Accelerating Commercialization: A New Model of Strategic Foundation Funding

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Abstract: This paper presents an overview of a new model of research funding, venture philanthropy, that actively manages the commercialization process, with the goal of accelerating scientific progress to materialized outcomes. We begin by documenting the growing importance of foundations as a source of funding academic research as industry and government sources decline with the economic downturn. After considering 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 as a result, 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 then conclude by evaluating the advantages and limitations to venture philanthropy for the academic researchers, industry partners, foundations, and universities.

Key Words: Venture philanthropy; Academic research; Drug development; Cystic fibrosis

Acknowledgements: We would like to acknowledge funding from the National Science Foundation Science of Science Policy Program, under grant 1158755 and comments from participants in the Johns Hopkins University Quantum Leap Workshop are appreciated.

I. 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 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.

Philanthropic disease-focused foundations 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, known 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 well-know valleys of death that adversely affect many promising technologies. A striking example, examined here, is the development of Kalydeco, a cystic fibrosis therapeutic, which became available in the spring of 2012 and provides an extreme example of a new model for conducting research that can be used as a counterfactual case when compared against more traditional funding sources.

While a large literature examines industry funding of academic research (Blumenthal et al. 1986; Blumenthal, et al. 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 2010). 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. This venture philanthropy model differs from traditional giving strategies in their preference to invest rather than contribute, take an active role in designing the research project, maintain ongoing relationships with researchers, and set and enforce benchmarks as a condition for additional funding. Despite its importance little is known is about philanthropic funding for academic research, in general and the specific impacts of venture philanthropy.

The purpose of this paper is to consider the role of one group of strategic foundations that are pioneering new development models. We begin by defining venture philanthropy and strategic funding and then document the growth of academic research 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. CFF has worked aggressively over the last twenty years to find a cure for cystic fibrosis. We follow their path to development of this new drug to show how venture philanthropy is impacting the drug development pipeline. We then consider the advantages 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.

II. Foundations Increased Role in Funding Academic Research

Over the long term, Federal funding is down with the US rate of R&D investment as a percentage of GDP at only 0.9% as compared to 1.3% in the 1960s (Hendricks 2011). More specifically, biomedical research is facing more complicated changes in funding. After Congress doubled the NIH's budget, not only did applications for grants greatly increase, but also investment into biomedical research capacity rapidly grew under the assumption that costs could be covered by future NIH grants (Couzin 2007). That growth in capacity and infrastructure began in 1999 from a combination of philanthropic, local & state resources, and loans (Zerhouni 2006). But after the doubling, the NIH budget did not keep up with rising biomedical costs and when adjusted for inflation NIH funding of biomedical research actually decreased by 8.6% from 2003 to 2007 (Dorsey et al. 2010). As a result, chances of being awarded an R01 on the first attempt decreased from 21% in 1998 to 8% in 2006 (Couzin 2007). These changes have left a hole from public funding for researchers, leading them to seek private funding sources (Ledford 2012).

Over the past twenty years, industry funding has provided between approximately five and seven percent of total university R&D funding (National Science Board 2010), however industry support for biomedical research has declined. From December 2000 to February 2008, 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: PhRMA is down to 11 members from the 42 it had in

1988 (LaMattina, 2011). The consolidation of firms causes R&D to suffer from cuts that occur as part of the mergers or acquisitions. As a result, the pharmaceutical industry, which once had the largest investment in R&D of revenues, sometimes as much as 20%, is now falling with Pfizer predicting an 11% rate for 2012 (LaMattina, 2011). The blockbuster approach has failed, and PhRMA is now too big to innovate (Hu et al. 2007). Bhattacharjee (2006) notes that declining R&D productivity has resulted in the search for new business models that frequently focus on acquiring start-up firms rather than developing an in-house research agenda and funding downstream university research. Alternately, it has also led PhRMA to rely increasingly on many smaller partners to supplement their pipeline (Hu et al. 2007; The Economist 2012).

While Federal and industry funding have decreased, overtime the role of foundation funding of academic research has been growing with the rise of neo-philanthropists like Gates and others from the tech-boom (Figure 1). Prior to 2010, the National Science Foundation considered foundations as part of the "other" source when reporting academic research funding, which also included foreign government investment. The "other" sources category increased over time and accounted for 7.84% of university R&D funding in FY 2009, a larger share than industry (National Science Board 2010) (Figure 2). But even this significant percentage is suspected to be an underestimate of foundation's contribution, as foundations also provide for research through back-door contributions to universities. Institutions' own funding of research, which makes up the second largest proportion, accounted for 20.38% of R&D investment in 2009 (National Science Board 2010). This represents the amount that universities are contributing to research from their own funds. But foundations often make donations directly to university endowments that then use the funds to invest in R&D. So while it is suspected that part of the universities' own contribution comes from foundations, the exact amount is unknown because of the lack of standardization in practices across institutions in classifying donations as gifts or grants.

