Venture Philanthropy: A Case Study of the Cystic Fibrosis Foundation

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This Version: 23 April 2019

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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. Historically, this has been particularly true for assets intended to treat rare diseases, where market sizes are often too small to attract much attention and funding. Venture philanthropy (VP)—which, for the purpose of this paper, is defined as a model in which nonprofit, mission-driven organizations fund initiatives to advance their objectives and potentially achieve returns that can be reinvested toward their mission—offers an alternative to traditional funding sources like venture capital or the public markets. Here we highlight the Cystic Fibrosis (CF) Foundation, widely considered to be the leading VP organization in biotech, which facilitated the development of Kalydeco, the first disease-modifying therapy approved to treat cystic fibrosis. We evaluate the CF Foundation's example, including its agreement structures and strategy, explore the challenges that other nonprofits may have in adopting this strategy, and draw lessons from the CF Foundation for other applications of VP financing.

Introduction

Venture philanthropy (VP) is a funding model within the broader movement of impact investing in which a nonprofit or "mission-driven" organization makes investments to advance its philanthropic mission. While not undertaken with a profit motive, these investments have the potential to generate returns to the nonprofit, to be reinvested in a virtuous cycle to support the nonprofit's mission. VP in the biotechnology industry began out of the desire of disease-focused nonprofit organizations to provide new forms of incentives to drug developers to focus on developing treatments to address unmet clinical needs. More and more nonprofits are exploring VP in previously neglected areas of medicine, including the treatment of rare diseases.

According to recent estimates, the typical drug development process requires over 10 years and $2 billion for a single successful therapy [1]. Due to the high risk and expense, this process favors candidates with lucrative markets, or later-stage assets that have already generated promising data. As a result, many early-stage assets do not receive the necessary funds to progress in the drug development cycle. Historically, therapies for rare diseases have been especially vulnerable because drug developers had little financial incentive to develop treatments for so few patients. Despite policies such as the Orphan Drug Act of 1983 [2], which created new incentives for the development of therapies for rare diseases (defined as diseases with fewer than two hundred thousand cases in the U.S.), many people with rare diseases continue to face significant unmet clinical needs. Over 7,000 rare diseases still have no approved treatment [3].

The Cystic Fibrosis Foundation is the world's leading mission-driven organization involved in the search for a cure for cystic fibrosis (CF), a rare, genetic disease which currently affects more than thirty thousand Americans. It is a pioneer in employing VP in orphan drug development. After funding decades of basic research in CF at academic laboratories, the foundation now also funds promising R&D efforts in private-sector biotechnology and pharmaceutical companies.

To this end, the CF Foundation founded a nonprofit drug development affiliate, Cystic Fibrosis Foundation Therapeutics Inc. (CFFT). As of January 1, 2018 the activities of CFFT were transferred to the to the CF Foundation and continued without interruption. One of CFFT's first VP funding agreements was an effort with a for-profit company to discover compounds that might compensate for the primary genetic mutation in CF patients. Over a period of twelve years, the CF Foundation committed $150 million to fund CF programs in development at Vertex Pharmaceuticals, a Boston-based biotechnology firm. The agreement included a provision for the CF Foundation to receive royalties calculated as a percentage of future sales of successful CF drugs resulting from the agreement.

This work led to the identification and development of Kalydeco, the first FDA-approved treatment to address the underlying cause of CF. Approved in 2012, Kalydeco was a game-changer for the 4% of CF patients eligible for treatment based on their genetic mutation (label expansions have since increased this number to 13% of CF genetic mutations). This approval was followed in 2015 by a combination drug called Orkambi, which has the potential to help up to 50% of all CF patients based on their mutation [4].

In 2014, CFFT sold the rights to its future Vertex royalties to an outside investment firm, New York City-based Royalty Pharma, for $3.3 billion. By divesting itself of its royalty stake in commercial products, CFFT sought to immediately capitalize on the availability of additional funds that could be used for the benefit of people with CF, and to remove any conflicts of interest in its VP strategy. This news sparked praise in the biotechnology community, but concern from critics worried about the future of the foundation's mission. CFFT had generated enough capital from the sale to fund dozens of new investments in even more promising CF treatments, including potential one-time cures via gene therapy and gene editing, but critics argued that the CF Foundation was being rewarded at the expense of patients, who might be faced with higher health-insurance deductibles for the $300,000/year price tag for Kalydeco [5].

