SPARK provided logistics support, regulatory expertise, and introductions to investors and private donors.

Bollyky notes that it is hard to raise money for repurposing a generic drug. The NIH and private foundations are possible donors, but they are typically very risk-averse and need to see extensive preliminary data in human studies before they will fund clinical trials. Bollyky has been able to move his repurposed drug project forward thanks to the SPARK program. Charities, foundations, and the NIH are other resources that repurposed drug projects typically look to for funding.

**Progress to Date**

The compound being studied is already approved, and has been on the market for around fifty years, approved in Europe and Asia to prevent biliary spasms from gallstones. Bollyky has been working on applications of the repurposed drug for autoimmune disease: treatment of primary sclerosing cholangitis (PSC) and prevention of T1D. Bollyky has submitted a proposal for the FDA’s Investigational New Drug (IND) program and is starting enrollment in the PSC trial. He plans to initiate a T1D trial in the near future.
A.3 Project Profile 3: Technical Failure

Project: Small-molecule Treatments for Chemotherapy Induced Peripheral Neuropathy
Scholar: Miriam B. Goodman, PhD
Years: 2012–2015

Unmet Medical Need

Chemotherapy Induced Peripheral Neuropathy (CIPN) dramatically reduces the quality of life for cancer patients and affects large numbers of people worldwide. There is no FDA approved treatment for CIPN, and no known method for predicting who will be affected and who will be spared.

Project Background

Treatment with chemotherapy drugs is linked to numbness and pain in the hands, in the feet, or peripheral neuropathy. This condition is now called chemotherapy-induced peripheral neuropathy, or CIPN. It affects approximately half of all patients receiving taxanes, vincristine, and bortezimib as chemotherapies. Exactly how chemotherapies affect sensory neurons is not known.

Dr. Goodman and her team started with the observation that disrupting microtubules alters transcriptional programs in C. elegans sensory neurons [59] via a well-characterized MAP kinase signaling pathway and the existence of ~20 drugs inhibiting a key enzyme in this pathway. Next, they set out to establish a C. elegans model of CIPN, and used genetics to test the therapeutic hypothesis that inhibiting MAP kinases could protect sensory neurons against damage.
SPARK Impact

Dr. Miriam Goodman is an associate professor of Molecular and Chemical Physiology at Stanford University. Her SPARK project was inspired by a conversation with a family member undergoing chemotherapy, and would not have been launched without support from the SPARK program. Additionally, the meetings with the SPARK community were invaluable for shaping and focusing the work.

Progress to Date

As of today, the project is on hold due to unanticipated experimental barriers that arose with the *C. elegans* model. The team has recently resolved this problem and may re-start the project in the near future. While the research has not yet moved beyond the academic setting, the project underscores the challenges of translational medicine, and SPARK’s role in supporting faculty research that aims to address significant unmet medical needs.
Appendix B

CFF Case Study Supplementary Materials

B.1 CFF Therapy Pipeline

![Pipeline Diagram]

Figure B-1: CFTR-Targeting Pipeline as of February 2017
B.2 Scope of the Ionis-SMA Foundation Collaboration

*provided by the SMA Foundation

Program Management

- SMA Foundation made the introduction of Frank Bennett (Ionis) to Alfred Sandrock (Biogen) which resulted in the $299 million partnering transaction
- Weekly research calls between Ionis and the Foundation: provided resources, advice, and contacts/introductions to key personnel in the SMA field

Preclinical work conducted by SMA Foundation

- Funded key Spinraza technology: Foundation support to Adrian Krainer and CSHL resulted in technology which was licensed by Ionis to create Spinraza
- Established mouse models of SMA [60, 61] and used them for in vivo testing of Spinraza in mouse models at CSHL, JAX, PGI

Clinical Study Contributions

- Clinical Sites: Foundation established a clinical network, PNCR (Pediatric Neuromuscular Clinical Research), comprised of five sites (Columbia, Boston Children’s, CHOP, Stanford, Nemours Children’s, and U of Rochester as a data management site). Spinraza studies were performed here. Additionally, they served as a key resource for the Ionis clinical team to learn about SMA, how to conduct trials in this complex disease, and how to implement many of the endpoints, etc. The PIs also were key experts for the FDA on SMA and Ionis matters
- Natural History and Trial Design: The SMA Foundation’s Natural History Study (NHS) contains data for more than 300 patients followed for over 10 years. The study provided critical data for trial design: it includes various outcome measures, lab measures, electrophysiology. Part of the study was also a tissue collection and repository. Data from

100
the study have been shared with industry partners including Ionis and the data were essential for planning Spinraza trials including some methods used in the trials [62, 63, 64].