In 2012, NSF redesigned and expanded the survey regarding academic R&D to include non-science and engineering fields (Britt 2012). Additionally, they released FY 2010 data reporting on all academic R&D with an expanded list of sources, now pulling nonprofit organizations out as their own category. From 2009 to 2010, academic R&D for S&E increased overall due to a large increase in Federal dollars as part of the American Recovery and Reinvestment Act of 2009 (Britt 2012) (Figure 3). Nonfederal funding also increased but by a smaller degree, with most of the increase coming from the category of other & nonprofit. Now reported separately, nonprofit funding accounts for 5.97% of S&E R&D, with only 1.67% from the remaining "other" category (Britt

2012) (Figure 4). The changes however do not account for foundation funding through institutions' endowments, still providing an underestimate of foundations' contribution to R&D funding and as a result, failing to show how their role has changed over time, especially with recent increases due to the decline of other funding sources. In addition to their role in funding research, foundations have an expanded role that includes defining the research agenda. The following section provides background on foundations and the increasingly active role they have taken in the broader sense.

III. Innovation in Philanthropy and the Search for New Models

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). 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". 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.

Modern American philanthropic foundations date back to the great 19th century fortunes created by industrialization. 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 and through the funding of academic research changed the ways to incentivize researchers to accomplish the foundation's articulated social goals.

Andrew Carnegie founded one of the first major philanthropic foundations, The Carnegie Institution for Science, in 1902 with $10 million as an independent research institution to support "exceptional individuals" as they answer "intriguing scientific questions" (Mission statement). The model focuses on funding research projects of individual investigators, and as a result, has funded Nobel Prize winning scientists like Alfred Hershey, who won in 1969 and Andrew Fire, who won in 2006 (Chang 2010).

The Rockefeller Foundation was another pioneer, founded in 1913 to "promote the well-being of humanity" (Mission statement). With an initial gift of $35 million from John D. Rockefeller

Sr., the Foundation was founded by an act of the New York State Legislature, and has now distributed over $14 billion (Chang 2010). The Rockefeller Foundation led the way in aggressive philanthropy by prioritizing the field of public health, with a focus on disease eradication that led to the development of the yellow fever vaccine in the 1930s, which would later win Theiler the Nobel Prize in 1950. The Foundation supported other major developments in genetics, neglected disease, and international health efforts throughout the century (Chang 2010).

The Albert and Mary Lasker Foundation, founded in 1942, expanded the role of philanthropy to include advocacy, as they worked to end disease and extend life. Mary Lasker lobbied to create what is now known as the National Health, Lung, and Blood Institute in 1948 and the Foundation continued their advocacy efforts by lobbying for the passage of the National Cancer Act in 1971 (Chang 2010). But the Lasker Foundation was also innovative in their philanthropic approach by introducing the use of prizes and awards as a means of promoting accomplishments. The Lasker Award, which is given annually to a researcher who makes a significant contribution, has funded seventy-six recipients who later went on to win a Nobel Prize (Chang 2010). The John D. and Catherine T. MacArthur Foundation, created in 1975, is one of the largest foundations in the US with a $1.8 billion endowment. They also use prizes through the MacArthur Fellows Program, also known as the MacArthur Genius Award, which grants five-year fellowships to 20-40 individuals a year (Chang 2010).

The March of Dimes Foundation was the first disease-focused foundation, created in 1938 as the National Foundation for Infantile Paralysis to fight polio. They support research, community services, education, and advocacy programs. The Foundation funded key work by Dr. Apgar, who developed the Apgar system for evaluating newborn babies, and the work of Dr. Salk and Abin on polio vaccines. After it achieved its mission of finding a cure for polio, the Foundation shifted its goals to ensuring greater infant survival (Chang 2010)

The 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.org 2012). Cystic Fibrosis was first defined as a disease in 1938 when Dr. Dorothy H. Anderson established its genetic basis and developed a definitive diagnostic test (Littlewood 2011), demonstrating the importance of academic research. However, the market, less than 30,000 patients, was considered too small for drug development efforts by large established firms, which traditionally seek so-called "blockbuster" drugs that will have large markets and high profitability. As a result, CFF adopted the mission to

assure the development of the means to cure and control CF and to improve the quality of life for those with the disease (CFF.org 2012). CFF, as an organization, reflected a very personal mission, which was to prolong the lives of children, often-family members, with the disease. There are currently over 80 local chapters that raise funds to support academic research and provide patient support (CFF.org 2012).