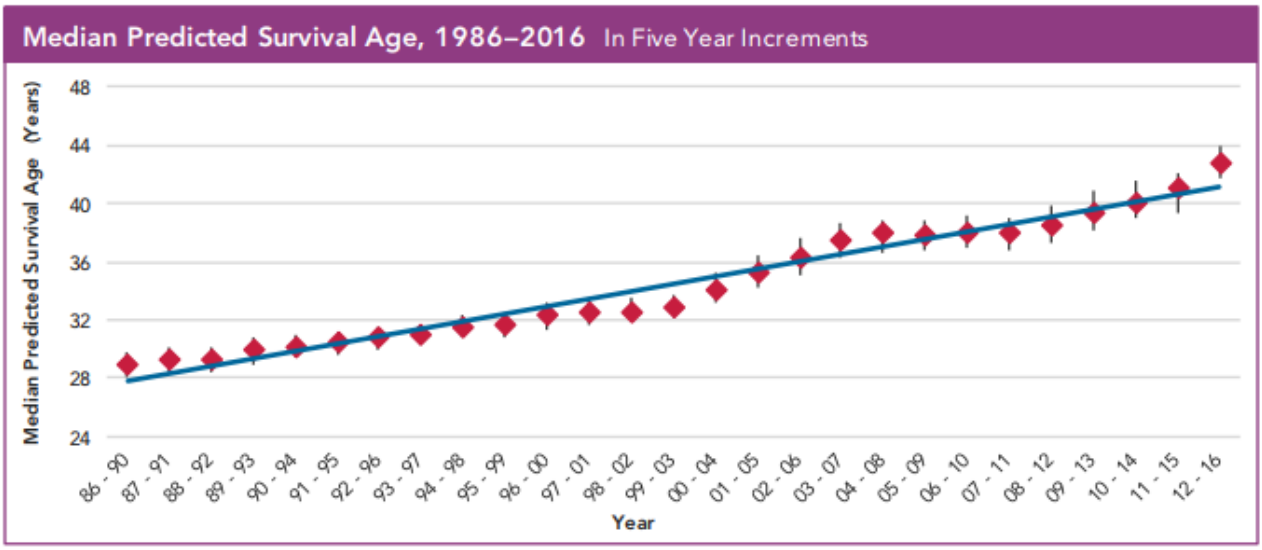
CFFT's use of contracted research in the development of Kalydeco has been analyzed previously [6,7]. This paper focuses instead on the CF Foundation's overall VP strategy, its decision-making process, the structural elements of CFFT's agreements and transactions (especially with respect to Royalty Pharma), and the challenges of continuing to fundraise after monetization. Although the CF Foundation is motivated solely by its mission to reduce the burden of disease on people with CF—and not on financial return—our focus in this case study is to understand how for-profit financing techniques can be used effectively to achieve mission-driven goals.

To that end, we consider the roles and incentives of all the major stakeholders, highlighting the keys to the CF Foundation's success and implications for best practices in VP. As government funding for early-stage compounds and basic science remains uncertain, we expect the role of mission-driven organizations will grow in importance, not only in providing much-needed capital, but also in offering disease-specific expertise from the patient community to accelerate and lower the risk of drug development. We analyze the CF Foundation's model with the goal of providing a framework for other mission-driven organizations looking to use VP to amplify their impact.

Overview of Cystic Fibrosis

Cystic fibrosis is a progressive, hereditary disease that causes persistent lung infections and limits the ability to breathe over time. It is caused by one of more than 1,700 known mutations to the CFTR gene. The CFTR defect causes mucus blockages in the lungs and airways, often leading to bacterial infection and difficulty breathing, resulting in severe

lung disease (although it affects multiple organ systems) [4]. Worldwide, CF affects approximately 70,000 individuals and is fatal, with patients typically dying young due to lung failure. Although there is still no cure, the outlook for CF patients has improved dramatically over the past several decades (see Figure 1).



Using the currently recommended method for calculating median predicted survival.

Figure 1. Median Predicted Survival Age of CF Patients over Time.
Source: Cystic Fibrosis Foundation's 2016 Patient Registry Annual Data Report

History of the Cystic Fibrosis Foundation

The Cystic Fibrosis Foundation, based in Bethesda, Maryland, was founded in 1955 by parents of children with CF. At the time, there were no approved treatments for CF, and no research was being conducted on the disease. Over the years, the CF Foundation has funded advances in the scientific understanding of the disease, including the discovery of the gene mutation that causes CF and the development of most therapeutics for CF. Beyond its efforts to advance new treatments and cures, the Foundation oversees an extensive patient registry, accredits and provides funding for more than 120 specialized CF care centers across the country, and in 1998 established the largest CF clinical trials network in the world, the Therapeutics Development Network (TDN), for which it is the primary source of funding. The mission of the Foundation 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 Foundation is undoubtedly tied to the CF community, which has vigorously fundraised for the cause, and to its leadership. The Foundation's management philosophy features a goal-oriented approach to achieve important milestones in CF

treatment, including the clinical trials network and a robust research and development program. The team was led by Dr. Robert Beall for 21 years until his retirement in 2015. Dr. Preston Campbell, formerly the Foundation's executive vice president of medical affairs, was named the new president and CEO, and under his leadership, the Foundation is expanding its role to better serve patients and families and accelerate drug development.

The CF Foundation's Venture Philanthropy Model

The CF Foundation's VP model is driven by the needs of people with CF. Well before the term "venture philanthropy" became popular, the Foundation used donations and royalties to accelerate the development of therapeutics for CF. Table 1 summarizes the royalty revenue and sales since 2010. A by-product of the Foundation's model are funds to act on its mission: any funds stemming from royalty sales are used to meet the needs of people with CF—from funding new therapies to providing additional support for care centers to investing in cutting-edge technologies that could produce a cure for CF.

The CF Foundation established Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), its nonprofit drug discovery arm, to facilitate drug development contracts, in line with its stated mission. The Foundation has invested about $425 million in its VP agreements through CFFT, and CFFT has diversified its funding efforts across many therapeutic programs. As is typically the case in drug development, many programs have been unsuccessful, but some have led to new treatments; of nearly a hundred agreements, only a few have resulted in significant financial return to the Foundation, including TOBI, Kalydeco, and a medical device for CF.

