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Accelerating commercialization: a new model of strategic foundation funding

Maryann P. Feldman · Alexandra Graddy-Reed

Abstract Venture philanthropy presents a new model of research funding that is particularly helpful to those fighting orphan diseases, which actively manages the commercialization process to accelerate scientific progress and material outcomes. This paper begins by documenting the growing importance of foundations as a source of funding academic research as traditional funding from industry and government sources decline. Foundations are known for their innovative techniques and we consider the evolution of the ways that foundations fund academic research and form partnerships across academia and industry. We examine the example of the Cystic Fibrosis Foundation and the development of the drug Kalydeco® as a demonstration of the principals of strategic foundation funding. The Cystic Fibrosis Foundation adapted to a venture philanthropy model and took an active role in drug development, stewarding the commercialization process from funding basic scientific work in academic institutions, to making an equity investment in a start-up firm. We conclude by evaluating the advantages and disadvantages to venture philanthropy for the academic researchers, industry partners, foundations, and universities and consider an agenda for future research.

Keywords Venture philanthropy · Academic research · Drug development · Cystic fibrosis

JEL Classification O32 · O33 · P43

1 Introduction

Philanthropic disease-oriented foundations are experimenting with new research funding models that challenge assumptions about the commercialization of academic research. The implicit social contract that guaranteed public support for science and academic research is eroding within a larger debate over calls to foster more innovation, a perceived need for more effective ways to organize research projects, incentivize individual scientists, and

M. P. Feldman · A. Graddy-Reed (✉)
University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
e-mail: agraddy@live.unc.edu

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generally speed the diffusion of scientific discoveries to market (Zerhouni 2006; Khoury et al. 2007). Concerns about the costs of academic research coupled with calls for greater public benefit (Gibbons et al. 1994; Hart 2001) have initiated a series of changes that are likely to be as transformative as the 1980 Bayh-Dole Act.

Disease-focused foundations, especially those targeted at orphan diseases, are experimenting with strategies used in venture capital in a search for faster cures for often very personal reasons, rather than motivated by profit. The result, well-known in the philanthropic world as *venture philanthropy*, actively manages the commercialization process from initial basic research to market introduction, bringing together diverse partners to form a community of common interest, reducing risk through financial incentives and bridging the valleys of death[1] that adversely affect many promising technologies (Auerswald and Branscomb 2003). A striking example, examined here, is the development of Kalydeco®, a cystic fibrosis therapeutic, which became available in the spring of 2012 and provides a novel example of a new model for conducting research that can be used as a counterfactual case when compared against more traditional funding sources.

While there is a large literature that examines industry funding of academic research (Blumenthal et al. 1986, 1996; Cohen et al. 1998; Berman 2002; Carayol 2003), there is very little research that examines philanthropic funding of academic research. This is surprising, as the dollar amount of foundation research funding has been growing, while the contributions of both industry and government funding have declined. In 2010, foundation funding of academic research was roughly equal to the contribution of industry (National Science Board 2012). This fact alone argues for greater examination of foundations, while the new strategic research funding model, primarily utilized by private foundations and based on venture capital investing, is radically changing the ways in which academic research is conducted and commercialized. Venture philanthropists deviate from traditional giving strategies by their preference to invest rather than contribute, take an active role in designing the research project, maintain active collaborative relationships with researchers, and their use of benchmarks as a condition for additional funding. Despite its importance little is known about philanthropic funding for academic research, in general and the specific impacts of venture philanthropy.

This paper contributes to the literature by examining the role of one group of strategic foundations that are pioneering new development models for disease research, a group that has previously been neglected in the literature in terms of their position within the distribution of academic funding. We begin by documenting the growth of foundation funding in academic research, and defining venture philanthropy and strategic funding. This paper then examines the Cystic Fibrosis Foundation (CFF) and its venture philanthropy model that led to the development of the first drug aimed at the cause of cystic fibrosis: Kalydeco®. We follow their path to the development of this new drug to show how venture philanthropy is impacting the drug development pipeline. We then consider the advantages and disadvantages of this model from the perspective of the funder, the researcher, and the university. This paper concludes by considering the implications of the new model and defining a research agenda to better understand this phenomenon.

2 The increased role of foundations in funding academic research

Federal funding, once the most dependable source for academic research, has decreased in recent years from 1.3 % of GDP in the 1960s to 0.9 % in 2010 (Hendricks et al. 2011).

[1] Valleys of Death are defined as the period of transition when a developing technology, while perceived as promising, is unable to attract funding for its continued development (Auerswald and Branscomb 2003).

This decline has created a funding gap for researchers, leading them to seek alternative funding sources (Ledford 2012). While industry funding has served as one alternative, it has not filled the gap, leading to an increased reliance on alternative funding sources such as foundations.

This trend is more salient in the field of biomedical research, which has faced more complicated funding changes. First, Congress doubled the NIH's budget from 1999 to 2003. In response, applications for NIH grants more than doubled and under the assumption that infrastructure costs could be covered by future NIH grants, biomedical research capacity grew even more rapidly (Couzin and Miller 2007). The growth in capacity was financed from a combination of philanthropic, local and state resources, and loans (Zerhouni 2006). But then the NIH budget did not keep up with rising biomedical costs: NIH funding actually decreased by 8.6 % from 2003 to 2007 (Dorsey et al. 2010). As a result, the probability of being awarded an R01 on the first attempt decreased from 21 % in 1998 to 8 % in 2006 (Couzin and Miller 2007).

Over the past 20 years, industry funding has provided between approximately 5 and 7 % of total academic R&D funding (National Science Board 2010). Industry funding for academic biomedical research has been less consistent (Dorsey et al. 2010). One reason is that from December 2000 to February 2008, just before the economic downturn, the top 15 pharmaceutical companies lost approximately $850 billion in shareholder value (Garnier 2008). LaMattina (2011), Pfizer's former R&D chief, blames the decreased R&D productivity on the mergers and acquisitions of large pharmaceutical companies. The 1990's were the highpoint of R&D productivity for the industry, but many of the firms that contributed to this success no longer exist: the Pharmaceutical Research and Manufacturers of America (PhRMA) is down to 11 members from the 42 it had in 1988 (LaMattina 2011). As a result of mergers and acquisitions, R&D programs were made redundant and cut. Moreover, Hu et al. (2007) argue that the blockbuster business model, which focuses on drugs generating more than $1 Billion in revenue per year, has failed. As a result, the pharmaceutical industry, which once had the largest industry investment in R&D at about 20 % of revenues, has fallen, with Pfizer predicting an 11 % rate for 2012 (LaMattina 2011). In sum, declining R&D productivity has resulted in the search for new business models that frequently focus on acquiring start-up firms to supplement their product development pipeline rather than developing in-house research capabilities and funding upstream university research (Bhattacharjee 2006; Hu et al. 2007; The Economist 2012). This strategy shifts product development risk to startups, which are frequently based on university research.