Venture philanthropy was coined in the 1960s as a new strategy for foundations to move beyond merely writing a check, and instead encouraging good use of the funding (Leibell 2009). Paul Tudor Jones pursued the idea of venture philanthropy with the creation of the Robin Hood Foundation in 1988 to alleviate poverty in New York City (Frumkin 2003). Robin Hood pioneered the use of metrics to measure the effectiveness of grants, active management of projects in a partnership rather than funding mode, and continuing relationships with successful grantees. Robin Hood's funding comes a variety of sources, including from board members who bear all the administrative costs as well as general fundraising and manage partnerships with other foundations and government (Frumkin 2003). However the venture philanthropy model did not take off until the idea was developed in the Letts, Ryan, and Grossman (1997) article that articulated and recommended a venture philanthropy approach for modern foundations (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, and set benchmarks and goals as a condition for additional funding.

This results oriented model fit 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. 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 rather than higher risk, potentially higher reward projects and the idea that researchers spent too much time applying for funding (Barbic 2012).

Disease-focused foundations like FasterCures and CFF have grown both in size and number in the last twenty years with the aim of finding drugs and cures for specific diseases that are usually receiving little attention from drug companies. (Chang 2010). Venture philanthropy has become a

strategy for some of the major disease foundations 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 measurement of outcomes (Chang 2010; Fielding 2011; Aebischer 2012).

The main strategy of venture philanthropy in disease-focused foundations is to invest in early stages of research to lower the risk for other parties to continue the research. Disease-specific foundations recognize that they do not offer the billions of dollars necessary to develop drugs, so they leverage their position by lowering the risk in the riskiest stage of development. On average, it takes ten years and almost two billion dollars to bring a new drug to market in the US (Gilbert et al. 2003). The major source of time and cost to this process is the rising attrition rate of drugs with one estimate reporting 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 (Murphy 2005). As a result of the decreasing success and general dryness of firm's pipelines, disease-specific foundations are able to leverage their meager millions to fight the valley of death and support academic researchers with resources for translational research and maintain a role throughout the entire process (Haugh 2010) (Figure 5).

Disease-focused foundations also help the drug discovery program by increasing participation in clinical trials through their network of patients (Finkbeiner 2010). They also utilize other strategies like matching grants to secure funding for their recipients 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). As a result of these combined efforts, US disease-focused foundations using venture philanthropy invested approximately $90 million in bio-pharmaceutical companies for drug development in 2008, a 20% increase from 2007, and 13 times more than in 2000 (Haugh 2010). Major disease-focused foundations practicing venture philanthropy include: Alzheimer's Drug Discovery Foundation, Muscular Dystrophy Association, CFF, Juvenile Diabetes Research Foundation, Foundation Fighting Blindness, Multiple Myeloma Research Foundation, Leukemia and Lymphoma Society, and the Michael J Fox Foundation (Haugh 2010).

IV. 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 bring to market the first drug targeted at the cause of cystic fibrosis. CFF was established in 1955 by a group of parents of children with cystic fibrosis seeking to find a cure. At the time, the mechanism of the disease was unknown and the median survival age was 1 year (CFF.org 2012; CFF Strategic Report 2009). While it is estimated that 1 in 29 Caucasian Americans carry the gene for cystic fibrosis, both parents must pass the gene on to 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.org 2012). They support the development of new drugs, improving the quality of life for patients, and finding a cure for the disease (CFF.org 2012).

CFF classifies their efforts 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. They are also stewards, using donations to fund the drug development pipeline, and caregivers, helping patients find care and information (CFF.org 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). Their total functional expenses in FY 2012 were $133,887,556 with 81.6% for program costs, 6.9% to administrative expenses, and 11.4% for fundraising (Charity Navigator Report 2012). The foundation receives most of its contributions through individual donations and special events like their walkathons, 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.org 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 (CFF.org 2012). They also sponsor the annual North American Cystic Fibrosis Conference, which in 2011 had nearly 4,000 doctors, researchers, and caregivers attend to share ideas and progress (CFF.org 2012).

While CFF expanded in other areas it has always maintained a focus on research, and had its major breakthrough in 1989, when a team of researchers, supported in part by CFF funding, identified the gene responsible for cystic fibrosis (CFF.org 2012). There was further success a few years later, when in 1993, the FDA approved Pulmozyme, the first drug developed specifically for CF (CFF.org 2012). With 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.org 2012; CFF Strategic Report 2009).

But the driving force behind CFF's success has been the shift in strategy to a venture philanthropy approach (CFF Strategic Report 2009; Bain 2006). CFF is now regularly referred to as the leading venture philanthropy organization because of their successful adaption (The Economist 2012; The Economist 2011; 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 experience working in academia and at NIH and had been working at CFF since 1980 (CFF.org 2012).