CFF Product Revenues ($M)	2010	2011	2012	2013	2014	2015	2016
Royalty Revenue and Sales of Licenses	54	0.12	156	257	3,280	32	52

Table 1. CFFT Royalty Revenues and Sales (Source: CF Foundation Financial Statements)

Agreement Structure

While each agreement is specific to the nature of the therapeutic under development, a few key components are implemented consistently to mitigate risk on behalf of CFFT. Its agreements feature milestone- or activities-based payment to align the incentives among stakeholders and ensure that progress is being made for the benefit of patients, and an early partial return on investment if the funded company licenses or sells a partially developed product to a third party. Another key element 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, such as when Altus Pharmaceuticals was unable to continue its trials, leading CFFT to take back the product candidate and sublicense it to a third-party company. In all of its VP transactions, CFFT also requires the funded company to acknowledge that CFFT may also fund competing research.

CFFT's primary goal is to speed development of new CF treatments by funding promising scientific research in academia and the biotechnology and pharmaceutical industries. Rather than take an equity stake in a 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 achieve a financial return.

The trade-off is limited control on the part of the Foundation during drug development and no influence over the biopharma partners' commercial plans. The most notable concession is that the Foundation has no input or control over the price of the therapy. As other organizations consider VP, they should be aware that while they can express their concerns about the cost of therapies, ultimately, the manufacturer alone sets the price.

From biopharma's perspective, financing from a disease-focused nonprofit provides two advantages: significant clinical expertise in the disease, and a low cost of generally non-dilutive capital. The capital provided by a disease-based nonprofit like the CF Foundation is often less encumbering than traditional venture capital or that provided by a large pharmaceutical company, allowing biotech companies to pursue programs with higher risk but higher reward than they might otherwise be able to sustain.

Most important, the CF Foundation is in a unique position to facilitate therapeutic development because of its collection of data in the CF Patient Registry, as well as its deep clinical expertise. The CF Patient Registry contains a wealth of data that amounts to a natural history of the disease. Individuals involved in the approval process cite this registry as critical to the speedy FDA approval of Kalydeco.

Portfolio Approach

CFFT has pursued a diversified portfolio in its R&D investments to ensure it is well positioned for ultimate clinical success. Since the identification of the CFTR gene and the protein it codes for, CFFT has continued its efforts to develop products that target this protein as well as other therapies to address complications from the disease. As of late 2016, it has funded a broad portfolio of over 30 programs, ranging from preclinical assets to drugs in mid-stage development when CFFT determines the therapy being developed is unlikely to reach patients without CFFT funding. The distribution of its current portfolio can be seen in Figure 2. Due in large part to successful VP efforts, CFFT has been able to increase its funding of research across the categories of therapies in the CF pipeline (see Figure 3). In 2012, CFF and CFFT allocated a medical and research budget of $87 million across more than 500 awards; in 2016, that funding was increased to over $160 million

across more than 1,100 awards. The Foundation is optimistic about the potential for developing a one-time cure for all people with CF, which has led to significant funding for promising new modalities such as gene editing and gene therapy. In 2015, the Foundation committed more than $15 million to begin advancing research in this field.