While Federal and industry contributions have fluctuated, the role of foundation funding of academic research has been growing with the rise of neo-philanthropists like Bill and Melinda Gates and others from the tech-boom. From 1996 to 2009, funding from foundations more than doubled,[2] increasing by 101 % (Table 1). In 2012, NSF redesigned and expanded the Academic R&D survey to separate nonprofit organizations as their own category, a signal of their growing importance to academic R&D (Britt 2012). Prior to 2010, the National Science Foundation considered foundations and nonprofits as part of the "other" source when reporting academic research funding, which also included foreign government investment. From 2009 to 2010, academic R&D for S&E fields increased overall due to a large increase in Federal dollars as part of the American Recovery and Reinvestment Act of 2009 (Britt 2012). Nonfederal funding also increased but by a smaller

[2] Until 2010, the National Science Foundation includes foundation and nonprofit funding in the "other" source category with foreign government investment.

Table 1 2005-constant $millions, academic S&E R&D dollar contribution by source over time

Years	Federal	State & local	Industry	Institutions' own	Other: nonprofits & international
1996	16,665	2,181	1,933	5,021	1,949
1997	16,937	2,259	2,054	5,557	2,025
1998	17,728	2,275	2,209	5,852	2,188
1999	18,569	2,330	2,343	6,203	2,299
2000	19,795	2,482	2,432	6,684	2,544
2001	21,229	2,560	2,448	7,297	2,676
2002	23,745	2,720	2,378	7,744	2,932
2003	26,324	2,813	2,298	8,145	3,036
2004	28,566	2,975	2,200	8,012	2,947
2005	29,209	2,940	2,291	8,266	3,093
2006	29,178	2,869	2,326	8,776	3,095
2007	28,662	2,959	2,514	9,137	3,326
2008	28,835	3,182	2,641	9,594	3,621
2009	29,687	3,322	2,912	10,201	3,922

Sources defined by NSF to include: Federal, State and Local Government, Industry, Institution's Own, and Other. "Institutions' Own" refers to funding within the university from the university's own resources. "Other" includes nonprofit and foundation funding and international government contributions

Data Source National Science Board (2010)

degree, with most of the increase coming from the category of other and nonprofit. Now reported separately, nonprofit funding accounts for 5.97 % of S&E R&D in 2010, a share slightly larger than industry's of 5.36 % (Britt 2012; Fig. 1).

However, even this significant percentage is an underestimate of foundation's contribution to academic research funding. Institutions' own funding of research, which makes up the second largest proportion, accounted for 20.38 % of S&E R&D investment in 2009 (National Science Board 2010). This represents the amount that universities contribute to research from their own funds, which are likely to include contributions from foundations. Foundations often make gifts directly to university endowments with specific stipulations for use on R&D project. This type of funding is not subject to university indirect cost calculations, which are levied on R&D projects funded as sponsored research. There are incentives for both foundations and individual scientists to favor this type of arrangement, as the full amount transferred is available for the research in comparison to a sponsored research project that has a percentage allocation to support university overhead. While universities stand to lose funds for operating expenses, the foundation's dollars have increased the total amount of resources available.[3] While it is apparent that part of the universities' own contribution to research comes from foundations, the exact amount is unknown because of the lack of standardization in practices.

[3] University practices are heterogeneous. Any gift that is targeted for a specific research project and for which there are expectations of a reporting relationship should be considered as sponsored research. There are, however, organizational issues related to credit for fundraising, accountability and donor relationships that limit these arrangements. Many foundation gifts provide funding for research on a specific topic for which the university holds competitions and provides oversight.

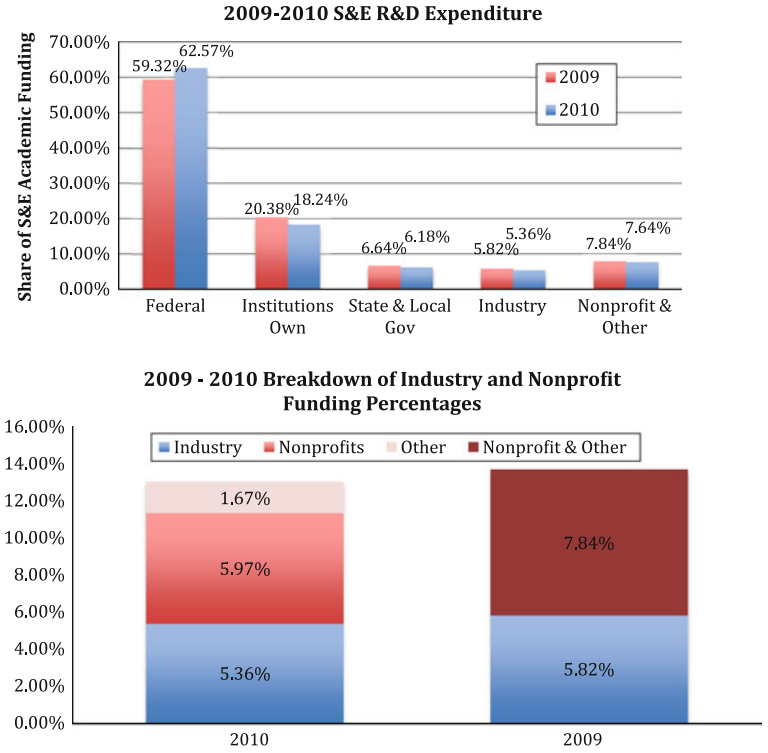

Fig. 1 2009–2010 academic S&E R&D sources by share of expenditures. *Data source* National Science Board (2010), Britt (2012)

In sum, current data on the role of foundations in funding academic research provides an underestimate of foundations' contribution to R&D funding and as a result, fails to show the full extent to which their role has changed over time. In addition to their role in funding research, foundations have an expanded role that includes defining the academic research agenda. The following section provides historical background on foundations and the increasingly active role they have taken in research.

3 Innovation in philanthropy and the search for new models of funding research

The word philanthropy translates from Greek as love of the people and builds on an American tradition of voluntary financial support to serve the public good and improve the quality of human lives (Salamon 2003). Modern American philanthropic foundations date back to the great nineteenth century fortunes created by industrialization and while the tax code now provides an incentive to give, the tycoon philanthropists were a strong force in the American economy preceding these incentives. For example, when Rockefeller gave $100 million to establish his foundation in 1913, he received no financial benefit for the gift (Hall 2006).

In contrast to government programs, which operate under a politically negotiated consensus mandate, private philanthropic foundations are, as the Treasury Department noted in 1965, "uniquely qualified to initiate thought and action, experiment with new and untried ventures, dissent from prevailing attitudes, and act quickly and flexibly" (Treasury Department 1965). As part of the voluntary third sector, philanthropic foundations can mobilize resources quickly, support politically unpopular programs and areas of research, develop information and serve as neutral conveners to inform policy debates. Building on demonstrated results, Section 501(c) of the Internal Revenue Code, established by the Revenue Act of 1954, provided tax incentives for the use of personal wealth to fund innovative and risky ideas that would benefit the greater social good. Over the past 100 years American philanthropic foundations have constantly innovated in the search to achieve their mandate (Table 2). Through the funding of academic research they have incentivized researchers to accomplish their articulated goals.