Beall has acted as the policy entrepreneur for cystic fibrosis. Policy entrepreneurs are advocates who invest their resources to promote a position. They are known for their political connections, persistence, and possessing a claim to be heard. They are focused, an insider of the field, risk-takers, and framers (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, and acted as a venture capitalist, investing at early risky stages of research (Pollack 2012; Opar 2011). In 1998, Beall set out to put the venture philanthropy approach in 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 solely 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 (Ledord 2011).

The transition to venture philanthropy has turned CFF into a "virtual drug company" by funding more research and forming partnerships between industry and academia and putting the majority of the foundation's budget into drug development (Moukheiber 2001). Since the mid 1990s, this has led to $260 million being invested in drug development (The Economist 2012; Haugh 2010). But this switch in strategy was not in line with the pace of contributions, the typical source of revenue for the foundation. As a result, in 2004, CFF launched the Milestones to a Cure major gift campaign to raise $175 million. This campaign is being met by gifts from individuals, corporations, and private foundations (CFF Strategic Report 2009).

While adopting the 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.org 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.org 2012). This is a successful model because it offers necessary funding at the early-stages of development (CFF.org 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.org 2012). Investments are decided on a case-by-case basis with no predetermined levels of distribution between academia and industry funding (Fielding 2011). They measure 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.org 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.org 2012; Haugh 2010) (Figure 6)

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.org 2012; Marshall et al. 2009). To match growing need, CFF expanded the TDN in 2009 from 18 to 80 centers (CFF.org 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 translational work to identify new therapies and new ways to measure outcomes from clinical trials (CFF.org 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.org 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.org 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.org 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.org 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. 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). 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 (Ledord 2011). Those rights were invoked by CFF in another deal with Altus Pharmaceuticals when the company realized they could not afford the Phase 3 trials. CFF took the license in search of a new firm (Ledord 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).

But the true art 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, Neale 2010). PathoGenesis, a small start-up biopharmaceutical firm, negotiated with CFF and Seattle Children's Research Institute to develop and license TOBI (Rose, 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, 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, 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 success alone, and CFF's high-risk approach has led to some disappointments. 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 has been quite successful overall, as seen at its finest by the development of Kalydeco, which began in 1998 when CFF started negotiations with Aurora Biosciences (Fielding 2011).

In May 2000, after two 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 and diversified CFF into drug discovery (DeFrancesco 2000). The terms stipulated at Aurora would identify and develop two to three new drug candidates in five 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 Kalydeco. The drug then entered clinical trails 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.org 2012; Vertex 2012). Finally, in January 2012, Kalydeco, the first drug to address 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.org 2012; LaPook 2012). Kalydeco will target about four percent (~1200 people) of patients with cystic fibrosis (CFF.org 2012).

But the gains of their investment did not end there: in 2007, Vertex begins to develop a second potential drug, VX-809 (CFF.org 2012). In May 2012, Vertex Pharmaceuticals announced that a clinical trial with a combination of its drug Kalydeco and the experimental drug VX-809 substantially improved breathing for some cystic fibrosis patients. With the mid-stage release of results of the combination drug, Vertex stock rose 55% to a share price of $58.12 (Reuters 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%, only removing part of the previous 55% gain. Vertex said the misreporting came from misinterpreting the results from an outside company.

The new release still shows positive signs from the new 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 five percentage points," and "19% improved by at least ten percentage points" (Loftus 2012). The corrected results included that no patients on placebo showed an improvement and the mean change was an 8.5 percentage 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 percentage 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 percentage 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 through the leadership of CFF that the academic and industry research could be combined to lead to the first ever drug aimed at the cause of cystic fibrosis.

V. Implications and Advantages of this Model

Although Kalydeco represents a 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 pressures universities to forego intellectual property rights and possibly licensing revenues (Kolata 2010). Thus, the value of the new model is mixed.

Benefits of this approach 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 some faculty appear to prefer. The approach also enables, or even requires partnerships between academics and industry partners, that may be appealing to some academics. 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.

However, 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 researchers concerns over the involvement level by foundations, others raise the point that a small group now dictates funding priorities, creating a strange hope that a wealthy investor has your disease. Philanthropists are not accountable to anyone else, which could lead to poor decision-making even as they add necessary funding to the pot (The Economist 2011). In the same vein, the rise of philanthropic funding has been made able by the decrease in other sources, which in turn has increased the bargaining power of foundations, especially as they focus on these early-stage, high-risk projects (Ledford 2011). And some foundations are handling the power inappropriately by getting greedy, as they want greater ownership of intellectual property (Ledford 2011).

Even with some concerns, the 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 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 foundations should take a more active role in managing research investments and realizing results.

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).