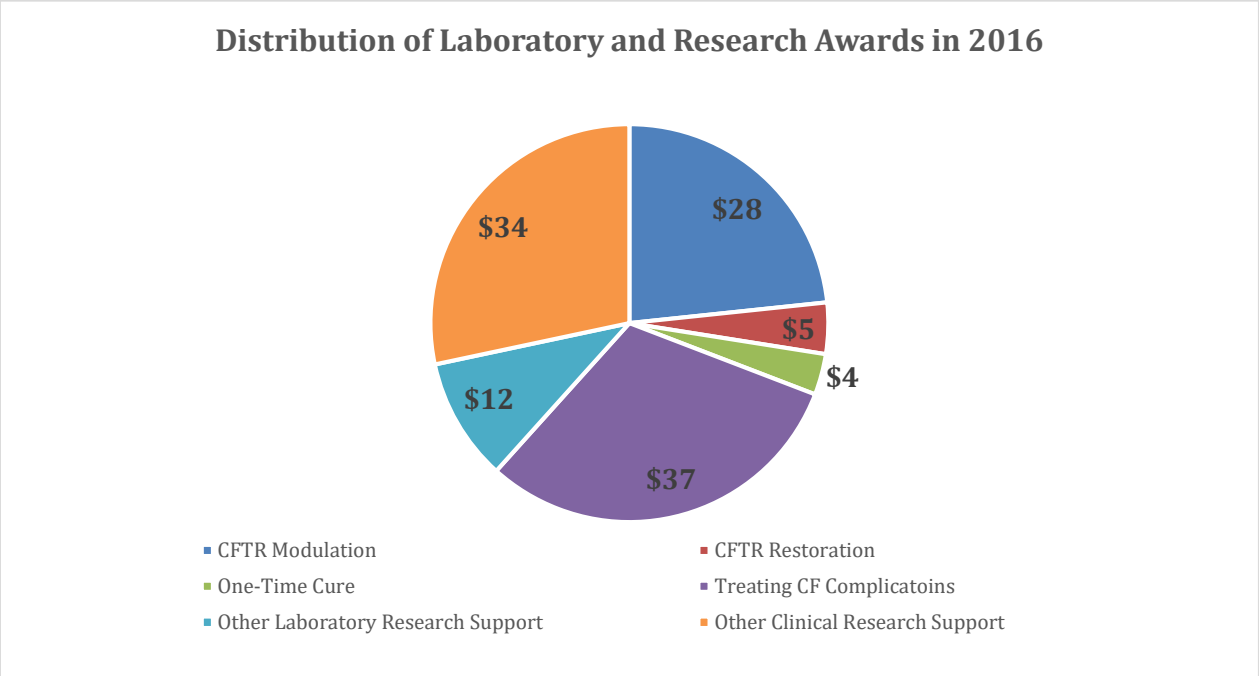


Figure 2. CFFT's Laboratory and Clinical Research Awards - 2016

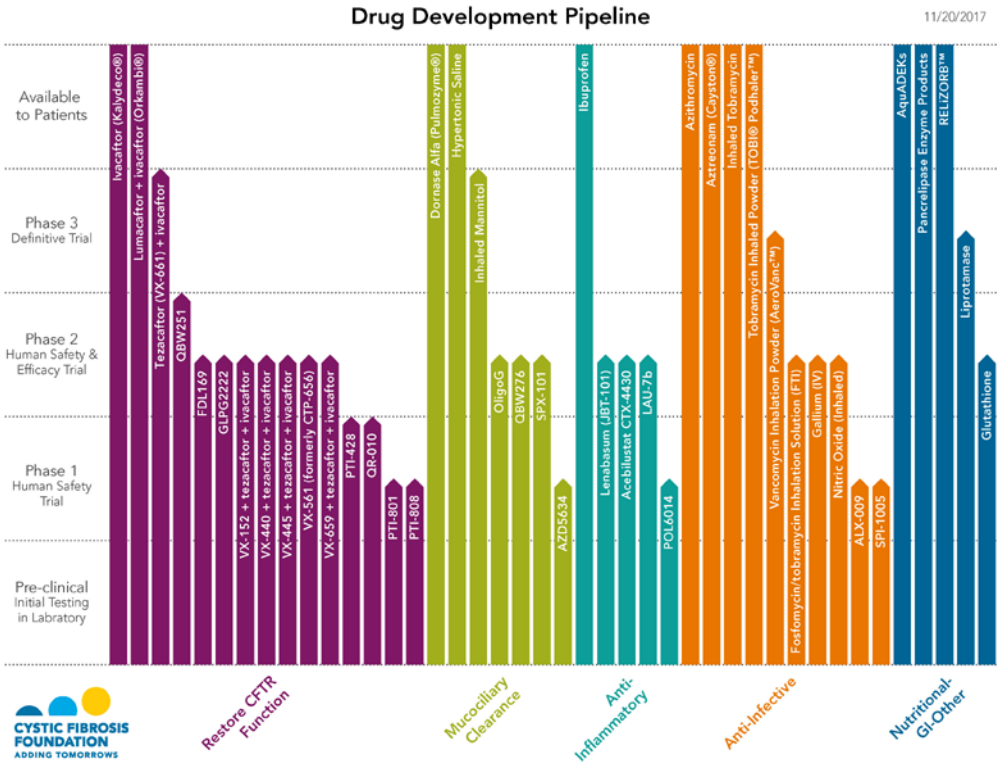


Figure 3. Drug Development Pipeline by Category, as of November 2017. Source: Cystic Fibrosis Foundation.

Divestment Strategy

A key part of the CF Foundation's VP strategy has been to divest any ties to commercial products and direct the proceeds to the Foundation's mission as quickly as possible. In contrast to certain types of investment funds, it is not a priority for the CF Foundation to take longer-term risk to achieve a better financial return. Time is the most precious commodity for the Foundation, as it is seeking to treat and cure a progressive disease as quickly as possible.

A Closer Look at the CF Foundation and Vertex Collaboration

The development of Kalydeco was built on decades of basic research, much of it supported by the CF Foundation. Foundation-funded research helped lead to the discovery of the gene responsible for the disease in 1989 [8]. Once the CFTR gene and its associated defective protein were identified, the scientific community recognized the possibility of targeting the protein for drug development and started screening potential compounds. At the time, it took research groups in academia two to three days to screen a single compound. To accelerate the pace, the Foundation began exploring the use of high-throughput screening methods for identifying drug targets. This led to an agreement in 2000 with the San Diego-based biotech company Aurora Biosciences to use and develop the company's advanced screening capabilities. Vertex Pharmaceuticals acquired Aurora Biosciences in 2001.

Decision to Collaborate

After the Aurora acquisition, Vertex had to determine whether to continue the collaboration with CFFT. The company had virtually no background in CF, and because there had been no previously successful clinical development programs based on the underlying cause of the disease, it was wary of the high risk. Financially, Vertex worried about CF diverting resources from its hepatitis C franchise, the small market size of CF, and the additional financial resources that would be required to commercialize CF research. (Vertex's decision is explored more fully in a Harvard Business School case study [9].)

Despite CF's small patient population, Vertex saw commercial potential in sales domestically and abroad. As treatments for a rare disease, CF therapies under development also qualify 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, and favorable EU Orphan Drug policies.