Initial greats like Andrew Carnegie and John D. Rockefeller, funded their foundations with large initial endowments with the goal of funding innovative researchers who could create substantial change. Their efforts led to the development of fields, like public health and molecular biology and funded the work of Nobel Prize winners. As foundations continued to grow, their methods and purpose expanded: foundations like Lasker and MacArthur introduced new funding mechanisms of awards and prizes, and increased their scope of work to include advocacy. The types of foundations also grew with the creation of the first disease-focused foundation—The National Foundation for Infantile Paralysis (now March of Dimes). Disease-specific foundations work to support the whole patient—through advocacy, services, and research, with the ultimate goal of curing disease.

Venture philanthropy was coined in the 1960s as a new strategy for foundations to move beyond merely writing a check, and instead encourage good use of the funding (Leibell 2009). Paul Tudor Jones, a venture capitalist, pursued the idea of venture philanthropy with the creation of the Robin Hood Foundation in 1988, with the mission to alleviate poverty in New York City (Frumkin 2003). Robin Hood pioneered the use of metrics to provide benchmarks to measure the effectiveness of grants, active management of projects in a partnership rather than patron model, and continuing relationships with successful grantees. Robin Hood's funding comes from a variety of sources, including board members who bear all the administrative costs as well as general fundraising and managed partnerships with other foundations and government (Frumkin 2003). This idea was developed in the Letts et al. (1997) article that articulated and recommended a venture philanthropy model for philanthropy (Leibell 2009). The result-oriented funding model then diffused rapidly among foundations (deCourcy Hero 2001). In general, what distinguishes this category of foundations is the view that their funding is an investment rather than a contribution, they take an active role in project management, often forming cohesive research teams across different organizations to work on goals, and they set measurable concrete benchmarks as a condition for continued funding.

The results-oriented venture philanthropy model fits well with the goals of disease-specific foundations seeking to fund research to cure or ameliorate disease. In 2003, FasterCures, a nonprofit based in Washington, D.C., was founded to focus on linking researchers, policymakers, and philanthropists to promote effective funding and accelerate research processes that get new treatments to patients (FasterCures Strategic Plan 2012). The founder was financier Michael Milken, who when diagnosed with prostate cancer created a foundation dedicated to funding research on that disease. Adopting a venture philanthropy model, Milken wanted to counter the tendency of foundations to pursue established research agendas rather than funding higher risk, potentially higher reward

Table 2 Summary of key foundations creation, mission, and contribution

Foundation	Founder	Year founded	Structure	Contribution	Sources
Carnegie Institution for Science	Andrew Carnegie	1902	Foundation	Pioneered American philanthropy. Funded innovative scientists	carnegiescience.edu Change 2010
Rockefeller Foundation	John D. Rockefeller	1913	Foundation	Led the way in agenda setting philanthropy and as a result have spurred new fields such as public health and molecular biology	rockefellerfoundation.org Kay 1993 Kohler 1991
March of Dimes Foundation	Franklin D. Roosevelt	1938	Public Charity	First disease-focused foundation. Worked to find a cure for polio and now works on infant survival	marchforbabies.org Chang 2010
Albert and Mary Lasker Foundation	Albert and Mary Lasker	1942	Operating Foundation	Expanded the role of philanthropy to include advocacy. Introduced the use of prizes as a means of promoting accomplishments	laskerfoundation.org
Cystic Fibrosis Foundation	Parents of children with the disease	1955	Public Charity	Developed the use of venture philanthropy for orphan disease nonprofits	CFF.org
Robert Wood Johnson Foundation	Robert Wood Johnson	1972	Foundation	Largest foundation exclusively dedicated to health and healthcare. States specific goals, measures success, and evaluating outcomes	rwjf.org
John D. and Catherine T. MacArthur Foundation	John D. and Catherine T. MacArthur	1975	Foundation	Uses awards to promising individuals to promote their research goals rather than funding achievement already created	macfound.org Chang 2010
Robin Hood Foundation	Gelnn Dubin and Paul Tudor Jones	1988	Public Charity	Expanded the use of metrics to measure the effectiveness of grants and has active management of projects in a partnership rather than patron model	robinhood.org Frumkin 2003
Bill & Melinda Gates Foundation	Gates Family	1997	Family Foundation	Largest US grant-making foundation. Follows a strategy of defined goals and measuring success	gatesfoundation.org
Faster Cures	Michael Milken	2003	Disease-Focused	Focused on linking researchers, policymakers, and philanthropists to accelerate the commercialization of research	fastercures.org

projects and to reduce the amount of time that researchers spent applying for funding (Barbic 2012).

Disease-oriented foundations have grown both in size and number in the last 20 years (Chang 2010). Many of these foundations are focused on orphan diseases, which are those that affect a small proportion of the population and are not seen as profitable by the pharmaceutical industry (Aronson 2006). These foundations have the mission not of funding research but of finding cures for diseases that are receiving little attention from drug companies, like San Fillipos and Justin's Just Begun, and for which little progress has been made, like the Multiple Myeloma Research Foundation, Alzheimer's Drug Discovery Foundation, Michael J. Fox Foundation and Foundation Fighting Blindness. Venture philanthropy has also been adopted by some of the larger disease-focused foundations, such as Muscular Dystrophy Association and Juvenile Diabetes Research Foundation as they engage in focused, driven research aimed at finding a cure quickly that demands collaboration across industry, government, and academia, and includes the use of milestones and specification of targeted outcomes (Chang 2010; Fielding 2011; Aebischer 2012).[4] As a result of these efforts, in 2008 US disease-focused foundations using venture philanthropy invested approximately $90 million in bio-pharmaceutical companies for drug development, a 20 % increase from 2007, and 13 times more than in 2000 (Haugh 2010).

Against this backdrop, the Cystic Fibrosis Foundation (CFF) was established in 1955 by parents of children with cystic fibrosis. CFF has been the catalyst for much of the progress made in treating cystic fibrosis, extending the life expectancy of those with the disease, and developing new, effective therapies (CFF 2012). Cystic Fibrosis was first defined as a disease in 1938 when Dr. Dorothy H. Anderson working at Columbia-Presbyterian Medical Center and Columbia University established its genetic basis and later developed a definitive diagnostic test (Littlewood 2011), demonstrating the importance of academic research. However, the market, less than 30,000 patients, is considered too small to motivate drug development efforts at large established pharmaceutical firms. As a result, CFF adopted the mission to "assure the development of the means to cure and control cystic fibrosis and to improve the quality of life for those with the disease" (CFF 2012). CFF, as an organization, captures a very immediate and intensely personal mission—to prolong the lives of children, mostly-family members, with the disease. CFF did not start with a large endowment like a traditional grant-making foundation, but instead adopted a fundraising model like that of March of Dimes, with most money raised from donations and then immediately poured into research and patient service. Today, there are over 80 local chapters of CFF that raise funds to support academic research and patient support (CFF 2012).