VI. Conclusions, Limitations, Future Research

Hands on venture philanthropy has changed the drug development pipeline by affecting the funding process and employing these more applied, goal-oriented, team emphasized 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 analysis and use of one positive-outcome case. However, as the field is still developing and being influenced by major players like CFF, such a broad approach is necessary to initially describe the model. Future research should include multiple foundations and quantitative analysis of funding and outcomes for researchers and their research. Overall venture philanthropy appears to offer disease-focused foundations a path to faster cures.

References

Aebischer, P. (2012). Philanthropy: The price of charity. *Nature*, 481(260).

Bain, L. J. (2006). Drug development in critical times. *Neurotherapeutics*, 3(4), 540-543.

Barbic, K. (2012). The Accelerator. *Philanthropy Roundtable*, http://www.philanthropyroundtable.org/topic/excellence_in_philanthropy/the_accelerator

Berman, E. (2002). The economic impact of industry-funded university R&D. *Research Policy*, 19, 349-355.

Bhattacharjee, Y. (2006). Industry Shrinks Academic Support. *Science*, 312(5774), 671.

Blumenthal, M., Gluck, K.S., Stoto, M.A., & Wise, D. (1986). University-industry research relationships in biotechnology: implications fro the university. *Science*, 232(4756), 1361-1366

Blumenthal, M.D., Causino, N., Campbell, E.G., & Louis, K.S. (1996). Participation of life-science faculty in research relationships with industry. *The New England Journal of Medicine*, 335, 1734-1739.

Britt, R. (2012). With Help from ARRA, Universities Report $61 Billion in FY 2010 Total R&D; New Details from Redesigned Survey. National Science Foundation, March 2012, NSF 12-313

Campbell, E. G. (2009) "The Future of Research Funding in Academic Medicine" *The New England Journal of Medicine*, 360, 1482-3.

Carayol, N. (2003). Objectives, agreements and matching in science industry collaborations: reassembling the pieces of the puzzle. *Research Policy*, 32, 887-908.

Chang, J. (2010). Best Practices for VP Collaborations between Disease-Focused Foundations and For-Profit Life Science Companies. Massachusetts Institute of Technology Masters Thesis.

Charity Navigator. (2012). Cystic Fibrosis Foundation Report. http://www.charitynavigator.org/index.cfm?bay=search.summary&orgid=9142

Cohen, W. M., Florida, R., Randazzese, L. & Walsch, J. (1998). Industry and the academy: uneasy partners in the cause of technological advance. In R. Noll (ed.) *Challenge to the University* (pp. 171-199). Washington, DC: Brookings Institution Press.

Couzin, J., Miller, G. (2007). Boom and Bust. *Science,* 316(5823), 356-361.

Cystic Fibrosis Foundation (2012). About the Foundation, Research Overview, and Treatments. www.cff.org

Cystic Fibrosis Foundation. (2009). Strategic Report, http://www.cff.org/UploadedFiles/aboutCFFoundation/Publications/StrategicReport/Strategic-Report-2009.pdf

deCourcy Hero, P. (2001). Giving Back the Silicon Valley Way: Emerging Patterns of a New Philanthropy. *New Direction for Philanthropic Fundraising*, 32, 47-57.

References

DeFrancesco, L. (2000). Aurora Biosciences Receives Funding from the Cystic Fibrosis Foundation. *Bioresearch Onilne*, June 5, 2000, http://www.bioresearchonline.com/doc.mvc/Aurora-Biosciences-Receives-Funding-from-the-0001

Doresey, E., de Roulet, J., Thompson, J., Reminick, J., Thai, A., White-Stellato, Z., Beck, C., George, B., & Moses, H. (2010). Funding of US Biomedical Research, 2003-2008. *Journal of the American Medical Association*, 303(2), 137-143.

FasterCures Strategic Plan. (2012). Fastercures.org

Federoff, H. J. and Rubin, E. R. (2010). A new research and development policy framework for the biomedical research enterprise. *Journal of the American Medical Association*, 304, 1003–1004.

Fielding, S. (2011). Nonprofit Disease Foundation Investments in Biotechnology Companies: An Evaluation of Venture Philanthropy. Massachusetts Institute of Technology Masters Thesis.

Finkbeiner, S. (2010) Bridging the Valley of Death of therapeutics for neurodegeneration. *Nature Medicine*, 16(11).

Fleischer-Black, M. (2002). Patient, Heal Thyself. *Corporate Counsel*, June 2002 edition.

Frumkin, P. (2003). Inside Venture Philanthropy. *Society: The Third Sector in Transition*, 40(4), 7-15.

Garnier, J. (2008). Rebuilding the R&D Engine in Big Pharma. *Harvard Business Review*, 86(5), 68-70.