- Standard of Care created by SMA Foundation PIs: Critical for conducting trials in Type 1 SMA and used/cited in these studies [65].

- Outcome measures: The Foundation sponsored research to establish endpoints and standards for their implementation for SMA clinical studies. These endpoints included the Hammersmith Functional Motor Scale-Expanded for assessing SMA Type II and Type III patients (the primary endpoint in the registration-enabling Phase 3 study in later onset-SMA), the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (“CHOP INTEND”) to evaluate the motor skills of SMA Type I patients (a key endpoint in the infantile-onset SMA studies), the timed “up & go” (TUG) test to measure balance and functional mobility of ambulatory SMA patients, and the Six-Minute Walk Test with gait analysis to assess fatigue and gait changes in ambulatory SMA patients. This also included establishing manuals standardizing implementation of these endpoints for clinical trials [66-71].

- Biomarkers: Foundation conducted a cross-sectional multicenter study called BforSMA that resulted in the identification of biomarkers that correlate with a commonly used functional motor scale in SMA, Hammersmith Functional Motor Scale (the modified version of the scale). This work yielded a plasma assay panel comprised of 27 markers that is commercially available at Myriad RBM. This panel accurately predicts the motor function score of SMA patients. We also developed a mouse panel that was used in preclinical studies with Ionis ASOs [72-75].

- Reagents: Foundation provided antibodies and resources for the SMN protein assay used for CSF measurements in Spinraza program

**FDA Matters**

- Created an International Coordinating Committee to organize global sites
- Foundation staff and clinicians provided support and attended Ionis’ FDA meetings
• Led and created a pre-competitive consortium of drug companies to align and work on common SMA drug development interests

• Led and created focus groups to better understand the experiences and needs of SMA patients and their families. A publication resulting from these studies have been used in FDA matters [76]
Appendix C

Bios of Interviewees

C.1 Solid Biosciences

Ilan Ganot is Founder and Chief Executive Officer of Solid Biosciences and Solid GT, and a member of the board of directors of both companies. He started Solid in 2013 to find treatments, and potentially a cure, for Duchenne muscular dystrophy, a disease that afflicts his son Eytani. Prior to starting Solid, Mr. Ganot was an investment banker at JPMorgan Chase in London, specializing in hedge fund-driven equities business for the firm. Mr. Ganot also worked at Nomura Securities in London, Hong Kong and New York, where he managed relationships with investors and clients of the firm. Prior to Nomura, Mr. Ganot was a senior salesperson for Lehman Brothers’ European Equities business. Mr. Ganot embarked on a banking career after practicing law at the Israeli law firm, Haim Zadok & Co, where his focus was private equity law and mergers and acquisitions. Prior to practicing law, Mr. Ganot was division head at Vir-Tech, a laser engraving business, and a captain in the Israel Defense Forces. Mr. Ganot received his MBA from London Business School and holds law and business degrees from the IDC in Herzliya, Israel.

Gilad Hayeem is a member of the board of directors of Solid Biosciences and Solid GT and is an active manager. Mr. Hayeem founded Solid Biosciences through his family office, Waverly Capital, and led the Series A round alongside JPMorgan. Mr. Hayeem was Managing Partner and CEO of Marble Bar Asset Management, a UK based investment fund he founded in 2002, which he exited in 2010. Mr. Hayeem then moved to New York, where he lives with his wife and four children. Mr. Hayeem received his MBA from City University, London, and holds history and politics degrees from the University of Leeds, England.

Andrey Zarur is Founder and Chairman of the Board of Solid. Dr. Zarur has been active in early-stage life sciences companies for more than 20 years, and has participated in the creation of more than a dozen companies in the healthcare and clean energy sectors. He is also Chairman, CEO, and Founder of GreenLight Biosciences, and a partner at Kodiak Venture Partners, a venture capital firm specializing in the formation of early-stage information and life technology investments. Prior to joining Kodiak Venture Partners, he was founder and CEO of BioProcessors, which was sold to Seahorse Biosciences in 2007. In addition to BioProcessors, he has led four life science companies from inception to exit. Dr. Zarur is also a co-founder and chairman of the board for Lumicell, and chairman of the board for Allegro Diagnostics. Dr. Zarur was named a Young Global Leader of the World Economic Forum in 2005. He is an
Overseer of the Museum of Science in Boston and a Senior Lecturer at the Massachusetts Institute of Technology (MIT) Sloan School of Management. Dr. Zarur holds Masters of Science degrees and a Ph.D. in Chemical Engineering from MIT and undergraduate degrees from the National University of Mexico. Dr. Zarur is the author of several peer-reviewed articles and holds close to 100 provisional and issued patents.