The disease-oriented foundation, the focus of this paper, is the primary user of the venture philanthropy model, although it is growing in other fields, notably topics related to the environment and energy, poverty alleviation and products for the developing countries—all fields where prevailing market outcomes are not adequate. The venture philanthropy model appeals to organizations that are driven by a mission or cause that has a desired concrete outcome but that has limited resources. The following section explores this model in greater detail.

[4] Even established medical research funding organizations, such as Robert Wood Johnson are experimenting with this model in their Complex Chronic Care program.

4 The emergent venture philanthropy model

On average, the federal drug approval (FDA) approval process takes 10 years and almost two billion dollars to complete (Gilbert et al. 2003). Murphy (2005) reports that between 1991 and 2000, target attrition rates approach 90 %, with 38 % of drug targets failing in Phase 1, 60 % of the remaining set failing in Phase 2, 40 % of those survivors failing in Phase 3 and 23 % of those that managed to pass Phase 3 failing to gain approval by the FDA. This means that only 10 % of projects are likely to be successful. It also implies that projects further along in the drug development process are less risky and more likely to attract interest from pharmaceutical firms.

Figure 2 depicts an adapted view of the drug development pipeline, which shows the differences in approach between industry and foundation sponsors. In the traditional model of R&D funding, the Federal government offers funding of basic research in the first stage. Once there is a discovery and some initial, pre-clinical work, venture capital (industry funding) would step in and pick up the project, carrying it through to other private funding sources that would bring the product to sales. But ironically, venture capital financing has become more risk adverse and less willing to invest in the early stages of research. As a result, there are fewer funds available for drug development, creating what is well known as the valley of death.

As a result, venture philanthropy has stepped into provide funding in this gap created by the absence of industry funding. The main strategy of disease-focused venture philanthropy can be conceptualized as decreasing the risk inherent in commercializing new drugs and treatments by leveraging their smaller funds in the valley of death and by incentivizing firms to join in translational research (Haugh 2010). And rather than leave the process of commercialization to the market mechanism, disease-focused venture philanthropy firms also engage in active management of the process. Similar to the role of a product manager

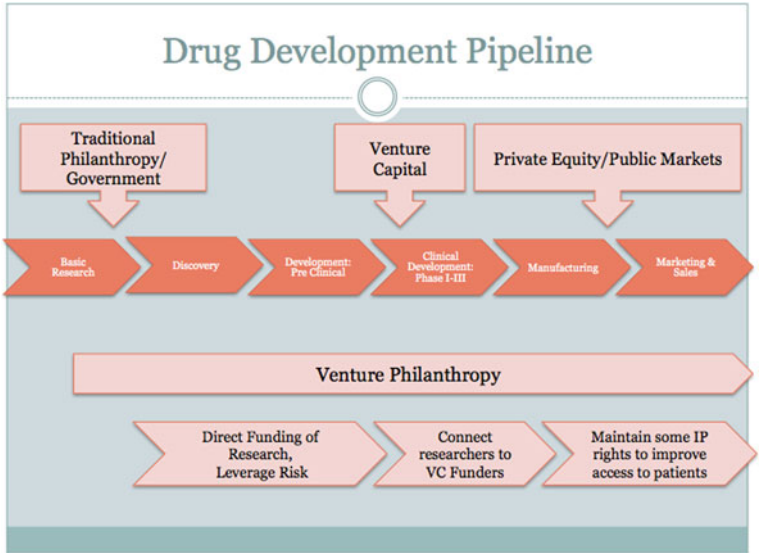

Fig. 2 Drug Development Pipeline. Adapted from: Institute for the Study of Aging & The Alzheimer's Drug Discovery Foundation (2008), Finkbeiner (2010), and Ministry of Commerce & Industry Task Force (2008)

in the development of new innovations in large firms, these foundations actively shepherd research through the entire commercialization process.

In addition to providing funding for researchers, our interviews with foundation leaders find that disease-specific venture foundations organize communities of scholars to work together to create epistemic communities around specific topics. These communities legitimize research topics by providing a body of work that can be cited and built upon and creating a pool of potential collaborators, referees and reviewers. As a result, the ease of publishing is expected to increase and, with greater legitimacy, other potential funding sources become available. For researchers, the risk of pursing a new research topic or disease target is reduced. In addition, foundations are working to increase the likelihood that major technological breakthrough may occur by handpicking teams of researcher with complementary expertise, increasing the utility for a researcher to join a project. By transcending traditional principal investigator-led exploration they are creating opportunities for collaboration and offering a new model of conducting research.

After significant progress is made through research, disease-specific foundations combat other difficulties of the drug development pipeline by using their patient registries to organize clinical trials, one of the significant bottlenecks of the drug development process (Finkbeiner 2010). Disease-oriented foundations also work to maintain their relationship by utilizing matching grants to secure further funding for their researchers, as well as define royalty payments and future intellectual property agreements to help sustain their own foundation and future research efforts (Chang 2010; Fielding 2011).

Through these varied efforts, disease-focused foundations have gained bargaining power even though their funding packages are much smaller than that typical of old industry investments. The pipeline has changed as industry has consolidated into a set of fewer yet larger players, and this new organizational structure has produced an approach by industry that is less risky than the definition of venture capitalist would imply. It has then created a niche for foundations to leverage their position and become a stronger funding source in the world of R&D.

5 CFF and Kalydeco®: an illustrative example

CFF was the first major disease focused foundation to utilize the venture philanthropy model to its full potential and brings to market the first drug targeted at the cause of cystic fibrosis. At the time of its formation the mechanism of the disease was unknown and the median survival age was 1 year (CFF 2012; CFF 2009). While it is estimated that 1 in 29 Caucasian Americans carry the gene for cystic fibrosis, both parents must pass the gene onto a child for that child to contract cystic fibrosis (Wulffson 2012). As a result approximately 30,000 people have cystic fibrosis in the US. CFF is now the driving force behind the search for a cure for cystic fibrosis. It is a donor-supported nonprofit "dedicated to attacking cystic fibrosis from every angle" (CFF 2012). CFF supports the development of new drugs, improving the quality of life for patients, and finding a cure for the disease (CFF 2012). In part from CFF's aggressive approach, the life expectancy for children with cystic fibrosis has increased drastically over the years, reaching 18 years by 1980 and 37 years by 2007 (CFF 2012; CFF 2009).

