

The “New” Venture Philanthropy: A Case Study of the Cystic Fibrosis Foundation

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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 challenging for rare diseases, where market sizes are often too small to attract much attention and funding. Venture philanthropy (VP)—a model in which nonprofit mission-driven organizations make investments to advance their program and potentially achieve returns that can be reinvested toward their mission—offer an alternative to traditional funding sources like venture capital or the public markets. Here we highlight the Cystic Fibrosis Foundation (CFF), 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 CFF’s example, including its agreement structures and strategy, explore the challenges that other nonprofits may have adopting this strategy, and draw lessons from the CFF 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. These investments have the potential of significant returns to the nonprofit, which would be reinvested in a virtuous cycle to support the nonprofit’s mission. VP can range from a nonprofit venture investment to nonprofit entrepreneurship to strategic nonprofit activities. 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 unmet clinical needs. Many disease-focused nonprofits, including the Bill and Melinda Gates Foundation, employ VP both strategically and tactically, and more nonprofit organizations are now 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 high risk and expense, this process typically favors candidates with lucrative markets, or later-stage assets that have already generated promising data. As a result, 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, therapies for rare diseases have been especially vulnerable to this Valley 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 (CFF) is the world’s leading mission-driven organization involved in the search for a cure for the rare disease cystic fibrosis (CF), which currently affects over 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. This strategy arose from the desire to bridge the Valley of Death by creating incentives for biopharma companies to translate basic scientific knowledge of CF into drug development programs.

To this end, the CFF founded a nonprofit drug development affiliate, Cystic Fibrosis Foundation Therapeutics Inc. (CFFT). One of CFFT’s first funding agreements was an effort with a for-profit company to discover compounds that might compensate for the primary genetic mutation in CF patients. This work ultimately led to the identification and development of Kalydeco, the first FDA-approved treatment for CF to address 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 biotechnology firm. Its agreement included receiving a percentage of royalties on future sales of successful CF drugs in exchange for funding CF R&D efforts at Vertex. This agreement was of tremendous benefit to the CF community—in 2012, Vertex’s Kalydeco, which had been initially approved for 4% of CF patients, was quickly followed by a combination drug called Orkambi, which extended treatment to 50% of all CF patients [4].

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. By divesting itself of its royalty stake in commercial products, CFFT intended 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 CFF’s mission. On the one hand, 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. On the other hand, critics argued that the CFF 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 CFF’s overall VP strategy, its decision-making process, and the structural elements of CFFT’s agreements and transactions, especially with respect to Royalty Pharma. Although the CFF’s VP model is motivated solely by its mission to reduce the burden of disease on CF patients—and not at all 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 CFF’s success and implications for best practices in VP. As government funding for early-stage compounds and basic science continues to decline, 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 CFF’s VP model with the goal of providing a framework for other mission-driven organizations looking to use VP to magnify their impact.

Overview of 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 lungs and airways, often leading to bacterial infection and difficulty in breathing, resulting in severe lung disease (although it affects multiple organ systems) [4]. Worldwide, CF affects nearly 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). 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 [8].

Earlier drugs approved for CF, such as Pulmozyme and TOBI, addressed the symptoms of CF, but not the underlying cause, unlike new therapeutic options such as Kalydeco and Orkambi. Today, 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 U.S. with mild lung impairment was estimated to be around \$40,000 annually [9].

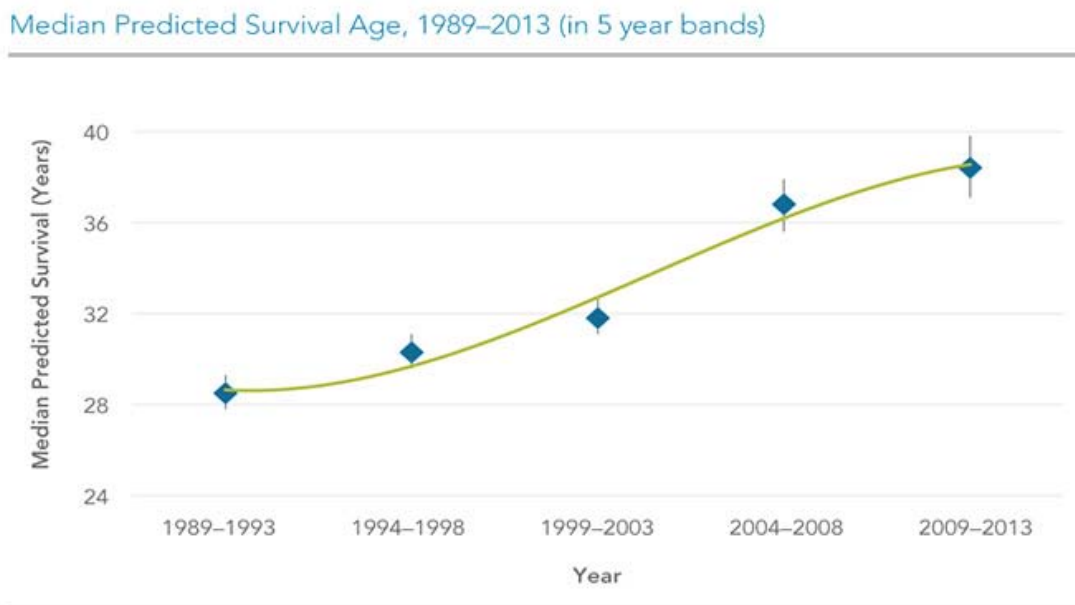


Figure 1. Median Predicted Survival Age of CF patients over Time. Source: CFF.org