Carl Morris is the Vice-President of Research and Development, responsible for overseeing the drug development processes for Solid Biosciences. Prior to joining Solid, Dr. Morris was a Senior Director for Pfizer’s Rare Disease Research Unit, leading their efforts in neurologic diseases and the muscle biology programs. While at Pfizer, Dr. Morris directed several small molecule and biotherapeutic development programs, including a program that led to a Phase 2 study in Duchenne Muscular Dystrophy, while also heading an internal research group responsible for advancing programs from target identification to the clinic for many of the rare neurologic and muscle-related diseases. Dr. Morris identified key external opportunities, and worked closely with patient groups, academic laboratories, and other industry partners to advance drug development in the rare neuromuscular space. His scientific and drug development experience at Pfizer also included investigations into broader muscle wasting conditions, as well as tendon and bone repair biology. Prior to joining Pfizer in 2007, Dr. Morris was an Assistant Professor at Boston University School of Medicine, and a founding faculty member of the Muscle and Aging Research Unit, established to investigate strategies for improving muscle function during aging or disease. He completed his Postdoctoral fellowship in the Department of Physiology at the University of Pennsylvania, where he worked on multiple projects, ranging from molecular aspects of muscle protein interactions to therapeutic approaches for modulating muscle size and function. As a trained muscle physiologist, his academic pursuits have ranged from biophysical aspects of muscle contraction and enzyme kinetics to therapeutic interventions in a variety of in vivo muscle atrophy and disease models. Dr. Morris holds a B.A. in Biology from Franklin Pierce College (Rindge, NH) and a PhD in Physiology from UCLA.

Joel Schneider is the Director of Research & Development for Solid, responsible for the identification and development of promising therapies for DMD. Dr. Schneider's R&D focus includes Solid's gene therapy, small molecule, and biologics programs. Dr. Schneider previously completed a postdoctoral fellowship at Harvard University in the Department of Stem Cell and Regenerative Biology, characterizing and developing small molecules that enhance skeletal muscle regeneration. He holds a Ph.D. from Rutgers University and an undergraduate degree from Brandeis University. During his doctoral work, Dr. Schneider studied the cardiomyopathy associated with Duchenne muscular dystrophy and is the author of numerous peer-reviewed articles related to Duchenne muscular dystrophy and stem cell biology.

Andrea Ponti has 30 years of investment banking experience, focusing on healthcare since 1996. He created both JP Morgan’s and Goldman Sachs’ European investment banking healthcare franchises, advising on transactions for leading pharmaceutical, medical device and hospital companies. Over the last five years, he was Vice Chairman of European Investment
Banking and Global co-head of Healthcare at J.P. Morgan. Prior to that, Andrea was at Goldman Sachs, where he was Partner, Managing Director, Head of European Healthcare, Consumer and Retail and also Co-Global Head of Healthcare. Andrea sits on the board of Cell Medica, and received a B.A. in Economics from the University of North Carolina at Chapel Hill, where he is also a member of the Arts and Sciences Foundation Board of Directors.

**Pat Furlong** is the Founding President and CEO of Parent Project Muscular Dystrophy (PPMD), the largest nonprofit organization in the United States solely focused on DMD muscular dystrophy. Its mission is to improve the treatment, quality of life, and long-term outlook for all individuals affected by DMD through research, advocacy, education, and compassion. Along with leading PPMD, Pat speaks about DMD and related topics at conferences each year worldwide, and is an active Board member with the Genetic Alliance and the Muscular Dystrophy Coordinating Committee, U.S. Department of Health & Human Services. Pat graduated from Mt. St. Joseph College with a B.S. in Nursing, and also attended graduate school at Ohio State University.
C.2 SPARK Program

Daria Mochly-Rosen is the founder and co-director of Stanford University's SPARK program, Daria Mochly-Rosen helps academics navigate the so-called “valley of death” between drug discovery and development. Dr. Mochly-Rosen founded the SPARK Program at Stanford in 2006 after taking a leave of absence from academia to start a pharmaceutical company to translate her groundbreaking protein kinase C research into cardiovascular therapeutics. Challenging the academic dogma of how scientific discoveries should reach the pharmaceutical industry, the SPARK model has been implemented internationally, and has resulted in a book about drug development emerging from academia. Currently a professor of Chemical and Systems Biology at Stanford, Dr. Mochly-Rosen is from Israel, where she received her doctorate at the Weizmann Institute in chemical immunology.