CFF classifies its contributions into categories of: research pioneers, fundraisers, advocates, stewards, and caregivers. As research pioneers they innovate in the drug development process, as fundraisers they find funding to support the search for a cure, and as advocates they work to maintain steam and press of cystic fibrosis with government,

academia, and industry. CFF is also a steward, using donations to fund the drug development pipeline, and supports caregivers, helping patients find care and information (CFF 2012). In FY 2012, CFF had $117,525,922 in contributions, $21,812,310 in program service revenue, and $61,043,649 in other revenue for total revenue of $200,381,881 (Charity Navigator Report 2012). CFF's total functional expenses in FY 2012 were $133,887,556 with 81.6 % for program costs, 6.9 % to administrative expenses, and 11.4 % allocated for fundraising (Charity Navigator Report 2012). The foundation receives most of its contributions through individual donations and special events like their walk-athons, though in 1999 they also received a gift from the Bill and Melinda Gates Foundation for $20 million (Moukheiber 2001). CFF now employs 600 people and manages 250,000 volunteers (Marshall et al. 2009).

Over time, CFF has grown and expanded their operations to better reach and connect patients to evolving care. In 1966, CFF created a patient data registry of patients seen at care centers (CFF 2012; Marshall et al. 2009). CFF also funds a national care center network, recognized by the NIH as a model for chronic diseases, providing patients with access to treatment and resources across the country and they sponsor the annual North American Cystic Fibrosis Conference, which in 2011 had approximately 4,000 doctors, researchers, and caregivers attend to share ideas and progress (CFF 2012). CFF has always maintained a focus on funding research. One major breakthrough came in 1989, when a team of researchers, supported in part by CFF funding, identified the gene responsible for cystic fibrosis (CFF 2012). There was further success a few years later, when in 1993, the FDA approved Genentech's Pulmozyme®, the first drug developed specifically for cystic fibrosis, which was a result of CFF partnership with Genentech (CFF 2012).

The driving force behind CFF's success has been the shift in strategy to a venture philanthropy approach (CFF 2009; Bain 2006). CFF is now regularly referred to as the leading venture philanthropy organization because of their successful adaptation to the new funding model (The Economist 2011, 2012; Haugh 2010). The change is credited to Robert Beall, who became President and CEO of CFF in 1994 (Fielding 2011). Beall reports that this was an opportune time as it was soon after the discovery of the genetic marker of cystic fibrosis and so new methods and opportunities were open to research (Faster Cures.org 2012). Beall, with a doctorate in biochemistry, had prior experience working in academia and at NIH. Although he had been working at CFF since 1980 (CFF 2012), he redefined the organization when he took on the leadership position in 1994.

Beall has acted as the policy entrepreneur for cystic fibrosis. Policy entrepreneurs are advocates who invest resources to promote an innovative point of view. Known for their political connections, persistence, and possessing a claim to be heard, policy entrepreneurs are focused on a particular objective. A policy entrepreneur is an insider to a field, but rather than being conservative and sticking with the status quo they are risk-takers who pursue organizational change. Policy entrepreneurs frame and define a mission and then use their political and institutional reach to direct resources towards that mission (Kingdon 1994). Beall exhibited all of these characteristics as he shepherded CFF into a new era of venture philanthropy practices. He changed CFF so that it took philanthropic dollars from other foundations, and acted as a venture capitalist, investing not only in risky stages of research, but also investing in companies (Pollack 2012; Opar 2011). In 1998, Beall set out to put the venture philanthropy approach into full action and find a company who would partner with CFF to find a cure (Fielding 2011; Fleischer-Black 2002).

Beall was motivated to convert to a venture philanthropy approach because of the nature of cystic fibrosis as an orphan disease. Since the disease affects such a small number of people, the pharmaceutical industry has little incentive to research treatments for it. Thus

the burden of funding research falls on CFF (Potts 2011). But the venture philanthropy approach helps counteract the lack of industry funding, by reducing the risk of the disease for firms and offering some of the resources of advocacy groups, like networks of volunteers for clinical studies (Fielding 2011; Bain 2006; Moukheiber 2001). It also allows CFF to take a more active role in the drug development process (Pollack 2012). Further, it helps to sustain the foundation itself, through the additional income of royalties off of their investments. Traditional fundraising is still down after the recent economic crisis, so the royalties CFF is receiving are simply being reinvested into new research projects. These royalties provided $53 million to CFF in 2010 alone (Ledford 2011).

The transition to venture philanthropy has turned CFF into a "virtual drug company" by funding more research, forming partnerships between industry, and academia and putting the majority of the foundation's budget into drug development (Moukheiber 2001). Specifically, this effort has led to $260 million being invested in drug development by the foundation since the mid-1990s (The Economist 2012; Haugh 2010). With this new approach at work, Beall is "making big bets on new genomics technologies and shepherding drugs through human trials, much like a pharmaceutical company partnering with start-ups" (Moukheiber 2001). However, it is important highlight that the foundation has chosen to describe itself in a business term, as a virtual company, moving away from its nonprofit mission. Instead the focus now is on an incentive structure common to that of a profit-driven entity.

While adopting this venture philanthropy model, CFF introduced a further innovation by creating a separate arm, the Cystic Fibrosis Foundation Therapeutics (CFFT) in 2000 "to bridge the gap between what has been learned in the laboratory and the evolution of new therapies" (CFF 2012). The premise of CFFT is to offer the infrastructure necessary to support a "virtual pipeline" from discovery to clinical trials by offering both industry and academia investment capital in early stages of development (CFF 2012). This is a successful model because it offers necessary funding at the early-stages of development (CFF 2012).

CFFT offers matching research awards to scientists in both academia and industry and access to the network of cystic fibrosis clinical research centers to support research through several stages of the pipeline (CFF 2012). Investments are decided on a case-by-case basis with no predetermined levels of distribution between academia and industry funding (Fielding 2011). CFFT measures success with metrics of milestone achievement and progress through the pipeline (Fielding 2011). Since 2005, this approach has led CFFT to invest more than $55 million in diverse projects all working towards finding a cure for cystic fibrosis (CFF 2012). CFFT investments have thus far consisted of 70 % related to discovery and preclinical investments and 30 % in clinical investments (Fielding 2011). Fifteen of the investments have led to clinical stage progress and two commercial products (Fielding 2011). CFFT's research work has increased the size of the cystic fibrosis pipeline with CFF listing over 30 drugs in development with 22 companies (CFF 2012; Haugh 2010; Fig. 3).