Gibbons M., C. Limoges, and H. Nowotny (1994) *The New Production of Knowledge: The Dynamics of Science and Research in Contemporary Societies*. Thousand Oaks, CA: Sage Publications.

Gilbert, J., Henske, P., & Singh, A. (2003). Rebuilding Big Pharma's Business Model. *IN VIVO, The Business & Medicine Report*, 21(10)

Hart, D. (2001). Antitrust and technological innovation in the US: ideas, institutions, decisions, and impacts, 1890-2000. *Research Policy*, 30(6), 923-938.

Haugh, R. (2010). Disease Foundations Prime the Drug Pump. *Hospitals and Health Network*, 84(2).

Hendricks, B., Pool, S., Kaufman, L. (2011). Low-carbon Innovation. Center for American Progress. www.americanprogress.org

Herper, M. (2012). Cystic Fibrosis Data That Sent Vertex Stock Soaring Were Incorrect. Forbes.com, May, 29, 2012, http://www.forbes.com/sites/matthewherper/2012/05/29/cystic-fibrosis-data-that-sent-vertex-stock-soaring-were-incorrect/

Higgins, R., LaMontagne, S., Kazan, B. (2007). *Vertex Pharmaceuticals and the Cystic Fibrosis Foundation: Venture Philanthropy Funding for Biotech*. Boston: Harvard Business School Publishing.

References

Hu, M., Schultz, K. Sheu, J., & Tschopp, D. (2007). The Innovation Gap in Pharmaceutical Drug Discovery & New Models for R&D Success. Kellogg School of Management.

Institute for the Study of Aging & The Alzheimer's Drug Discovery Foundation. (2008). The Pipeline Project Report. Alzheimer's Drug Discovery Foundation.

Khoury, M., Gwinn, M., Yoon, P., Dowling, N., Moore, C., Bradley, L. (2007) The Continuum of Translation Research in Genomic Medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genetics in Medicine*, 9:665-674.

Kingdon, J. (1994) *Agendas, Alternatives, and Public Policies*. New York: Harper Collins

Kolata, G. (2010) Sharing of Data Leads to Progress on Alzheimer's, New York Times, August 12.

Kolata, G. (2011) Vast Gene Study Yields Insights on Alzheimer's, New York Times, April 3.

LaMattina, J. (2011). The impact of mergers on pharmaceutical R&D. *Nature Reviews Drug Discovery*, 10, 559-560.

LaPook, J. (2012). Cystic fibrosis drug Kalydeco approved by FDA: What does it mean for patients? CBS News, http://www.cbsnews.com/8301-504763_162-57368992-10391704/cystic-fibrosis-drug-kalydeco-approved-by-fda-what-does-it-mean-for-patients/

Ledford, H. (2011). Charities seek cut of drug royalties. *Nature*, 475

Ledford, H. (2012). Alternative Funding: Sponsor my science. *Nature,* 18

Leibell, D. T. (2009). Gates Embraces Philanthro-capitalism. Wealth management.com, http://wealthmanagement.com/financial-planning/gates-embraces-philanthro-capitalism

Letts, C., Ryan, W. and Grossman, A. (1997). Virtuous Capital: What Foundations Can Learn from Venture Capitalists. *Harvard Business Review*, Mar-Apr, 2-7.

Littlewood, J. (2011). The History of Cystic Fibrosis.
http://www.cfmedicine.com/history/index.htm

Loftus, P. (2012). 2nd UPDATE: Vertex Overstated Efficacy Of Cystic Fibrosis Drug. Dow Jones Newswires, WSJ.com

Marshall, B. C., Penland, C. M., Hazle, L., Ashlock, M., Wetmore, D., Campbell, P. W., & Beall, R. J. (2009). Cystic fibrosis foundation: Achieving the mission. *Respiratory Care*, 54(6), 788-795.

Ministry of Commerce & Industry Task Force. (2008). Strategy for Increasing Exports of Pharmaceutical Products. Department of Commerce, Government of India.

Morrissey, S.R. (2006). Elias A. Zerhouni: NIH director has steered agency through congressional inquiries and paltry budget increases with bold actions to position agency for future. *Chemical & Engineering News*, 84(27), 12-17.

Moukheiber, Z. (2001). Drug Money. Forbes, April 2, 2001.

Murphy, S. (2005). Industry Overview Report: Pharmaceutical Drug Discovery & Development. http://www.bioinfogen.com/publications.html

National Science Board (2010) Science and Engineering Indicators 2010. Arlington, VA: National Science Foundation (volume 1, NSB 08-01; volume 2, NSB 08-01A).

Opar, A. (2011). Excitement mounts for first disease-modifying cystic fibrosis drugs. *Nature Reviews Drug Discovery*, 10(7), 479-480.