Kevin Grimes is the co-director of the SPARK program in translational research, and an associate professor in the Department of Chemical and Systems Biology at the Stanford University School of Medicine. He received his M.D. from Brown University, and completed his residency in internal medicine at Stanford University. Upon completion of his training, he became a Clinical Assistant Professor of Medicine at Stanford, where his primary duties include the teaching and practice of internal medicine. Dr. Grimes received a Hartford Foundation Fellowship to study health economics at the Stanford Graduate School of Business, where he obtained an MBA. He has since spent fifteen years in industry, working in life sciences consulting and in the medical device and biotechnology sectors prior to returning to Stanford to co-direct SPARK. In addition to SPARK, Dr. Grimes teaches graduate student courses on drug discovery and development, and continues to teach and practice internal medicine.

Marcia Cohen is the Senior Associate Dean for Finance and Administration for the Stanford University School of Medicine, a position she has held since 2006. Reporting to the Dean of the medical school, Marcia is responsible for the oversight and direction of strategy and operations of the School’s financial, administrative, and information technology functions. She has financial oversight for the School’s $2.0 billion budget, and sets financial and administrative policy for the School, including its 27 academic departments and 8 interdisciplinary institutes and centers. Prior to joining Stanford in 2003, Ms. Cohen served as the Director of Finance in the Department of Medicine at the University of California, San Francisco (UCSF). Prior to UCSF, Marcia was a management consultant with Touche Ross (now Deloitte), including 5 years based in Hong Kong. Marcia graduated with a B.A. magna cum laude from Carleton College, majoring in Economics, and holds an MBA from the Yale University School of Management.

Merhdad Shamloo received his doctoral degree in 1999 from the Wallenberg Neuroscience Center of Lund University in Sweden. He was recruited to the San Francisco Bay Area the same year, where he held several positions at biopharmaceutical companies, including Affymax and AGY Therapeutics, until 2008. During this time, he was responsible for the discovery and
development of novel neuroprotective and regenerative small molecule and peptide therapeutics for multiple diseases. In 2008, Dr. Shamloo joined Stanford University to establish a new behavioral neuropharmacology center for the Stanford Neurosciences Institute. He also formed his own research laboratory to focus on understanding normal and pathological brain functions for neurological disorders such as stroke, Alzheimer’s disease (AD), and autism. Its efforts are currently directed towards a subset of genes and proteins involved in neuroprotective or neurodegenerative pathways, which are regulated in these disorders. Through these investigations, Dr. Shamloo and his team hope to understand the processes leading to the functional and behavioral malfunction in these disorders, and develop experimental therapeutics. The ultimate goal is to accelerate the translation of these experimental discoveries into novel therapeutic approaches, to improve the quality of life for patients with brain disorders.

**Steve Schow** was formerly Vice President of Research and Development at Telik, Inc., and is currently a consulting professor at Stanford University. He has over 35 years of experience in pharmaceutical, biotech and agrichemical industrial research and development. Dr. Schow served as Telik’s Vice President of Research and Development from 2007 until his retirement in 2014, and was Telik’s Vice President of Chemistry Research beginning in 2000. At Telik, Dr. Schow was responsible for manufacturing, drug discovery, and business development. Before joining Telik, Dr. Schow served as Director of Medicinal Chemistry at CV Therapeutics, a biotechnology company, and as a Senior Group Leader at Lederle Laboratories, a major pharmaceutical company. Prior to joining Lederle, Dr. Schow was a Research Leader in the Dupont Biochemicals Department. Dr. Schow started his industrial career as a Senior Research Chemist in the Medicinal Chemistry Department of Sterling Drug. Dr. Schow holds a doctorate in organic chemistry from the University of California at San Diego, and completed his postdoctoral training at the University of California at Los Angeles and the University of Pennsylvania. Dr. Schow is a co-author/co-inventor on 76 papers and patents. Dr. Schow was appointed Consulting Professor at Stanford University in the Department of Chemical and Systems Biology in the School of Medicine in 2013.