History of the Cystic Fibrosis Foundation

The Cystic Fibrosis Foundation, currently based in Bethesda, Maryland, was founded in 1955 by parents of children with CF. At that time, there were no approved treatments for CF, and no research was being conducted on the disease. Over the years, the CFF 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. The organization oversees an extensive patient registry, accredits and provides funding for 120 care centers specializing in CF treatment, and has established the Therapeutics Development Network, the largest CF clinical trials network in the world, for which it is the primary source of funding. The stated 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 its leadership. In particular, Dr. Robert Beall has been critical in shaping the evolution and strategy of the foundation. Before his retirement, Beall was associated with the organization for over 30 years, the last 21 as its president and CEO. Beall was a pioneer in redefining the activities of a medical charity. With the aid of former Chief Operating Officer C. Richard Mattingly, the foundation under Beall successfully raised more dollars per patient than any other disease-focused organization in history. Beall was particularly known for his goal-oriented approach to leadership, reorganizing the foundation to achieve important milestones in CF treatment, including a clinical trials network, a robust research and development program, and its forays into VP. In 2015, the leadership of the foundation made a successful transition to its current president, Dr. Preston Campbell, formerly the CFF's executive vice-president of medical affairs. During his 17-year tenure in that role, Campbell oversaw research and medical activities that led to the discovery of Kalydeco and Orkambi, as well as other important advances in CF treatment and care. Under Campbell's leadership, the CFF is expanding its role to serve patients and accelerate drug development to realize its stated mission.

The CFF's Venture Philanthropy Model

The primary driver of the CFF's venture philanthropy model is the needs of CF patients. Internally, these are achieved by having clear criteria that support efficient decision-making about those needs. Well before the term "venture philanthropy" became popular, the CFF used donations and royalties to accelerate the development of therapeutics for CF. A by-product of the CFF's model are funds to act on its mission. Any funds stemming from royalty sales are reinvested (see Table 1). These investments may be in research and development, the expansion and enhancement of the CF care network, support programs like its mental health and lung transplant initiatives, or other elements of the foundation's mission.

The CFF established Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), its nonprofit drug discovery arm, to facilitate drug development contracts, in line with its stated mission. An early case in point is the CFF's use of its rights to the inhaled antibiotic, TOBI, approved to help reduce symptomatic lung infections in CF patients. In the late 1990s, the lack of industry attention to CF therapeutic development frustrated the CFF's Board of Trustees, who challenged the organization to take on more risk in the private sector. CFFT used the sale of TOBI royalties, and a grant from the Bill and Melinda Gates Foundation for an additional \$20 million, to fund its initial \$40 million agreement with Aurora Biosciences, later acquired by Vertex, which began the development of Kalydeco.

Over its history, the CFF has invested about \$500 million in total into its VP agreements through CFFT, and CFFT has diversified its funding efforts across many therapeutic programs. CFFT has had a hand in nearly all the products approved for CF in

recent years. 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 6 in the Appendix). 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 CFF, including TOBI, Kalydeco, and a medical device for CF.

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

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

Agreement Structure

Kenneth Schaner, the CFF’s general counsel since 1983, and a founding partner of the law firm Schaner and Lubitz, has been the lead in structuring VP agreements for the organization. Because the foundation pioneered this model for nonprofit funding of drug development, it “set the market,” creating the baseline structure now used by other disease-focused organizations. Schaner has been involved in over 400 VP agreements, 80 to 100 of which have been with the CFF.

While each agreement is specific to the nature of the therapeutic under development, they share many similarities. One of the first features that CFFT negotiates in its agreements is milestone- or activities-based payment. Payment by milestone is meant to align the incentives among stakeholders, to ensure that progress is being made on an asset for the benefit of patients.

Another key element 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, for example, with Altus Pharmaceuticals. When Altus was unable to continue with its trials, the foundation took back the product candidate to control the re-licensing and future development of the product.

As part of a nonprofit organization, CFFT’s primary goal is to lower the bar for a biopharma company to engage in CF research. When structuring an agreement, 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 a commercial success. 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. The trade-off is limited control on the part of the CFF during drug development, and no ability to set prices or to influence the biopharma partners' commercial plans.