The CF program also had champions within Vertex's leadership who saw a collaboration with the CF Foundation as an opportunity to work with a neglected but engaged patient community to develop a new transformative therapy. Later, as Vertex came to believe that FDA approval of Kalydeco was likely, the prospect of future approvals for new drugs motivated the company to continue its collaboration with the Foundation.

Clinical Development of Kalydeco and Orkambi

Most forms of CF are caused by mutations in the CFTR gene that lead to the production of defective forms of the CFTR protein. There are two primary classes of therapeutics that address CFTR protein defects: "potentiators" and "correctors." Depending on the mutation, the CFTR protein defect either limits the movement of the CFTR protein to the cell surface, which is addressed by correctors, or disrupts the activity of CFTR protein at the cell surface, which is addressed by potentiators.

Vertex debated which CFTR mutations to target, seeking to maximize the number of people who could be reached with an attainable therapeutic. The CF Foundation provided critical expertise in this decision. While the F508del mutation affects nearly 90% of the CF population, Vertex decided to focus on the G551D mutation, which affects only about 4% of the population, because the company believed it would be able to bring the medicine to CF patients more quickly. This mutation could be addressed with a potentiator, while the other mutation would require both a potentiator and a corrector. It also affects the second-largest CF population after the F508del mutation, ensuring there would be sufficient patients to participate in a development program. (The timeline of major Kalydeco milestones is displayed in Figure 4.)

It was evident early in the process that Kalydeco would be able to improve the lung function for some CF patients. Both Vertex and the Foundation realized that targeting the

CFTR protein was going to be a successful strategy for a future CF treatment, and it was becoming clearer that a combination therapeutic of Kalydeco plus a corrector had the potential to address the nearly 50% of CF patients with two copies of the F508del mutation. This combination was ultimately approved, and is marketed under the brand name Orkambi.

The development of Kalydeco benefited not only from incentives of the Orphan Drug Act, but also from the Food and Drug Administration Safety and Innovation Act (FDASIA), which gave Kalydeco a "breakthrough" designation and priority review within the FDA approval process. Kalydeco was approved in 2012 for individuals of ages 6 years and older who had the G551D mutation. The FDA approval of Kalydeco took only 100 days, an accelerated timeline credited to the drug's strong signal of safety and efficacy. In May of 2017, the FDA expanded the use of Kalydeco to people aged 2 years and older who have at least one of 23 residual function mutations in the CFTR gene. A few months later, the FDA expanded the use of Kalydeco yet again to people with one of five splice mutations. With this latest expansion, Kalydeco is now approved to treat 38 different mutations of the CFTR gene among people with CF.

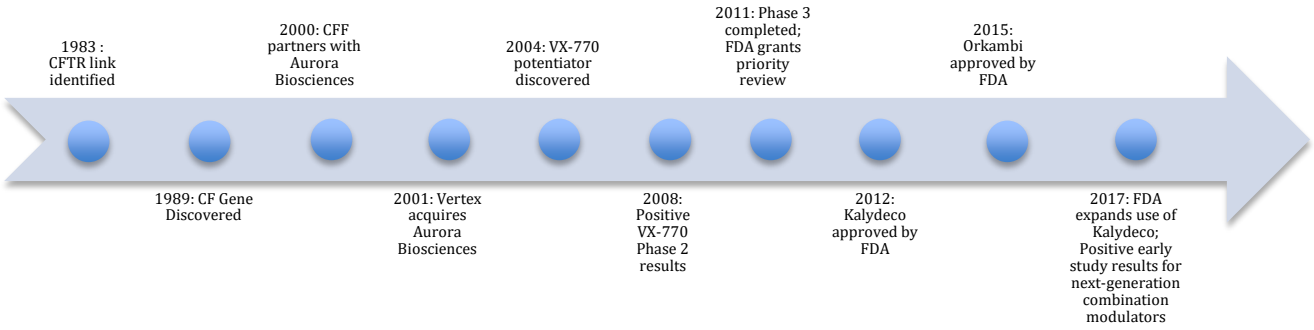


Figure 4. Abridged Timeline of Kalydeco's Development

CF Foundation Support

Throughout the development of Kalydeco and Orkambi, the Foundation followed and supported the program's progress through significant additional funding and quarterly steering committee meetings. Vertex shared updates on clinical planning, trial design, profiles of assets, and progress per dollars spent, while the Foundation provided extensive non-financial resources and expertise. These resources included scientists on Foundation staff to help interpret clinical data and improve study design, and the ability to conduct extensive clinical trials quickly and efficiently due to a large network of care centers. The expertise the Foundation provided during these quarterly steering meetings proved critical

to the success of Kalydeco's development, in some cases materially impacting the direction and success of the program.

The collaboration's success led to a number of follow-up agreements between the two stakeholders. The largest one-time agreement was in 2011, when the Foundation committed up to $75 million as part of a 5-year collaboration centered on the candidate VX-661 (tezacaftor)—designed to treat people with the Delta F508 mutation—and other new correctors developed up to 2016. Nearly 90 percent of people with CF in the U.S. have at least one copy of this mutation.