**Edda Spiekerkoetter** is an Assistant Professor in the Division of Pulmonary and Critical Care in the Department of Medicine at Stanford University, and Staff Physician at Stanford Hospital and Clinics. Her main clinical and research interest is pulmonary arterial hypertension (PAH). She received her medical training in Tübingen and Freiburg, Germany, and performed her residency and a Pulmonary and Critical Care Fellowship at Hannover Medical School, where her interest in PAH started. During her postdoctoral fellowship, she focused on genetic and environmental factors involved in the pathogenesis of PAH, and studied 2 genes important in PAH, S100A4/Mts1 and BMPR2. In addition, she showed that a herpes virus infection would lead to the development of pulmonary vascular disease by inducing elastase. Dr. Spiekerkoetter was awarded a postdoctoral fellowship by the American Heart Association / Pulmonary Hypertension Association.
**Katharine Ku** has been the Director of the Office of Technology Licensing (OTL) at Stanford University since 1991. OTL is responsible for the licensing of various state-of-the-art university technologies, such as biotechnology and semiconductor inventions, software, medical instrumentation, etc. Concurrently from 1994 to 1998, Ms. Ku was responsible for Stanford's Sponsored Projects Office. Previously, she served as Vice President of Business Development at Protein Design Labs, Inc., now a publicly traded biotechnology company in Mountain View, California. Prior to PDL, Ms. Ku spent 12 years at Stanford in various positions. Previously, she was also a researcher at Monsanto and Sigma Chemical, an administrator of a dialysis clinical trial at University of California, where she also taught chemistry and basic engineering courses. Ms. Ku has been active in the Licensing Executive Society (LES), serving as Vice President, Western Region and Trustee of LES and various committee chairs. She has also served as President of the Association of University Technology Managers (1988-90). She recently received the AUTM Bayh-Dole Award for her efforts in university licensing. Ms. Ku has a B.S. in Chemical Engineering (Cornell University), an M.S. in Chem. Eng. (Washington University), and is a registered patent agent.

**Robert F. Booth** is currently CEO of Virobay. From July 2006 to May 2010, Dr. Booth served as an Operating Partner and Senior Advisor at TPG Biotechnology Partners, LP, a venture capital company. From December 2006 to July 2007, Dr. Booth served as the acting Chief Scientific Officer of Galleon Pharmaceuticals, Inc., a company developing new therapeutics for diseases of the respiratory system. From 2002 to 2006, Dr. Booth was the Chief Scientific Officer at Celera Genomics Corporation (Celera), a drug discovery and development company. Dr. Booth served as Senior Vice President at Roche Bioscience, a part of F. Hoffmann-La Roche Ltd. (Roche), from 1996 to 2002. Dr. Booth currently serves on the boards of directors of Pharmacyclics, Inc., Galleon Pharmaceuticals, Inc. and Glialogix, Inc., and is Chairman of the Scientific Advisory Board at Galleon Pharmaceuticals, Inc. Dr. Booth also serves as a member of the Scientific Advisory Boards of ShangPharma Corporation, Eicelyx Therapeutics, Inc. and NaZura Biohealth, Inc. Dr. Booth received a B.Sc. and a Ph.D. from the University of London in biochemistry.

**Kristina Bender** is currently a scientist at Achaogen, a Bay Area-based biopharmaceutical company, where she focuses on the development of therapeutic antibodies. She was a former SPARK scholar while a postdoctoral fellow at Stanford and now currently serves as an advisor to the SPARK program. She received her bachelor's degree from the University of Zagreb and her Ph.D. in Biochemistry from the University of Ljubljana. Dr. Bender has published numerous papers and has extensive experience in translational medicine research.

**Josh Lichtman** is currently a scientist at NGM Biopharmaceuticals, an early stage biotech company based in the Bay Area focused on treatments for metabolic disorders. He is a former SPARK scholar, and a student of the accompanying SPARK graduate course. He received his B.S. from Dickinson College in Biochemistry and Molecular Biology. He received his Ph.D.
from Stanford University in the Department of Chemical and Systems Biology. He currently serves as an advisor to the SPARK program.

**Leon Chen** is a Venture Partner with OrbiMed. Prior to joining OrbiMed, Dr. Chen was the co-founder of KAI Pharmaceuticals, where he built the company as the first employee. He held responsibilities in research, intellectual property and business development before Amgen acquired KAI in 2012. He was previously an Entrepreneur in Residence at Venrock, and most recently was a Partner at Skyline Ventures, where he served on the board of a number of biotech and diagnostic companies. Dr. Chen has a B.A. in Biochemistry from U.C. Berkeley, a Ph.D. in Molecular Pharmacology from Stanford and an M.B.A from the Stanford Graduate School of Business.

**Nina Kjellson** joined the Canaan healthcare team in the fall of 2015. She focuses on early-stage investments in biopharmaceuticals and digital health. Her current investment themes include therapeutics for serious and underserved conditions such as cancer, autoimmune disease and life-threatening infections; patient/consumer engagement; and IT-enabled transformation of healthcare delivery. She is the co-founder and co-chair of ConsumerMed.org, a forum to address the convergence of health care and consumer innovation, and serves as a mentor to Blueprint Health, a digital health incubator, and to Springboard Life Sciences, an accelerator for healthcare companies driven by women entrepreneurs. She is a member of the advisory board for the Oliver Wyman Health Innovation Center. Prior to Canaan, Ms. Kjellson was a General Partner at InterWest Partners, where she had been investing in healthcare startups since 2002. Before InterWest, she was an investment manager at Bay City Capital, a life sciences merchant bank, and a research associate at Oracle Partners, a health care-focused hedge fund. Ms. Kjellson began her career conducting health policy and survey research with the Kaiser Family Foundation. Ms. Kjellson was born in Scandinavia and grew up in the Northeast. Ms. Kjellson received a B.A. in Human Biology from Stanford University.