Prior to the founding of CFFT, CFF created the Therapeutics Development Network (TDN) in 1998 as a subset of the CFF's Care Center Network. It is composed of a nationwide network of care centers, coordinated at Seattle Children's Research Institute, with laboratories that specialize in conducting clinical trials, interpreting cystic fibrosis outcome measures, and standardizing the research process of clinical trials (CFF 2012; Marshall et al. 2009). To match growing need, CFF expanded the TDN in 2009 from 18 to 80 centers (CFF 2012). Of the 80 centers, all but six are affiliated with universities with the remainder tied to hospitals or medical research centers. Thirteen centers are focused on

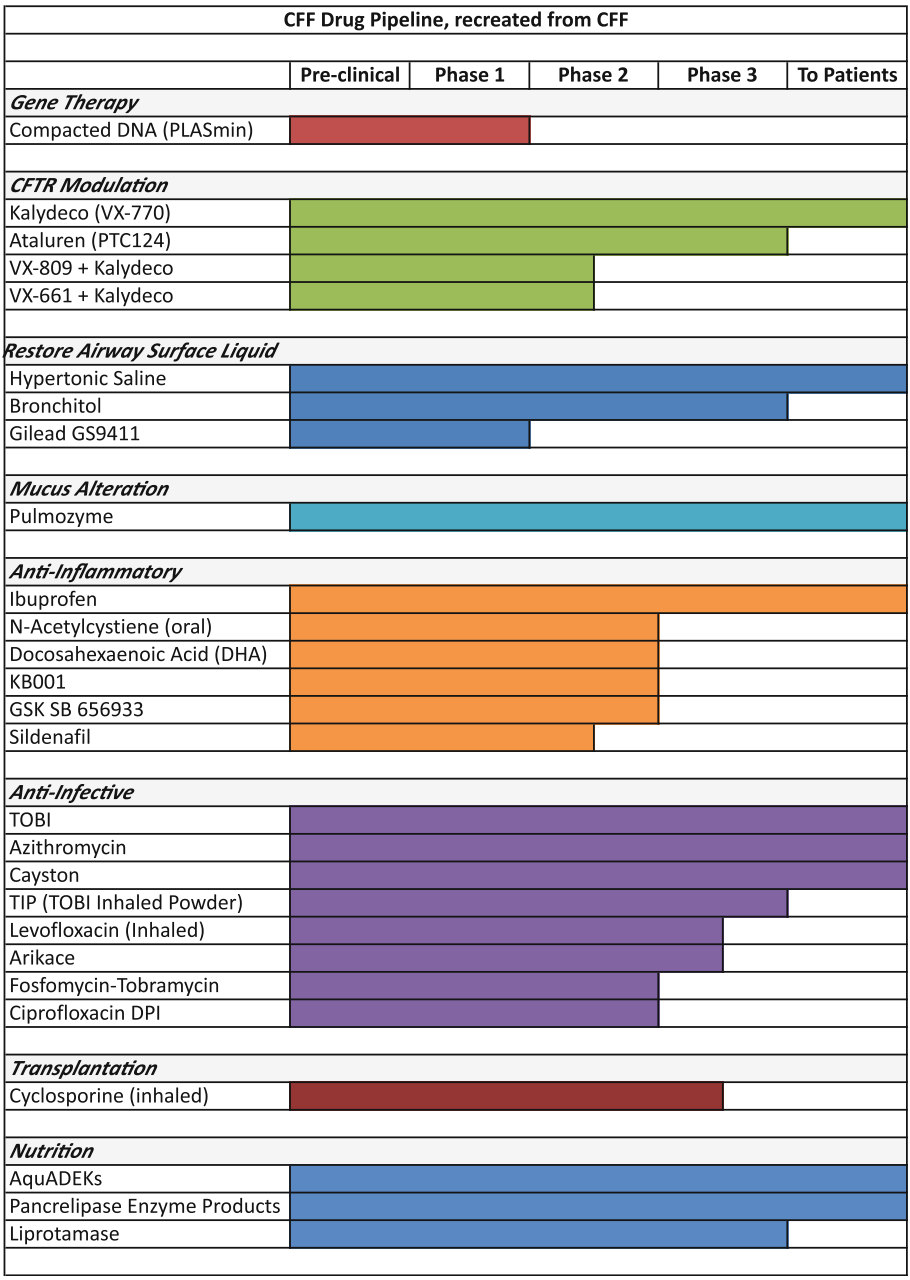

Fig. 3 CFF drug pipeline. *Source* CFF (2012)

translational work to identify new therapies and new ways to measure outcomes from clinical trials (CFF 2012). TDN provides financial, intellectual, and physical resources to researchers, which has led to over 50 clinical trials (Marshall et al. 2009; Bain 2006).

The TDN program developed after the success of the Research Development Program (RDP), the concept of bringing together top scientists from multiple fields at major universities to pool talent and direct it at basic cystic fibrosis research. The first RDP was established in 1982 at the University of Alabama, Birmingham (CFF 2012). RDP centers serve as "core supply centers" that share tools, resources, and information with other researchers around the world to speed the process of finding a cure (CFF 2012). There are a total of eleven centers in ten states including centers at the University of California at San Francisco, the Johns Hopkins University School of Medicine, the University of North Carolina at Chapel Hill, and the University of Washington School of Medicine (CFF 2012). The RDP centers have successfully produced some of the critical R&D for cystic fibrosis. For example, Dr. Cutting at Johns Hopkins University introduced the CFTR2 database in 2011 that is an international research program to classify the over 1,800 different mutations of cystic fibrosis and the relationships between the mutations and symptoms (CFF 2012).

But while academic research has been vital to cystic fibrosis research and CFF's strategy, CFF has also been novel for the extensive involvement with industry partners. One of the first major deals with such a start-up, Aurora, paved the way for contracts between foundations and firms for drug development. While this deal was being negotiated, the legal team was concerned about what would happen to the foundation's investment if the firm lost interest. So they added an interruption license that is now widely used by charities to give the foundation the intellectual property rights of a project if the company abandons it (Ledford 2011). Those rights were invoked by CFF in another deal with Altus Pharmaceuticals when Altus realized it could not afford the Phase 3 trials. CFF took the license in search of a new firm (Ledford 2011). Intellectual property rights and royalties are key to making industry partnerships valuable to CFF in the long run, which CFF co-owns with the biotech firms (Fleischer-Black 2002). As a result of these efforts, biotech firms have seized some of the market for basic research from universities (Fleischer-Black 2002).

While good or bad remains to be determined, the skill of venture philanthropy, as practiced by CFF, comes in the formation of partnerships of academic researchers and industry firms. For example, Tobramycin Inhalation Solution USP (TOBI), a therapy developed to treat lung infections associated with cystic fibrosis (CF), was developed by PathoGenesis Corporation in collaboration with CFF, NIH, and academic researchers (Rose and Neale 2010). PathoGenesis, a small start-up biopharmaceutical firm, negotiated with CFF and Seattle Children's Research Institute to develop and license TOBI (Rose and Neale 2010). But when the FDA put a hold on PathoGenesis's Phase 3 clinical trials, the academic research team worked quickly on studies to revise and form a more efficient therapy, which saved a year of development time (Rose and Neale 2010). CFF, through Beall, worked to initially bring together the academic researchers and PathoGenesis and provided access to patients for clinical trials, structuring the entire development of TOBI (Rose and Neale 2010).

While CFF forms partnerships and offers direct funding, the aspect of clinical trials is an important factor to its success with industry. A typical delay to the drug development process is the difficulty in recruiting patients for clinical trials. However, because of CFF's network of care centers and patient registry, CFF is able to cut lengthy recruiting times for trials (Bain 2006). CFF also funds the Therapeutic Development Award, a peer-reviewed, milestone based award that allows researchers to pursue innovative ideas for cystic fibrosis research (Bain 2006) and uses a point system to evaluate the progress of therapies through the pipeline (Potts 2011), two concepts closely aligned to venture philanthropy principles of the use of milestones and metrics of success.