In total, CFFT provided nearly $150 million in support of the Vertex collaboration as of 2016. Despite the size of the investment, CFFT's funding provided only a portion of the total cost incurred by Vertex in developing Kalydeco, albeit the portion with the highest risk. Vertex would still need to invest its own financial resources into its CF research over a lengthy development cycle. Nevertheless, former CF Foundation president Beall estimates that Kalydeco was brought to market approximately two years earlier than expected, due to the expertise and financing provided by the Foundation. (Two years may be a significant underestimate given that Vertex may not even have pursued CF if it weren't for the CF Foundation's involvement.)

The Vertex Royalty Sale

In 2014, the CF Foundation engaged in discussions with Royalty Pharma (see the Appendix for further background) about selling its royalties in Kalydeco and other future Vertex CF products. Royalty Pharma first interacted with the Foundation during a 1997 transaction when the company acquired a royalty interest in 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 breakthrough in alleviating the symptoms of infection for CF patients, Royalty Pharma knew that this patient population still had a significant unmet clinical need.

CFFT Rationale for Monetization

When received, the funds from monetization represented over 80% of CFF's total assets. Although the Foundation now had much greater funding, its assets were highly concentrated in a single, illiquid investment. Royalty Pharma, with its large and diversified royalty portfolio, did not face the same issue of risk concentration. By selling its Vertex royalty streams to Royalty Pharma, the Foundation could meet several objectives simultaneously. It would liquefy its assets, which could then be immediately reinvested into work in support of the Foundation's mission. Critically, the sale would also help remove the potential for a conflict of interest for the nonprofit resulting from an ongoing

interest in the sales of a commercial product. The monetization of the royalties meant the Foundation would no longer receive royalties from Vertex on sales of Kalydeco, Orkambi, or future Vertex combinations, thereby freeing it from the perception that it had a vested interest in the financial success of Vertex or its CF products rather than being focused exclusively on its mission to help CF patients.

Royalty Pharma Rationale for Investment

In its preparation for the CFFT negotiations, Royalty Pharma examined the Vertex pipeline well beyond Kalydeco. It was excited about the potential of the combination drug Orkambi, as well as combinations in earlier stages of development. The pipeline was critical to its investment decision since Kalydeco was only initially approved to treat about 4% of CF patients, while Orkambi had the potential to reach up to 50%, and future combinations with Kalydeco had the potential to reach up to 90% of the CF population.

Royalty Pharma saw CFFT's royalty stake from the Vertex collaboration as attractive for two primary reasons. The first was its obvious potential to achieve long-term financial returns. The second was that, in completing a deal with the CF Foundation, Royalty Pharma would position itself to be the future partner of choice for patient-advocacy nonprofits. It saw increased engagement with these groups as a way to advance its mission of making drug discovery more efficient.

Agreement Structure

Prior to its discussions with Royalty Pharma, CFFT had already monetized a portion of its royalties with a Canadian pension fund for about $400 million. Royalty Pharma proposed purchasing the entire asset for an upfront payment of $3.3 billion, in addition to sharing with CFFT a portion of the royalties on sales in excess of a very high threshold. After securing competitive bids to ensure the deal was fair, CFFT agreed to a discounted value on the asset so that it could divest immediately and use the money without delay to benefit people with CF.

Impact of Monetization

The CF Foundation has an ambitious goal of achieving a cure for CF in the coming decades, and is basing its future capital needs on this objective. The sale of its Vertex royalties and the strategic management of the resulting assets give it considerable flexibility in planning for the next two decades.

Together with the range of possibilities resulting from monetization, the Foundation also faces a number of significant challenges. For decades, the CF Foundation has been an exemplar of effective grassroots mobilization, and the CF community has been highly engaged in fundraising at the local level. Since Kalydeco's approval, however, the Foundation has experienced a 3–5% decline in fundraising totals annually (see Figure 5). This is critical because the Foundation's financial models indicate that if aggressive

fundraising does not continue, they will likely run out of funds before finding a one-time cure. They project that the path to a cure, including the development of additional treatments and therapies to address complications of the disease, could cost roughly $9 billion—far beyond their current funds.

The CF Foundation continues to evolve and execute its strategy for managing the funds acquired through monetization. With its sudden influx of cash, it faces important decisions about asset allocation and portfolio management, which led to the establishment of an investment management office to maximize the future resources allocated to its mission. It will have to consider diversifying its existing portfolio of investments, including riskier but potentially ground-breaking therapies for the treatment of CF. As an example, the Foundation is pursing CRISPR gene editing as a potential one-time cure for CF, and has funded CF research programs underway at biotechnology companies pioneering this approach, such as Editas.