Pollack, A. (2012). FDA Approves New Cystic Fibrosis Drug. New York Times, February 1, 2012.

Potts, J. K. (2011). Venture philanthropy: A case study of three nonprofit organizations. Dissertations, Theses and Capstone Projects. Paper 483. http://digitalcommons.kennesaw.edu/etd/483

Reuters (2012). A Cystic Fibrosis Treatment Is Called 'Game Changing'. New York Times, May 8, 2012.

Rose, L. M., & Neale, R. (2010). Development of the first inhaled antibiotic for the treatment of cystic fibrosis. *Science Translational Medicine*, 2(63)

The Economist. (2011). Giving for results. The Economist, May 12, 2011.

The Economist. (2012). All together now, charities help Big Pharma. The Economist, April 21, 2012.

Tierney, T., & Fleishman, J. (2011). *Give Smart: Philanthropy that Gets Results*. New York: Public Affairs

Treasury Department. (1965). Report on Private Foundations: Committee on Finance of the United States Senate. 89th Congress, 1st Session.

Salamon, L. (2003). *The State of Nonprofit America*. Washington DC: Brookings Institution Press.

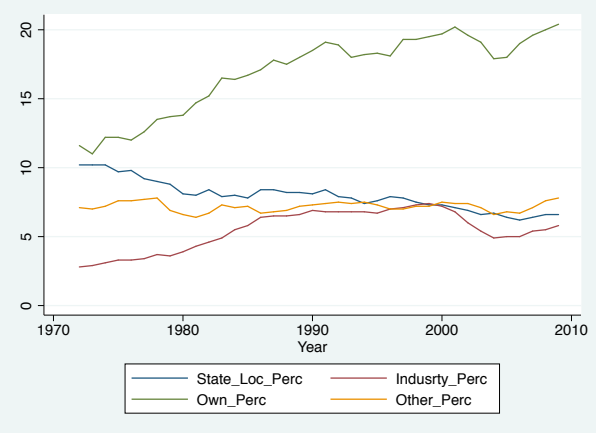
Vertex(2012). Kalydeco. Vertex Firm Publication, http://mms.businesswire.com/bwapps/mediaserver/ViewMedia?mgid=309631&vid=1&download=1

Wulffson, R. (2012). Breakthroughs continue for cystic fibrosis treatment, Examiner.com, May 7, 2012, http://www.examiner.com/article/breakthroughs-continue-for-cystic-fibrosis-treatment

Zerhouni, E. (2006). NIH in the Post-Doubling Era: Realities and Strategies. *Science*, 314(5802), 1088-1090.