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 CFF 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.

However, the CFF also brings extensive non-financial resources and expertise to the drug development process. These resources include scientists on staff to help interpret clinical data and improve study design, the ability to conduct extensive clinical trials quickly and efficiently, and a large network of care centers. Depending on its stake in a particular program, members of the CFF may attend periodic research meetings or participate on scientific advisory committees to provide insight into the disease.

Most important, the CFF accumulates data that can significantly lower the risk of the drug development process, particularly in the early stages where the chances of technical and scientific failure are high. During the development of Kalydeco and Orkambi, the CFF provided access to decades of data from the CF patient registry, which amounted to a natural history of the disease (remarkably, this registry included nearly all U.S. CF patients). Individuals involved in the approval process cite this registry as critical to the speedy FDA approval of Kalydeco.

Portfolio Approach

The CFF has pursued a diversified portfolio in its R&D investments to ensure it is well positioned for ultimate clinical success. Since successfully identifying the CFTR gene as a therapeutic target, the CFF has continued its efforts to develop products that target this protein, but as of late 2016, CFFT has funded a broader 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 2.

CFFT has recently been able to increase its funding of research across the categories of therapies in the CF pipeline (see Figure 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. The CFF is optimistic about the potential of gene therapy and gene editing for CF, investing \$12 million toward this goal in 2016 alone, and allocating over 40 awards to advance research in this field.