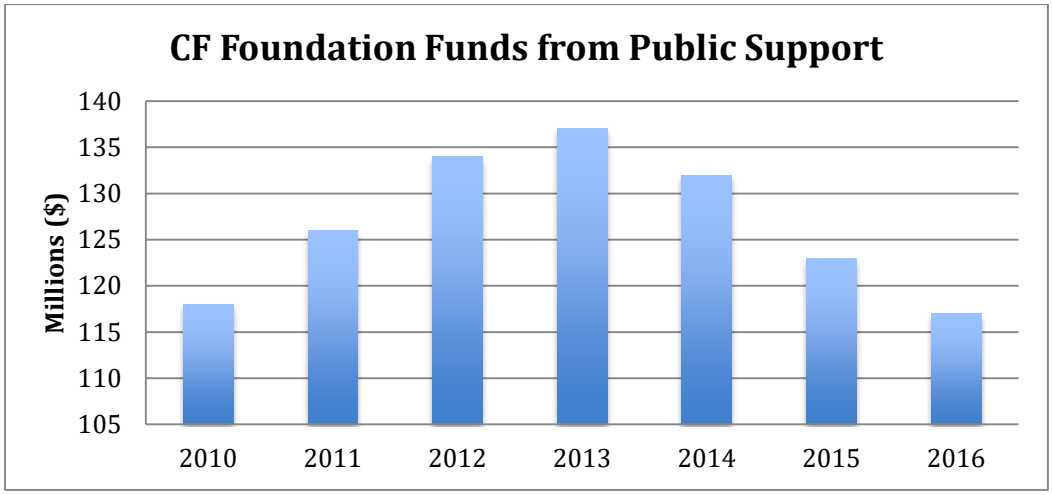


Figure 5. CF Foundation Public Support Funding

Implications for Other Nonprofits

There has been an increase in the number of organizations employing creative funding solutions in recent years, many of which emulate the CF Foundation model, according to FasterCures, a nonprofit think tank dedicated to accelerating medical research. FasterCures has launched a network of nonprofits, The Research Acceleration and Innovation Network (TRAIN), providing a forum to encourage further VP activity in medical research. This initiative supports strategic thinking about what patient organizations can bring to a partnership besides capital, such as funding registries, clinical networks, and oversight of basic science, as was the case with the CF Foundation and Vertex.

In a 2014 FasterCures survey of 250 disease-specific nonprofit organizations, about 60% of respondents had governance policies that permitted investing in for-profit biotechnology companies. Of those nonprofits that funded biotechnology companies, the majority (74%) funded at levels less than $1 million. While not funding drug development directly, the vast majority of nonprofits (96%) were developing research tools to lower the risk of later-stage development within the biotech sector (e.g., animal models and patient registries). These tools are essential to building critical expertise as a strategic collaborator in the drug development ecosystem [10].

Lessons Learned

The CF Foundation example offers several insights about best practices for the employment of VP by nonprofit, mission-driven organizations. In addition to the vision and strong leadership necessary to take on risky entrepreneurial activities, it is critical that nonprofits understand the constraints and objectives of drug developers. Funding from nonprofits is most attractive in the early stages of drug development, when costs to drug developers are highest and risks are greatest. Rather than structuring agreements like typical venture capital deals, the CF Foundation model suggests that nonprofits should focus on lowering the barriers for drug developers to work in their disease area by providing clinical expertise and an infusion of early capital.

According to FasterCures, organizations that embrace VP share several common characteristics. These organizations tend to pursue novel or breakthrough therapeutics for their disease and have in-house (or access to) scientific expertise, which is essential to conduct the due diligence required when financing or supporting a drug development program. These nonprofits are centralized and ready to mobilize quickly when making decisions. Critically, they also have strong relationships with patients; insights from individuals living with a disease are not always readily available to drug developers, and can significantly lower the risk of clinical trials and development decisions, as evidenced in the CF Foundation example. Finally, divesting at the earliest opportunity helps mitigate real and perceived conflicts of interest, as patient organizations prefer to avoid a financial interest in a commercial product they funded and their patient community will use.

Despite the growing interest in entrepreneurial approaches to philanthropy among nonprofit organizations, challenges remain. The CF Foundation's VP activities stood out for the number and size of its investments. While other organizations rarely have the capital required to sustain a "many shots on goal" strategy like the CF Foundation, they can use their disease expertise and patient access as leverage. While the CF Foundation successfully utilized the VP model, the practice carries inherent financial risks. Nonprofits can invest funds as wisely as possible based on current information about the disease and financial landscape, but they must be comfortable with the fact that there is no guarantee of a return in the form of therapies. Just as venture capitalists accept that their investments may not produce a return in the desired timeframe or quantity, VP investors must accept the same

risk. Nonprofits will also need approval from their boards to participate in risky endeavors, and to manage potential conflicts of interest with their mission and nonprofit status.

Nonprofits must not underestimate the importance of communicating 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 must also take care to reconcile their nonprofit status with investing in for-profit entities, and manage public perception and address actual and perceived conflicts of interest, particularly about drug profits. Because the CF Foundation has been involved in the development of nearly all CF products that have come to market, or are in the pipeline, it participates—either directly or indirectly—in creating competition for these products, thus further reducing the risk of conflicts of interest.

Finally, and most important, the CF Foundation is actively working to ensure that all people with CF have access to needed treatments and care. Any barrier to care can delay treatment and pose significant health problems for people with CF due to the progressive nature of the disease. One potential barrier to treatment is the price of modulators. As of August 2017, the list prices of Kalydeco and Orkambi were $311,000 and $272,000 per year, respectively. Most patients will not have to cover this entire cost because of insurance or charitable organizations, and Vertex currently offers financial assistance programs in cases of economic hardship [5]. However, there has been an increasing trend in coverage restrictions from insurance providers—particularly from public insurers such as Medicaid—and, given the rise of overall health care costs and the promise of additional innovative CF therapies on the horizon, there is concern that the current approach to drug pricing could lead to even more access barriers for people with CF. The Foundation is working to ensure every person with CF who can benefit from these drugs will be able to access them in a timely manner. To this end, it regularly engages with public and private insurers, connecting them with clinical experts so their coverage decisions support the delivery of high-quality CF care. It has also established CF Compass, a free service that helps patients navigate financial, legal, insurance, and other issues.