**Paul Bollyky** is an assistant professor at Stanford University in the Infectious Diseases Department of Medicine and Microbiology and Immunology Department. Dr. Bollyky’s lab studies how immune responses are regulated within injured and infected tissues. They work at the intersection of immunology, structural biology, bioengineering and microbiology with the goal of developing novel therapeutics to promote wound healing and immune tolerance. Dr. Bollyky is an active member of Bio-X, Child Health Research Institute, and Stanford Neurosciences Institute. He received a B.A. in Biology from Columbia University before completing his PhD at Oxford University and MD at Harvard Medical School. Dr. Bollyky was awarded an Innovation Grant from SPARK in 2013, an Outstanding Faculty Mentor Award from Stanford Immunology in 2015, and a Catalyst Award from the Dr. Ralph and Marian Falk Medical Research Trust in 2015, amongst other impressive awards.
Miriam B. Goodman is a professor of Molecular and Cellular Physiology at the Stanford University, School of Medicine. Dr. Goodman started working at Stanford University in 2002 after completing her PhD at the University of Chicago in 1995 and postdoctoral work in C. elegans neurophysiology and genetics at the University of Oregon and Columbia University. Dr. Goodman’s history working in labs dates back to high school, when she began writing scientific software in research labs at the NIH. She continued working in research labs throughout her undergraduate studies in biochemistry at Brown, save for one summer working as a material scientist. Dr. Goodman has received multiple awards for Excellence in Graduate Teaching and one for Excellence in Diversity and Inclusion from the Stanford University, School of Medicine. She currently serves as an Editorial Board Member in the Section on Ion Channels and Transporters for the Biophysical Journal.
C.3 Cystic Fibrosis Foundation

*Note: The former Vertex employees interviewed for this case study are not authorized spokespeople of the company.

Robert J. Beall is the former President of the CF Foundation and was with the organization for over 35 years. He began his tenure at the CF Foundation as Executive Vice President for Medical Affairs, and for the last 21 years he served as President and Chief Executive Officer. Prior to joining the CF Foundation, Dr. Beall was on the medical school faculty of Case Western Reserve University in Cleveland, and at the National Institutes of Health where he managed a large portion of their cystic fibrosis program. Under Dr. Beall’s leadership, the CF Foundation has become one of the most respected voluntary health organizations in the country, and is recognized for its innovative approaches to bring new therapies to patients with the disease. The creation of an innovative research centers program in the 1980s (the Research Development Program) attracted many leading institutions and first-rate scientists to the CF research effort. In 1998, the CF Foundation launched its ground-breaking Therapeutics Development Program, a unique coalition between industry, academics and the CF Foundation that is directed at the discovery and development of additional approaches to CF drug discovery and development. As a result of the pioneering business model of the Cystic Fibrosis Foundation, there are currently nearly 30 potential CF therapeutic products in the pipeline, and the prospects for a cure and control for cystic fibrosis have never been higher.

Preston Campbell is the current president and chief executive officer of the CF Foundation. He previously served as the Foundation's executive vice president for medical affairs. Dr. Campbell has more than 25 years of experience caring for people with CF. Most recently, he oversaw the Foundation's research, drug discovery, drug development and clinical research programs, and directed clinical research, the Foundation's network of care centers, clinical training programs and the national patient registry database. He initially became interested in CF as a CF camp counselor while earning his medical degree from the University of Virginia Medical School.

Terry Coyne joined Royalty Pharma in 2010. Prior to joining Royalty Pharma, Mr. Coyne worked as a biotechnology equity research associate, and most recently as a senior analyst at JP Morgan from 2007 to 2010. From 2006 to 2007, he worked as a biotechnology equity research associate at Rodman & Renshaw. Prior to this, Mr. Coyne worked in various commercial roles at Wyeth Pharmaceuticals. Mr. Coyne received a BS in business administration from La Salle University and an MBA from La Salle University.