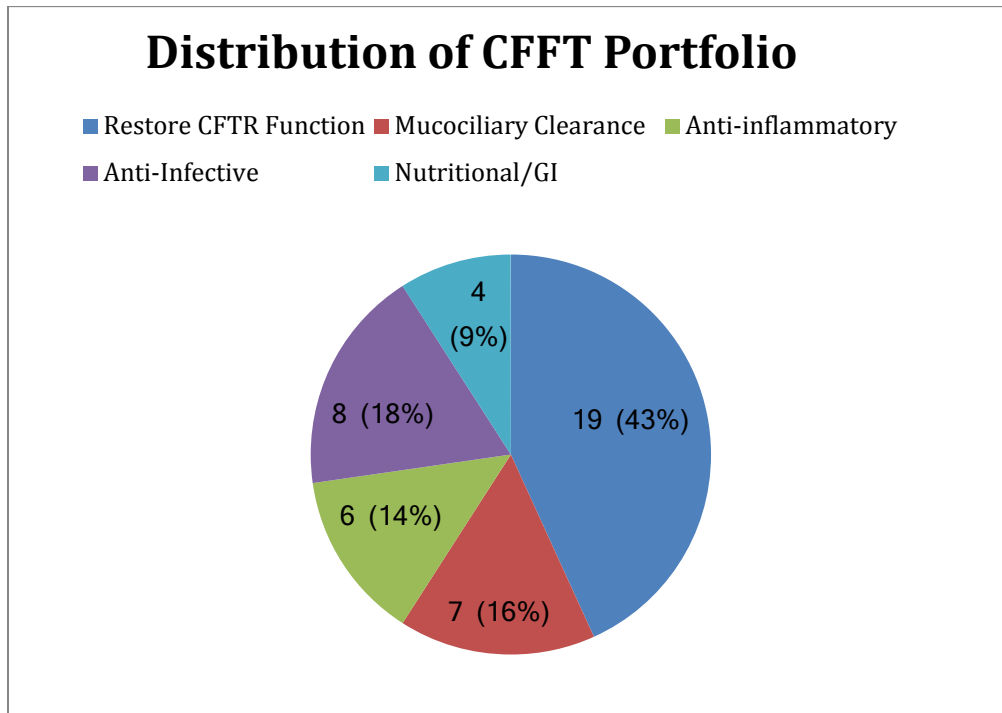


Figure 2. Distribution of CFFT Portfolio as of February 2017

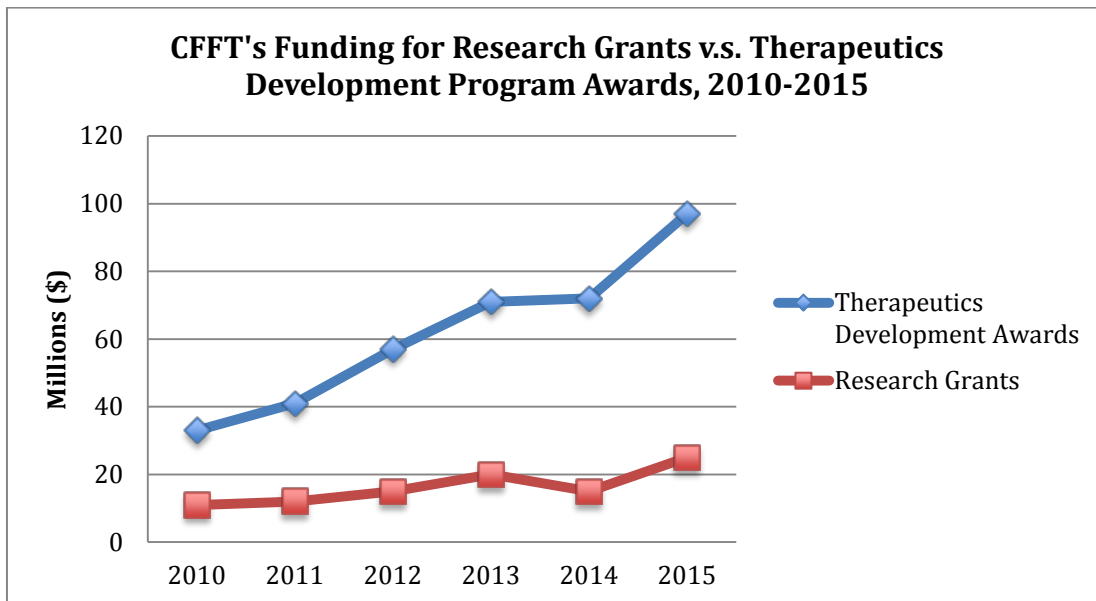


Figure 3. CFFT's Funding for Research Grants vs. Therapeutics Development Program Awards from 2010 to 2015

Divestment Strategy

A key part of the CFF's VP strategy has been to divest any ties to commercial products, and reinvest the proceeds as quickly as possible in the foundation's mission. In

contrast to typical investment firms, it is not a priority for the CFF to take longer-term risk to achieve a better financial return. Time is the most precious commodity for the CFF, as it is seeking to treat and cure a progressive disease as quickly as possible.

A Closer Look at the CFF and Vertex Collaboration

The path that led to the development of Kalydeco was built on decades of basic research, much of it supported by the CFF. In its earliest stages, scientists discovered that CF was connected to the obstructed movement of chloride ions into and out of cells. CFF-funded research led to the discovery of the gene responsible for the disease in 1989 [10]. 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. However, it took research groups in academia two to three days to screen a single compound. The CFF realized that this pace was too slow and began exploring the use of high-throughput screening methods for identifying drug targets. This ultimately 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 later acquired Aurora Biosciences in 2001.

Decision to Collaborate

After completing the Aurora acquisition, Vertex had to determine whether or not to continue the collaboration with CFFT. Vertex had several concerns about the research focus on CF. Vertex had virtually no background in CF, and because there had been no previously successful clinical development programs based on the underlying cause of CF, it was wary of the high risk. Financially, Vertex worried about CF taking away 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 much more fully in a recent Harvard Business School case study [11].)

At the earliest stages of the partnership, both Vertex and the CFF had some difficulty foreseeing the eventual clinical and commercial success of the CF program. However, Vertex's hepatitis C program allowed it to become a commercial entity, and its CF program benefited from this success. Despite CF's small patient population, Vertex saw commercial potential in sales beyond the U.S. As a rare disease, CF 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.

The CF program also had champions within Vertex's leadership. A collaboration with the CFF was an opportunity to work with a neglected but engaged patient community to develop a new transformative therapy. Later, as the development of Kalydeco began, and Vertex came to believe that an FDA approval of Kalydeco was likely, the prospect of a

second approval—ultimately, the combination drug, Orkambi—motivated the company to continue its collaboration with the CFF.

Clinical Development of Kalydeco

Most forms of CF are caused by mutations in the CFTR gene that lead to the production of defective forms of the CFTR protein. However, not all CFTR mutations are the same. 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 it 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 CFF 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 a sufficient number of patients to participate in a development program. (The timeline of major Kalydeco milestones is displayed in Figure 4.)

Vertex saw a likely pathway to reach more patients after succeeding with this initial target. It was evident early in the process that Kalydeco would be able to improve the lung function of CF patients. The phase 2 results were a particular turning point. Both Vertex and the CFF 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 candidate had the potential to address the 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 the incentives of the Orphan Drug Act, 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 only 100 days, an accelerated timeline credited to the drug’s strong signal of safety and efficacy.

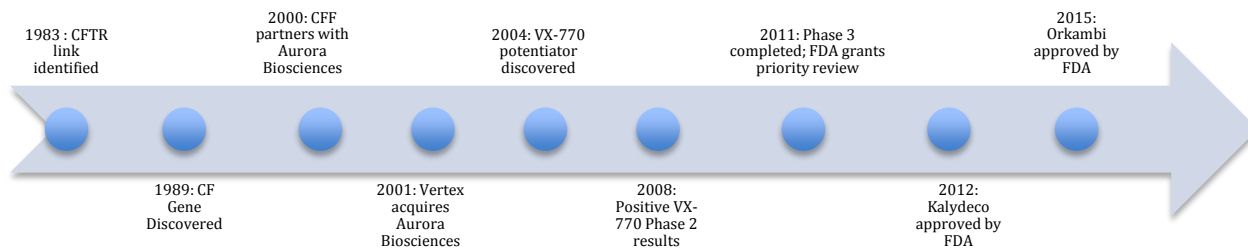


Figure 4. Abridged Timeline of Kalydeco Development

CFF Support

After the collaboration with Vertex had begun, the CFF followed the development program’s progress through quarterly steering committee meetings, where it received updates on clinical planning, trial design, profiles of assets, and progress per dollars spent. 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 \$75 million as part of a 5-year collaboration centered on the candidate VX-661 (tezacaftor) and second-generational correctors developed up to 2016.