Looking Ahead

The CF Foundation's philanthropic model to create incentives for biotechnology companies to work in CF remains effective. In the early days of its model, few drug development companies responded seriously to the Foundation's inquiries. In 2016 alone, however, the Foundation discussed potential collaborations with 140 companies.

Despite the development of groundbreaking treatments for many people with CF, there remain segments of the population with no treatment for the underlying cause of the disease. Currently, the Vertex program has several next-generation corrector candidates progressing in the pipeline, including several potential triple-combination therapies on the horizon. In early 2017, Vertex released positive phase 3 clinical data for tezacaftor in

combination with ivacaftor, and additional phase 2 and phase 3 studies are currently underway. Vertex's next-generation, triple-combination therapies could potentially bring the benefits of disease-modifying therapies to up to 90% of people with CF [11].

The CF Foundation also continues to invest in its clinical care and research capabilities. Its clinical trials network now has more than 85 locations, which conduct increasing numbers of studies. In 2012, there were 28 clinical trials in the network; in 2016, there were 57. The Foundation also opened a CF research lab in the Boston area in 2012 to help expedite drug discovery. Furthermore, the Foundation increased its support of its CF care model considerably in 2016, investing over $40 million to improve care delivery through its nationwide network of more than 120 accredited CF care centers.

Perhaps the CF Foundation's biggest challenge in supporting its mission to find a cure for all people with CF and support those living with the disease today is overcoming the public perception that fundraising is no longer needed. The very success of the Foundation's VP efforts—more therapies on the market and more money in the coffers—also makes it difficult for some potential donors to see why their support is still needed. However, people with CF are still dying far too young, and as financial modeling shows, aggressive fundraising must continue if the CF Foundation is to meet its goal of a cure for all people with CF. Without continued support from donors, funds from royalties would be depleted before the Foundation can reach the finish line. As more nonprofits enter the VP space, they should be prepared to face a similar "Why give?" messaging challenge if and when they see significant financial returns.

While the CF Foundation is an inspiring model for other nonprofits, a robust VP ecosystem in biotechnology does not yet exist. In addition to formulating a VP strategy, organizations must also overcome significant obstacles. The initial capital required is a large barrier, and many organizations do not have the fundraising capacity that the CF Foundation developed over its decades-long history. Given the current funding environment, more nonprofits are likely to fund drug development in the near future, but drug companies will have their pick of indications to work on, and foundations will need to invest money and resources to be heard.

Furthermore, the mission of some nonprofits may dictate that they support more academic research rather than investing in drug development. 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 discovered. The CF Foundation spent decades advancing basic science that led to a comprehensive understanding of the biology of CF, which led to the identification of the CFTR gene and potential therapeutic targets. Without this scientific groundwork, it would have been difficult to make the transition to supporting translational projects.

Most disease-focused nonprofits have the potential to fill funding gaps and provide important expertise to accelerate drug development for their patients. Despite the many challenges to adopting VP, there is a growing interest among nonprofits for entrepreneurial

engagement in drug development. We expect that many rare disease nonprofits will be able to apply learnings from the CF Foundation to develop their own strategies.

ACKNOWLEDGMENTS: We thank the CF Foundation for agreeing to participate in this case study and providing access to data and their leadership team. We thank Bob Beall, Preston Campbell, Terry Coyne, Loren Eng, Pablo Legorreta, Cam McLoud, Eric Olson, Robert Pacifici, Marya Postner, Ying Qian, Ken Schaner, Kristin Schneeman, Christiana Stamoulis, and Doug Zingale for participating in interviews for this article. We also thank Olivia Bowen, Laurie Fink, Jess Rowlands, and Ansley Walker for helpful guidance, introductions, and facilitating interviews, and Genevieve Maul for helpful comments. And we are grateful to Jayna Cummings for editorial assistance. The views and opinions expressed in this article are those of the authors only, and do not necessarily represent the views and opinions of any institution or agency, any of their affiliates or employees, or any of the individuals acknowledged above.

FUNDING: No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No direct funding was received for this study; general research support was provided by the MIT Laboratory for Financial Engineering and its sponsors. The authors were personally salaried by their institutions during the period of writing (though no specific salary was set aside or given for the writing of this paper).

AUTHOR CONTRIBUTIONS: Both authors contributed equally. Both authors contributed to the preparation of the manuscript.

COMPETING INTERESTS: E.K. declares that she has no competing interests. A.W.L. reports personal investments in several biotech companies and venture capital funds and is an advisor to BridgeBio Capital, and a director of Roivant Sciences and the MIT Whitehead Institute for Biomedical Research.

DISCLAIMER: No representative of Vertex was interviewed for this case study, and Vertex did not contribute to its preparation. The views, opinions, and statements included in this case study are those of the authors and do not reflect the position or views of Vertex.

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Appendix

A.1 Biographical Sketches of Interviewees*

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 CF patients. 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.

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

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

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.

Ken Schaner has more than 40 years of private practice experience, and has represented many for-profit and nonprofit 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 the CF Foundation 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 nonprofits. 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.

A. 2 About Royalty Pharma

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 [12]. 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 [12].

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.