Loren Eng is the President of the SMA Foundation, responsible for overseeing all projects and relationships. Prior to establishing the SMA Foundation, Ms. Eng worked in investment banking at Morgan Stanley, merchant banking at the Lodestar Group, and as a director of business
development at KKR’s media company, K-II. Ms. Eng and the work of the SMA Foundation have been featured in national media including ABC News, Bloomberg Markets, Forbes, Fox News, The New York Times, Nightline, Parents Magazine, and the Today Show. Ms. Eng has testified before Congress on SMA, NIH funding and biomedical research. Ms. Eng received a BA from Wellesley College, and an MBA as well as an MA in education from Stanford University.

**Pablo Legorreta** founded Royalty Pharma in 1996. Royalty Pharma is the industry leader in acquiring revenue-producing intellectual property, with approximately $17 billion in royalty assets. Royalty Pharma funds innovation in life sciences, indirectly, when it acquires existing royalty interests from the original innovators (academic institutions, research hospitals, foundations and inventors) or, directly, when it partners with life sciences companies to co-develop and co-fund products in late-stage human clinical trials. Prior to founding Royalty Pharma, Mr. Legorreta spent a decade at Lazard Frères in Paris and New York where he provided cross-border merger and acquisition and corporate finance advisory services to European and U.S. corporations. Mr. Legorreta serves on the Board of Governors of the New York Academy of Sciences, and the Boards of Trustees of Rockefeller University, the Hospital for Special Surgery, the Pasteur Foundation (U.S. affiliate of the French Institut Pasteur), The Open Medical Institute, The Park Avenue Armory and Grace Church School. Mr. Legorreta founded and is currently Chairman of Alianza Médica para la Salud (AMSA), a privately-funded, not-for-profit foundation whose goal is to educate Latin American doctors and healthcare providers to improve the quality of healthcare in Latin America. Mr. Legorreta received a degree in industrial engineering from Universidad Iberoamericana (Mexico City).

**Catherine (Cam) C. McLoud** is currently the Chair of the CF Foundation’s National Board of Trustees. She is a seasoned executive with more than 35 years' experience in leadership positions in the hospitality business, most recently as president of the consulting company Commonwealth Hospitality, LLC. She was elected chair of the Foundation's Board of Trustees in 1999 and has served on the Board for more than 30 years. Ms. McLoud became involved in the CF community after her son, Will, was diagnosed with CF.

**Eric R. Olson** is Chief Scientific Officer at Syros Pharmaceuticals, Inc. He is also on the Board of Trustees at the CF Foundation. Dr. Olson was previously employed as Research Scientist by The Upjohn Co., Vice President-Research by Vertex Pharmaceuticals, Inc., and Director-Antibacterials & Molecular Sciences by Warner-Lambert Co. At Vertex, Dr. Olson led the successful CF program. He received his undergraduate degree from the University of Minnesota and a doctorate degree from the University of Michigan.

**Robert Pacifichi** is currently the Chief Scientific Officer at CDHI, which he joined in 2004. Previously, he was the Site Director and Chief Scientific Officer at the Research Triangle Park
Laboratories of Eli Lilly and Company. There he oversaw the company's global screening and quantitative-biology efforts. Prior to joining Lilly, Dr. Pacifici was Vice President of Discovery Technologies at Xencor, a privately held biotechnology company that applied rational design principles to the development of protein therapeutics and held various roles at Amgen. Robert received a BS in Biochemistry from the University of Massachusetts, Amherst, and a PhD in Biochemistry from the University of Southern California. He holds an adjunct appointment at the University of Southern California's Department of Molecular Pharmacology and Toxicology. He is also Chair of the Spinal Muscular Atrophy Project's Scientific Steering Committee, which is part of the National Institute on Neurological Disorders and Stroke (NINDS). He currently sits on several additional external boards and advisory committees, including the Cooperative International Neuromuscular Research Group, SMA Foundation, and TREAT ALS Steering Committee.

Marya Postner represents public and private life sciences companies, especially biotechnology and biopharmaceutical companies, in a variety of transactions. She counsels clients with respect to the structuring and negotiation of agreements designed to maximize the value of the company's products and technology assets. She has particular experience handling strategic alliances with pharmaceutical companies in areas as diverse as collaborative research and the development and marketing of late-stage pharmaceutical products. Dr. Postner has received recognition from The Best Lawyers in America for Biotechnology Law. She received a JD from the University of California, Berkeley, Boalt Hall School of Law, in 1996. While at Boalt Hall, she was editor-in-chief of the Berkeley Technology Law Journal. She earned MA and PhD degrees from Princeton University in 1989 and 1993, respectively. In 1987, she was awarded a BS in Biology, magna cum laude, from Georgetown University and a National Science Foundation graduate fellowship. Dr. Postner is admitted to practice in California and before the United States Patent and Trademark Office. She is a member of the State Bar of California, the American Bar Association, Sigma Xi and the American Association for the Advancement of Science.