In total, CFFT provided nearly \$150 million in support of the Vertex collaboration. Despite the size of the investment, CFFT’s funding only provided 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 CFF president Beall estimates that Kalydeco was brought to market approximately two years earlier than expected, due to the expertise and financing provided by the CFF (two years may be a significant underestimate given that Vertex may not even have pursued CF if it weren’t for the CFF’s involvement).

The Vertex Royalty Sale

From 2012 to 2014, the CFF engaged in discussions with Royalty Pharma (see the Appendix for further background) about selling its royalties in Kalydeco and other future Vertex CF products. Prior to 2012, Royalty Pharma had not worked actively with nonprofit patient advocacy groups, primarily because there were so few that invested in therapeutics. Royalty Pharma’s first interactions with the CFF were in a transaction involving TOBI. 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 CF patients, Royalty Pharma knew that this patient population still had a significant unmet clinical need.

CFFT Rationale for Monetization

Due to the success of the CFF's investments, the value of the CFF's Vertex royalty streams had become over 80% of its total assets. Although the foundation now had much greater funding, its assets were highly concentrated in a single investment, which implied higher risk than a more diversified portfolio, and that investment was illiquid. 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 CFF was able to meet several objectives simultaneously. It would liquefy its assets which could then be immediately reinvested into the pipeline of future CF therapies. More importantly, as a nonprofit organization, the sale would also remove the perception of any conflict of interest. In particular, a complete monetization of the royalty would mean that the foundation would no longer receive royalties from Vertex on sales of Kalydeco, Orkambi, or future Vertex combinations, thereby freeing it from any 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. For strategic guidance, CFFT called on the services of Morgan Stanley and L.E.K. to advise it in the royalty sale, in addition to the legal counsel it engaged since the start of its VP strategy.

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 only treats about 4% of CF patients, while Orkambi reaches up to 50%, and future combinations had the potential to reach up to 90% of the CF population. Future candidates that fell under the royalty agreement included a combination of Kalydeco and VX-661, a corrector in early development at that time, and other second-generation correctors in the pipeline.

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 attractive long-term financial returns. The second was Royalty Pharma's desire to be the future partner of choice for patient-advocacy nonprofits. It saw increased engagement with these groups as an attractive 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 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 sharing with CFFT a portion of the royalties on sales in excess of a very high threshold.

Impact of Monetization

The CFF has an ambitious goal of achieving a cure for CF in the coming decades, based on the status of promising new technologies such as gene editing. The foundation is basing its future capital needs on this objective, and the sale of its royalties from Vertex and the strategic management of these assets give it considerable flexibility in planning for the next two decades.

The CFF faces the major challenge of maintaining its culture and sense of mission following the approvals of Kalydeco and Orkambi. For decades, the 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 CFF has experienced a 3–4% decline in fundraising totals annually (see Figure 5). At the same time, the CFF's financial models indicate that there may be a gap where the foundation runs out of funds while pursuing a one-time cure. The foundation must actively convey the message that only 50% of CF patients will potentially benefit from currently approved therapies, and that much additional work remains to be done to develop similar treatments for all CF patients.

The CFF will also have to develop and execute a strategy for managing the funds it recently acquired through monetization. With its sudden influx of cash, it faces important decisions about asset allocation and portfolio management. The foundation is establishing an investment management office to maximize the future resources allocated to its mission. It will have to consider expanding the diversity of its existing portfolio of investments, including riskier but potentially ground-breaking therapies for the treatment of CF. As an example, the CFF is pursuing 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.