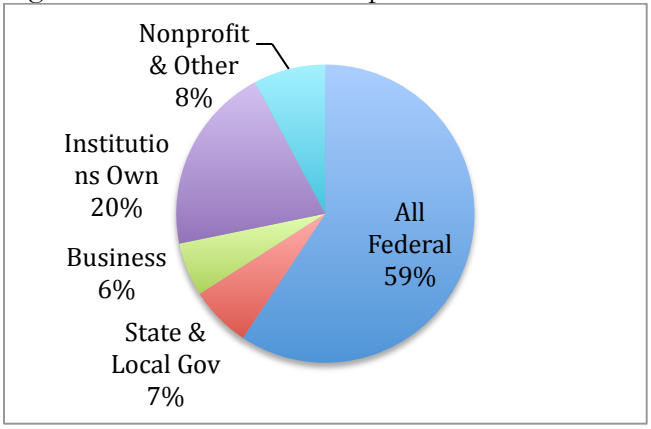
Figures

Figure 1: Academic R&D by source over time



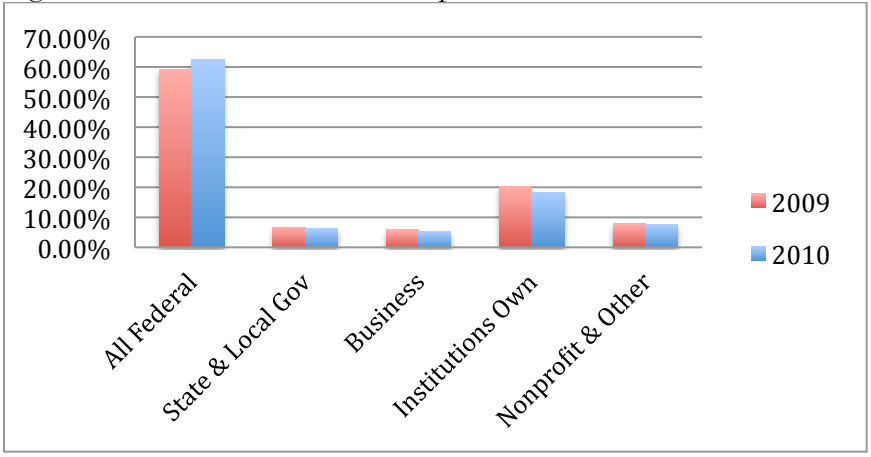
Source: National Science Board 2010

Figure 2: 2009 S&E R&D Expenditures



Source: National Science Board 2010

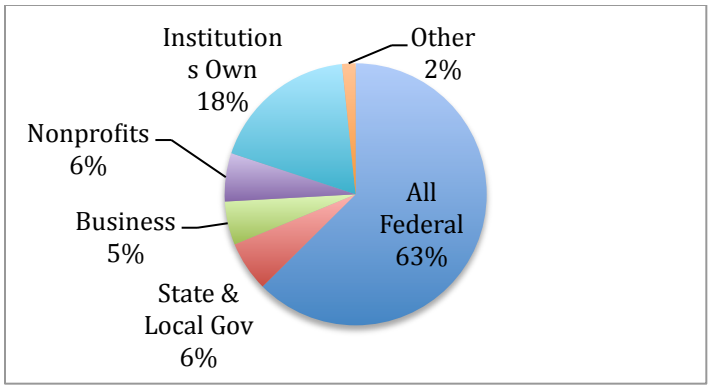
Figure 3: 2009-2010 S&E R&D Expenditure



Source: National Science Board 2010, Britt, R. 2012

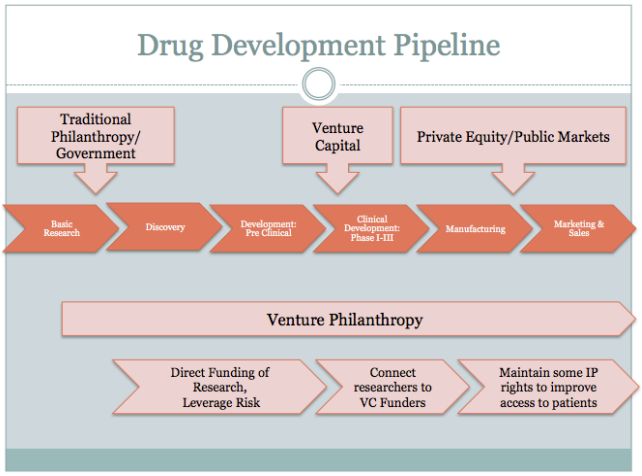
Figure 4: 2010 S&E R&D Expenditures

Figures



Source: Britt, R. 2012

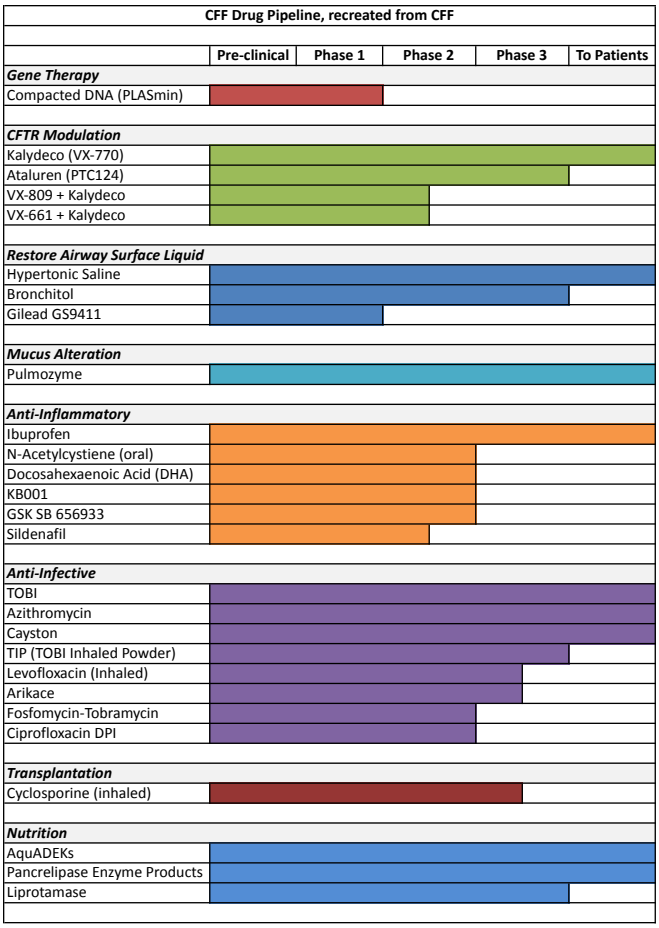
Figure 5: Drug Development Pipeline



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

Figure 6: CFF Drug Pipeline

Figures



Source: CFF.org, 2012