Ying Qian is an Associate Director of Strategy and Operations at the SMA Foundation. She has over 5 years of experience improving organizational operations and managing working groups within organizations in a range of industries. She joined the SMA Foundation from the Children’s Hospital at Montefiore (CHAM) where she served as the Special Assistant to the Chairman, Dr. Philip Ozuah. At CHAM, she led projects to improve efficiencies in hospital operations. Prior to CHAM, she was a consultant to companies in the insurance, energy and utilities sectors with The Brattle Group in San Francisco. Ms. Qian holds a Masters in Public Health with a concentration in Health Policy and Management from Columbia University’s Mailman School, where she focused on the operations and management of hospitals and non-profit healthcare organizations. She received her BA in Mathematics from Wellesley College.
Ken Schaner has more than 40 years of private practice experience, and has represented many for-profit and non-profit entities in the corporate and tax aspects of a wide variety of agreements, transactions, financings, licenses, mergers and acquisitions. Mr. Schaner began his career at the Internal Revenue Service’s (IRS) legislative and regulations division. During his time with the IRS, Mr. Schaner worked on the 1969 Tax Reform Act and was one of the principal drafters of the new private foundation provisions. In 1982, Mr. Schaner co-founded Swidler Berlin, LLP. While a partner in that firm, he also served as managing member and chair of the corporate group. After Swidler Berlin’s merger with Bingham McCutchen, LLP in 2006, Mr. Schaner remained a partner until 2008, when he formed Schaner & Lubitz to focus on representing tax-exempt organizations. Since 1983, Mr. Schaner has served as general counsel to the CF Foundation. In that capacity, he represented CFF in its first VP transaction with Aurora Biosciences Corporation (now Vertex), and subsequently represented CFF’s affiliate, CFFT, in the historic monetization of the Vertex royalty interest in 2014. He has represented numerous clients in VP transactions and related legal matters. Mr. Schaner also serves as general and outside counsel to many non-profits. He advises on the full range of issues faced by Section 501(c)(3), (c)(4) and (c)(6) organizations, including board governance, business, and tax-exempt compliance issues.

Kristin Schneeman joined FasterCures in April 2005 as director of programs, with primary responsibility for its innovation portfolio of projects and activities, focused on best practices in the funding and conduct of medical research and innovative collaborations among players in the research enterprise. Among other initiatives, she runs The Research Acceleration and Innovation Network (TRAIN) program, which provides a platform for knowledge-sharing and relationship-building to support the growth of VP in medical research. Ms. Schneeman brings to FasterCures 25 years’ experience in public policy, politics, academia and the media. She served for three years as a senior adviser and policy director to a gubernatorial candidate in Massachusetts, as a policy aide to a U.S. Congressman, and for four years as the front-line manager and chief-of-staff for a senior adviser to Vice President Al Gore. At Harvard University, she directed research projects on future challenges facing governments and on complex negotiations in business, politics and international relations. Schneeman began her career as a producer of documentary films, for which she was the recipient of an Emmy Award in 1990.

Christiana Stamoulis is currently the CFO and Head of Corporate Development at Unum Therapeutics. She is responsible for leading Unum’s financial strategy, capital-raising activities, and the forging of business development partnerships. She brings extensive experience in developing strategies for growth, strategic collaborations and capital-raising transactions. Ms. Stamoulis most recently served as SVP and Head of Corporate Strategy and Business Development at Vertex Pharmaceuticals, where she helped develop the company’s vision, corporate strategy and the identification and execution of its strategic business collaborations. Prior to Vertex, Ms. Stamoulis was a senior investment banker with Goldman Sachs and
Citigroup. Christiana received her Bachelors of Science and MBA from the Massachusetts Institute of Technology.

**Douglas A. Zingale** is currently the manager of Blue Goose Capital, a seed stage tech investor. Prior to Blue Goose, he was the CFO and co-founder of hotdotTV, CEO of Wilson Solarpower and General Manager for Strategic Partnerships at Microsoft. He began his career at Bain Consulting and practiced law for many years at Mintz Levin. He served as Co-Chairman of the Business Practice at Mintz and represented many technology companies, venture capital funds and investment banks, including Vertex, Biogen, AOL, Thermo Electron, Atlas Ventures, North Hill Ventures, SG Cowen and Alex Brown. He worked closely with Josh Boger, Vertex's CEO, on the negotiation of the Aurora Biosciences acquisition. He has degrees from the Sloan School at MIT and from the University of Michigan Law School.
Appendix D

Additional Acknowledgements and Notes

Case Study Acknowledgements

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