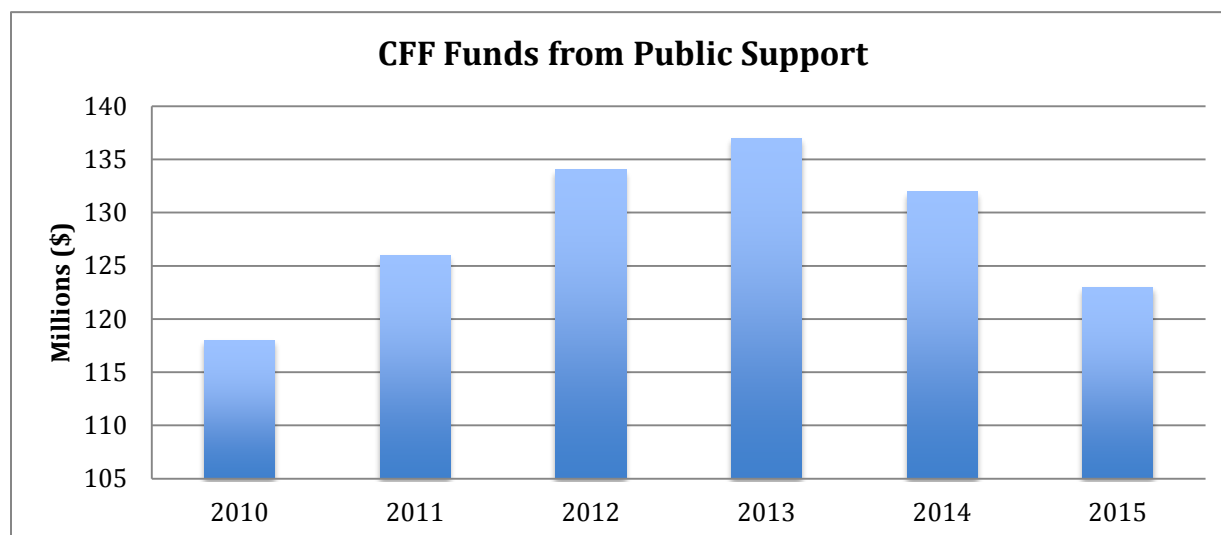


Figure 5. CFF Public Support Funding

Implications for Other Nonprofits

A handful of other disease-focused nonprofit organizations have also been involved in VP, or more broadly, in entrepreneurial engagement with biotechnology companies. These 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 [7], 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 willing to invest. While institutional investors must balance risk with their financial incentives, nonprofits have a higher appetite for risk because they are driven by long-term impact, not short- or medium-term 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 to allow groups to connect, including the CFF, providing a forum to encourage further VP activity in medical research. This initiative, known as The Research Acceleration and Innovation Network (TRAIN), has been growing in membership and attracting increasing public attention. FasterCures sees a “new generation of philanthropy” in which nonprofits provide not only funding, but also strategic engagement in the drug development process. TRAIN supports strategic thinking about what patient organizations can bring to a partnership besides capital. These include funding registries, clinical networks, and oversight of basic science, as was the case with the CFF and Vertex.

In a FasterCures survey of 250 disease-specific nonprofit organizations conducted in 2014, 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 [12].

Many nonprofit organizations in the FasterCures survey pool are focused on rare diseases. One rare disease community that has been successful in realizing the potential capability of its nonprofit groups is the Duchenne muscular dystrophy (DMD) community. DMD is a fatal hereditary rare disease known for its strongly mobilized patient network. DMD-focused organizations have been involved in financially supporting drugs, e.g., Sarepta Therapeutics' eteplirsen, which received FDA approval in 2016. The SMA Foundation is another example of a nonprofit to support an asset, which later became the first treatment approved for spinal muscular atrophy (see the SMA Profile below).

Lessons Learned

The CFF example offers several insights about best practices for the employment of VP by other nonprofit organizations. Nonprofits require vision and strong leadership to take on risky entrepreneurial activities. Furthermore, it is critical that they understand the constraints and objectives of drug developers. A drug developer's cost of capital, especially in the earliest stages of development, 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 their disease area.

According to FasterCures, organizations that are embracing VP share some common characteristics. First, these organizations are pursuing a novel or breakthrough therapeutic for their disease. Second, they have in-house scientific expertise, or access to scientific expertise. This is essential 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, these organizations have a strong relationship with patients—insights from individuals living with a disease are not always readily available to drug developers. These insights can significantly lower the risk of clinical trials and development decisions, evidenced in the CFF example. Finally, divesting at the earliest opportunity is key. This strategic decision helps mitigate real and perceived conflicts of interest, as patient organizations prefer to avoid a financial interest in a commercial product they funded and which their patient community will use.

Despite the growing interest in entrepreneurial approaches to philanthropy among nonprofit organizations, challenges remain. It is clear 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 has been able to make these financial commitments more easily due to its larger size and decades-long organizational history. Other organizations rarely have the capital required to sustain a “many shots on goal” strategy like the CFF. Even without significant capital, however, nonprofits can use their disease expertise and patient access as leverage. Nonprofits will also need approval from their boards to participate in risky endeavors, and to manage emerging 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.

One often-overlooked point is the importance of communication in VP. 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. There is also a significant cultural divide between nonprofit organizations and for-profit investment activities that must be bridged before VP can be successfully employed. Part of this divide is the challenge of nonprofits reconciling their nonprofit status with investing in for-profit entities. They must manage public perception and address actual and perceived conflicts of interest, particularly about drug profits. Because the CFF 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. The CFF could potentially favor one approach over another and bias the market outcome, which poses an additional conflict of interest that the CFF must manage closely.