But as with any venture organization, there is not success alone, and CFF's high-risk approach has led to some disappointments. As mentioned above with its partnership with Altus Pharmaceuticals, CFF has had to twice end partnerships with firms that had insufficient capital to finish the project that discouraged some investor's support, and decreased their Charity Navigator Rating (Potts 2011). Despite these minor setbacks, CFF's approach appears to have been successful, as seen by the development of Kalydeco®, which began in 1998 when CFF started negotiations with Aurora Biosciences (Fielding 2011).

In May 2000, after 2 years of negotiation and a prior research agreement, CFF entered into a Research Alliance and Commercialization Agreement with Aurora Biosciences, and agreed to provide $30 million in funding, with another $17 million in milestone payments if milestones were met. At the time, this was the largest contract ever awarded by a non-profit health organization to a company. This investment diversified CFF into drug discovery (DeFrancesco 2000). The terms stipulated that Aurora would identify and develop two to three new drug candidates in 5 years using its high throughput screening technology. The investment was motivated to develop a drug development pipeline that would be active in every stage and shorten the average 14-year time period of drug development (DeFrancesco 2000).

According to Stuart J. M. Collinson, chairman, CEO, and president of Aurora: "The important science that CFF has funded over the years in university labs and medical centers has created new opportunities for therapies. To convert these opportunities quickly and efficiently into compounds that can be tested in the clinic requires skill sets, technologies and expertise that may be beyond those in the basic research lab. These are the capabilities Aurora brings to this partnership" (DeFrancesco 2000). Aurora, like CFF, recognized the importance of CFF's long-term work, especially with university researchers. It had been the years of research investment with academic centers and partnerships that brought them to the point where an industry firm, like Aurora, could come to the table.

Under the agreement, licensing revenues from any resulting drugs would be split equally; terms noted to be more favorable than biotech companies usually negotiate with large pharmaceuticals (Fleischer-Black 2002). But then Aurora Biosciences was purchased by Vertex in 2001, an acquisition that could have ended the efforts of CFF. However, as chronicled in a Harvard Business School case (Higgins et al. 2007), Vertex decided to continue the relationship with CFF. Vertex reports that more than 200,000 compounds were screened in the process of discovering VX-770, the compound that later became the drug ivacaftor (Kalydeco®). The drug then entered clinical trials in 2006. In 2008, VX-770 showed unprecedented gains for patients in Phase 2 trials, which were maintained in Phase 3 trials in 2011 (CFF 2012; Vertex 2012). Finally, in January 2012, Kalydeco®, the first drug to address a specific protein change caused by genetic variation in the CFTR gene sequence—and thus target the underlying cause of cystic fibrosis—received FDA approval marking a significant therapeutic breakthrough through a compound that CFF was instrumental in bringing to market (CFF 2012; LaPook 2012). Kalydeco® will target about 4 % ($\sim$1,200 people) of patients with cystic fibrosis (CFF 2012).

But the gains of their investment did not end there: in 2007, Vertex began to develop a second potential drug, VX-809 (CFF 2012). In May 2012, Vertex Pharmaceuticals announced that a clinical trial with a combination of Kalydeco® and the experimental drug VX-809 substantially improved breathing for some cystic fibrosis patients (Reuters 2012). With the mid-stage release of results of the combination drug, Vertex stock rose 55 % to a share price of $58.12 (Loftus 2012). However, it was later revealed that Vertex overstated the efficacy of the cystic fibrosis therapy combining Kalydeco® and VX-809, causing shares to fall 12 %, removing part of the previous 55 % gain. Vertex said the misreporting

came from misinterpreting the results from an outside company (Loftus 2012). Although the drug is still showing positive signs, the finger pointing by Vertex is a political move typical of any organization trying to recover from a blow to public trust. However, there may now be consequences to CFF from the nature of their public relationship with Vertex. If this changes how CFF itself responds to problems, there could be greater issues of trust between the foundation and the general public.

The new release still shows positive signs from the new combination therapy, and Vertex says it will continue late-stage trials. The combination of Kalydeco® and VX-809 would treat a larger population of cystic fibrosis patients then Kalydeco® alone. The new results show that 35 % of patients receiving the "therapy had an absolute improvement of at least 5 % points," and "19 % improved by at least 10 % points" (Loftus 2012). The corrected results concluded that no patients on placebo showed an improvement and the mean change was an 8.5 % point increase for patients taking the combination, statistically significant with a p value of 0.002. "The result was due to both a 4 point increase in lung function by patients in the group getting the company's drug combination and a 4.6 % point decrease among the patients taking placebo." Even if the control group had less of a decline, there would still be a marked improvement of 4–5 % points from the drug (Herper 2012).

In sum, CFF has funded $75 million in Vertex up to the introduction of Kalydeco® (Pollack 2012; Opar 2011) and committed another $75 million through 2016 (Vertex 2012). It will also earn royalties from the sale of Kalydeco® that it can reinvest in future research (Pollack 2012). It was with the help of CFF that academic and industry research could be combined to lead to the first drug treating the cause of cystic fibrosis.

6 Advantages and disadvantages of the model

Although Kalydeco® represents a seemingly successful example of venture philanthropy, it is a different approach than most researchers are used to, as acquiring funding from a philanthropist requires cultivating a relationship with them (Ledford 2012). There is concern that the overly involved philanthropists are intruding on academic freedom while providing needed funding. But others counter that philanthropists often offer sage advice regarding financial and strategic matters (Ledford 2012). The model of these foundations is also predicated not only on simply raising money to conduct research on a vast scale, but on an aggressive collaboration model that requires researchers to share their data, make findings public, and pressure universities to forego intellectual property rights and possible licensing revenues (Kolata 2010). The common element of venture philanthropists—the belief that the problem is institutional and can be fixed through new management—has led to mixed results with clear advantages and disadvantages of the approach.

Benefits of venture philanthropy include the goal-oriented agenda that leads to an emphasis on getting drugs to patients and filling in funding gaps. Dr. John Q. Trojanowski, researcher at the University of Pennsylvania reported in Kolata (2010) that, "It's not science the way most of us have practiced it in our careers. But we all realized that we would never get biomarkers unless all of us parked our egos and intellectual-property noses outside the door and agreed that all of our data would be public immediately."

There is also an active management of commercialization that can benefit faculty who lack supportive departments and/or technology transfer offices. By maintaining an active role in securing a commercial path, faculty are allotted resources based on their research that they might otherwise not have access to. The approach also enables, and sometimes

even requires, partnerships between academia and industry, that can be appealing to some academics as again it offers non-traditional relationships that can create new research, or can lead to commercialization benefits. For industry, these foundations are de-risking many intriguing projects that make them accessible to small start-up firms. They also provide access to a patient community and resources by creating patient registries and facilitate access to scientific experts and clinicians.