Finally, and most important, the CFF is actively working to ensure that all CF patients have access to needed treatments and care. Any barrier to care can pose significant health problems for CF patients and one of the current barriers to treatment is the cost of modulators. In 2017, Orkambi had a list price of \$259,000/year and Kalydeco had 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 assistance programs in cases of economic hardship [5]. The foundation is working to ensure all CF patients who can benefit from these drugs will be able to access them in a timely manner. The CFF 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. Ultimately, the foundation is hopeful that accelerating the development of additional drugs for CF will create a more competitive environment that will drive prices down.

Profile of the SMA Foundation

At its beginning, the SMA Foundation faced a number of difficult challenges. There was little public awareness of SMA (spinal muscular atrophy), a rare disorder that is the leading genetic cause of infant mortality in the United States. There was limited scientific understanding of the disease, poor clinical treatment for patients, and few available funds. Only \$1-3 million was spent on SMA annually by the National Institutes for Health, 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.

Under the leadership of President Loren Eng, the SMA Foundation developed a two-part strategy: 1) to fund the development of the clinical infrastructure and tools to facilitate R&D in SMA (e.g. cell lines and biomarkers), and 2) to repurpose drugs from other indications to SMA. As one of its strategic approaches, the foundation funded work at academic institutions, and then licensed it from the universities to share the results widely. If biotech companies were successful using these tools, the SMA Foundation would share in their upside.

Extending this strategic approach, the SMA Foundation started to engage with biotech companies directly. The underlying idea was to induce companies to work in the historically neglected area of SMA without expensive stipulations. The foundation's initial engagements were via grants to fund research programs and through the creation of SMA-specific incentives. Later, its philosophy evolved, and the foundation sought to recoup its investment should the companies prove successful. (In a few cases, if an investment had been sufficiently large, the foundation required a multiple of its initial investment.) Given a success, the foundation wanted to recoup its costs to support its programs for patients and clinical care as well as other ongoing R&D projects. Despite these provisions, the SMA Foundation nevertheless reduced the cost of capital for biotechnology companies.

Founded by parents of a child with SMA, the focus of the SMA Foundation has never been its own sustainability, but rather, the fastest path to a cure. The SMA Foundation's takeaway from these partnerships is that they are primarily tools to accelerate drug development in SMA. The foundation's ultimate goal is not to make the best deal; the SMA Foundation is happy to leave "money on the table" as long as it is able to drive the development of cures with its partners. The partners of the SMA Foundation have learned that beyond funding, the foundation can provide the important intangible resource of scientific expertise.

The right strategic guidance was key to the SMA Foundation's success. The foundation worked closely with experienced lawyers to develop its partnerships, and these efforts paid off in late 2016. The SMA Foundation helped fund Adrian Krainer's antisense RNA research at Cold Spring Harbor Laboratories, which resulted in a new technology licensed to Ionis (formerly Isis) Pharmaceuticals. The foundation was engaged throughout the development process by providing resources and access to SMA clinical expertise (a more extensive description of its involvement can be found in the Appendix). Ionis later partnered the SMA program with Biogen to develop nusinersen. In December of 2016, this became the first FDA-approved SMA drug, marketed as Spinraza. The drug price will be \$750,000/year in the first year, and \$375,000 a year thereafter for the life of the patient.

Looking Ahead

Since its founding in 1955, the CFF has made remarkable strides on behalf of CF patients and their families. The CFF's philanthropic model to create incentives for biotechnology companies to work in CF remains effective. In the early days of its model, 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.

Despite the development of groundbreaking treatments for CF patients who previously had no effective therapeutic option, there remains more work ahead for the CFF. There are still segments of the CF population with no treatment for the underlying cause of the disease. Currently, the Vertex program has several second-generation corrector candidates progressing in the pipeline, including VX-661, and 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 in the near future. Vertex's future triple-combination therapies could potentially help up to 90% of the CF patient population [13].

The CFF also continues to expand its clinical care and research capabilities. It has developed a clinical trials network that now has over 80 locations. In 2012, there were 28 clinical trials in the network, but in 2016, there were 56. The foundation also opened a CF research lab in Boston, perhaps the leading biotechnology hub in the country. In 2016, the foundation increased its support of its CF care model by over 44%, investing almost \$43 million to improve care delivery through its nationwide network of more than 120 accredited CF care centers.

While the CFF 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 CFF was able to build over its decades-long history. Given the current funding environment, more nonprofits are likely to fund drug development in the near future. However, drug companies will have their pick of indications to work on, and foundations will need to invest money to have their voices heard. Foundations will need to lower barriers and the cost of capital more than that provided by Big Pharma to engage biotechnology companies in their research.

Furthermore, in contrast to the CFF's mission to cure CF—which requires supporting drug development—some nonprofits may have different missions and constraints, choosing instead to support more academic research. In fact, most organizations will need to balance the tensions of supporting basic science versus translational medicine. 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 CFF 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. For the CFF, the balance between basic research and translational medicine is increasingly shifting towards the latter.

Most disease-focused nonprofits 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 its experiences as they develop their own strategies.

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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.

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-III. 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.

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

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. McCloud 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. McCloud 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 Pacifici 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 nonprofit 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 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 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 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 CFF's Therapy Pipeline

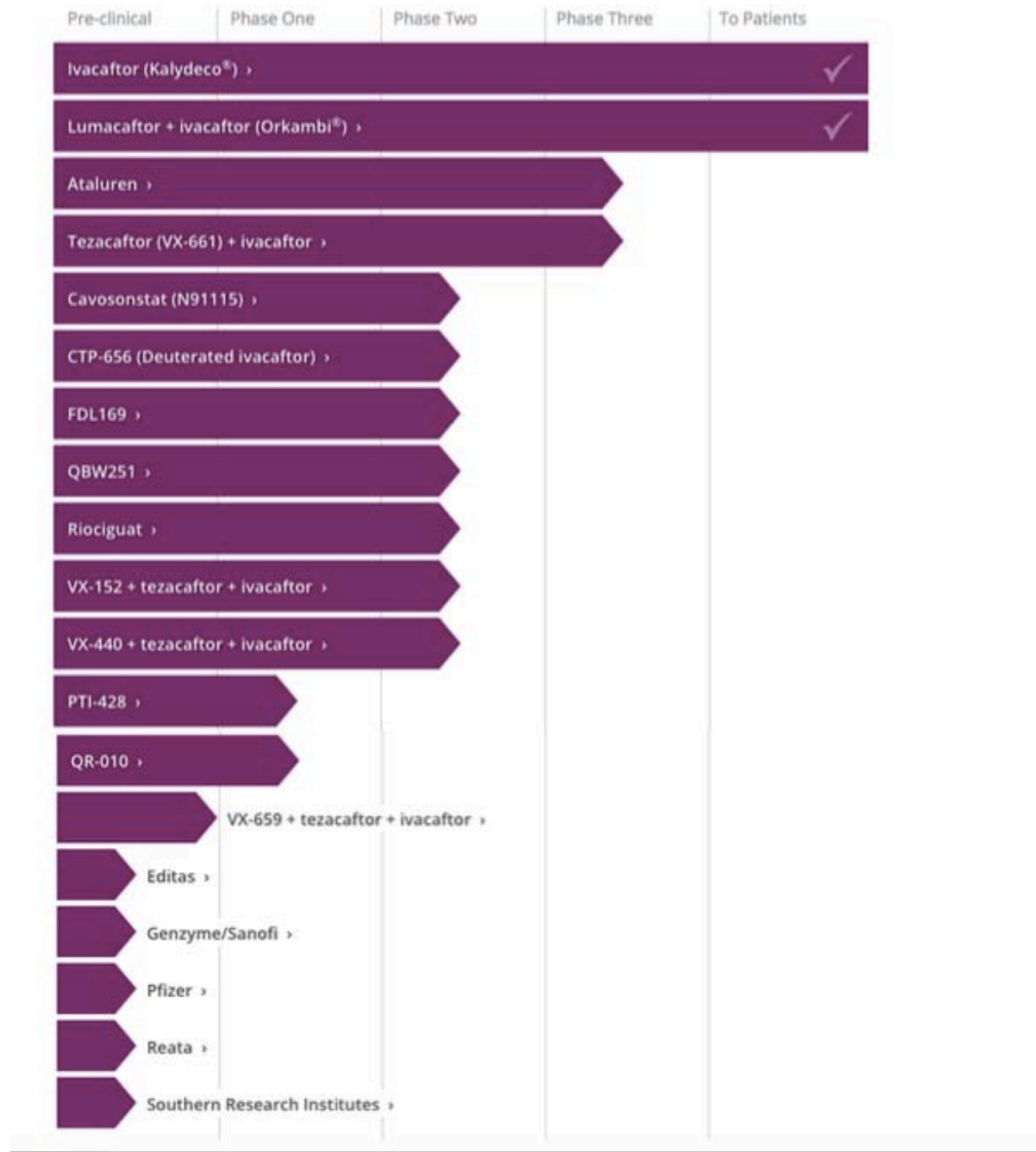


Figure 6. CFTR-Targeting Pipeline as of February 2017

A. 3 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 [14]. 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 [14].

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.

A.4 Scope of the Ionis-SMA Foundation Collaboration*

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 [1,2] 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 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 [3-5].
- **Standard of Care** created by SMA Foundation PIs: Critical for conducting trials in Type 1 SMA and used/cited in these studies [6].
- **Outcome measures:** The Foundation sponsored research to establish endpoints and standards for their implementation for SMA clinical studies. These endpoints included

* Provided by the SMA Foundation.

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 [7-12].

- **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 [13-16].
- **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 [17].

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