There are negative as well. For universities, there is a loss in licensing revenue and in overhead payments as foundations can usually negotiate for lower rates (Ledford 2011). In addition to some concerns over the involvement level of foundations, others point to the negatives of having a small group dictate funding priorities. It can create a peculiar wish that a wealthy investor has your disease as the model glorifies a celebrity face of a disease. In addition, philanthropists are not accountable to anyone else. They are private individuals who have been granted a tax break to invest as they wish; the public has no say in how those lost tax-dollars are distributed. This lack of accountability could lead to poor decision-making even as they add needed funding to the fields of research (Fleishman 2007; The Economist 2011).

In the same vein, the rise of philanthropic funding occurred at the same time as other sources decreased funding, which in turn has increased the bargaining power of foundations, especially as they focus on these early-stage, high-risk projects (Ledford 2011). Some foundations are handling the power inappropriately by getting greedy and demanding greater ownership of intellectual property (Ledford 2011). The shift in bargaining power and concerns over accountability raise issues of institutional corruption, public trust, research agenda distortion, and disproportionate funding to the size of the affected population. The latter is highlighted by the fact that the model is seen as a way for orphan disease foundations to overcome their smaller market share.

Also, CFF's self-titling as a "virtual drug company" raises questions about the consequences of the shift away from their nonprofit mission and towards a for-profit mentality. CFF is now intrinsically linked to Vertex both in the public eye and in their financial stability through their growing dependence on royalties. This could threaten the foundation's credibility or viability. Can a foundation be a credible source to the public if they are financially dependent on the industry it is supposed to hold accountable?

More specifically, CFF is in an ethical bind that it is trying to overcome with the pricing of Kalydeco®. As with most new drugs it is prohibitively expensive and while CFF is working with families to provide the drug to those who cannot afford it, they now have an interest both with the producers and users of a product with contradicting goals. Bob Beall has said that CFF was not in the room for the pricing decision of the drug, but the result leaves them rooting both for a price that will provide a high level of royalties, and a price that is affordable to their patients. Thus, maintaining IP rights and gaining royalties from these partnerships may not be the optimal strategy as foundations move forward and weigh the pros and cons of the model. At what price should foundations give up their own independence? And is that what the public wants given foundation's beneficial treatment in the tax code? These issues beg the question: will the public end up subsidizing for-profit companies if this model takes off?

Since this paper examines one example, we cannot draw conclusions about the success or long-term effects of the venture philanthropy model. But this case study does present how a new model is taking shape within the fight to find cures for specific diseases. Within these organizations there are varying preferences for IP rights as not all venture philanthropies maintain the control seen by CFF. The precise number and the contractual arrangements regarding IP warrant further investigation. The model's advantages and

disadvantages raise the question of what are the social cost and benefits of the special tax advantages conveyed to foundations. Since foundations receive special tax treatment it is important to understand how this model changes the way foundations operate and what it means when foundations start to profit from their investments.

Even with the concerns raised here, the advertising of the apparent success of the model has led to its diffusion to other types of foundations and government agencies. There is evidence that the venture philanthropy model is diffusing to more traditional foundations: for example the Robert Wood Johnson Foundation, which started in 1968, created the Pioneer Portfolio in 2003 to "accelerate the trajectory of innovation by investing in visionary thinkers, supporting exploration and helping great ideas to gain momentum…with the potential to generate significant health and social impact." Tierney and Fleishman's (2011) *Give Smart: Philanthropy that Gets Results* advocates for the wider adoption of strategic venture philanthropy, arguing that existing foundations should take a more active role in managing research investments and realizing results. Public dissatisfaction with the pace of medical advance have intensified the search for new ways to organize academic research.

Agencies within the federal government are also experimenting with new approaches that incorporate elements of venture philanthropy into an emerging model of strategic funding that focus on translational pathways and specific outcomes (Morrissey 2006). For example, a new program by the National Institutes on Aging and the National Institutes on Mental Health to find biomarkers associated with Alzheimer's disease has adopted a collaborative approach, open access to data and research findings, and the setting of specific outcomes and milestones (Kolata 2011). The incentives and organization that characterize venture philanthropy appear to be spreading to more traditional government funding agencies and expanding from medicine to the sciences and engineering. This experimentation is in no small part a response to an articulated need to find alternative models to finance research and demonstrate relevancy to an increasingly skeptical public (Campbell 2009; Federoff and Rubin 2010).

7 Conclusions, limitations, future research

Hands-on venture philanthropy has changed the drug development pipeline by affecting the funding process and employing more applied, goal-oriented, team-based approaches, along with new intellectual property requirements. The changes and cuts in federal and industry funding have led to more extensive relationships with foundations and their newly adapted strategic model. Philanthropists' call for action and results is well matched to the knowledge and resources of firms and academic researchers. While many researchers have focused on the industry aspects of this transition, more study of the foundation model on academic research is needed, along with data on their practices and the results of these partnerships. Questions remain on how these strategic principles are affecting university researchers, how funding expectations will change over time, and the viability of these funding relationships.

This paper is limited by its descriptive nature and use of one case study. While a single study cannot be generalized to the range of organizations engaged in venture philanthropy, this paper highlights the importance of philanthropic funding of research and also the experimentation in which foundations engage as they advance their objectives. Certainly, additional data are needed about the contractual terms foundations use and the specific types of research projects they fund. Moreover, the long-term consequences of this model

as seen through this example are still unknown. Based on the success of Kalydeco®, Vertex Pharmaceuticals is engaged in similar efforts with other venture philanthropy organizations on drug development and the model is still developing and being influenced by major players such as CFF and FasterCures.

With this initial effort we hope to motivate additional research on philanthropy in general and venture philanthropy in specific. Future research should include quantitative analysis of multiple foundations and their funding requirement and consider the range of outcomes for researchers and the conduct of research. As with any preliminary investigation many new questions are raised that warrant further investigation. One clear challenge is to determine how the various funding sources interact, as either complements or substitutes, and how this relationship changes with different types of projects and over an individual scientists career. The justification for foundation's tax-exempt status is the support of risky research and novel ideas, which can be tested empirically by comparing proposals made to and funded by foundations and to other funding sources. The consequences to society when foundations begin to act more like businesses can also be examined. Perhaps most fundamental is the investigation of the impact of this new model and how it influences the pace and direction of scientific inquiry.

Overall, venture philanthropy appears to offer disease-focused foundations, especially those addressing orphan diseases, a path to faster commercialization. Evidence suggests that this model is diffusing to other, more traditional foundations and that government agencies have incorporated some of the venture philanthropy practices into their calls for proposals. The evolution of research funding practices, and their impact of commercial outcomes and the overall research enterprise was widespread implications for the conduct of research and the pace of technological change. The importance of philanthropy to academic research in general and the specific ways in which scientists respond to the venture philanthropy model certainly warrant further study. With this simply start we hope to encourage others to join this inquiry.

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