

Cystic Fibrosis Patents: A Case Study Of Successful Licensing

By Mollie A. Minear, Cristina Kapustij, Kaeleen Boden, Subhashini Chandrasekharan and Robert Cook-Deegan

Abstract

From 2006-2010, Duke University's Center for Public Genomics prepared eight case studies examining the effects of gene patent licensing practices on clinical access to genetic testing for ten clinical conditions. One of these case studies focused on the successful licensing practices employed by the University of Michigan and the Hospital for Sick Children in Toronto for patents covering the CFTR gene and its $\Delta F508$ mutation that causes a majority of cystic fibrosis cases. Since the licensing of these patents has not impeded clinical access to genetic testing, we sought to understand how this successful licensing model was developed and whether it might be applicable to other gene patents. We interviewed four key players who either were involved in the initial discussions regarding the structure of licensing or who have recently managed the licenses and collected related documents.

Important features of the licensing planning process included thoughtful consideration of potential uses of the patent; anticipation of future scientific discoveries and technological advances; engagement of relevant stakeholders, including the Cystic Fibrosis Foundation; and using separate licenses for in-house diagnostics versus kit manufacture. These features led to the development of a licensing model that has not only allowed the patent holders to avoid the controversy that has plagued other gene patents, but has also allowed research, development of new therapeutics, and wide-spread dissemination of genetic testing for

This research is funded by the National Human Genome Research Institute (P50 HG 003391), and the Ewing Marion Kauffman Foundation. The contents of this publication are solely the responsibility of the Center for Public Genomics (Duke University) and not necessarily the views of NIH, NHGRI, or the Kauffman Foundation.

*The Center for Public Genomics is a national Center of Excellence for Ethical, Legal and Social Implications Research, funded by the National Human Genome Research Institute under grant P50 HG 003391. From 2004-2009 it was also co-funded by the U.S. Department of Energy. The Center for Public Genomics is administered by Duke's Institute for Genome Sciences & Policy, and also includes the DNA Patent Database, a core facility at Georgetown University.

cystic fibrosis. Although this licensing model may not be applicable to all gene patents, it serves as a model in which gene patent licensing can successfully enable innovation, investment in therapeutics research, and protect intellectual property while respecting the needs of patients, scientists, and public health.

Introduction

From 2006-2010, Duke University's Center for Public Genomics* prepared case studies on whether and how gene patenting and licensing practices affected clinical access to genetic testing, at the request of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). Eight case studies covering ten clinical conditions were published in the April 2010 Supplement to *Genetics in Medicine*.¹⁻⁸ One case study focused on genetic testing for cystic fibrosis (CF).² In the process of preparing this case study, we found no evidence that the licensing practices employed by the patent holders were impeding access to genetic testing. In order to learn more about how this successful licensing model came about, we expanded the previous case study by interviewing key players in the process:

■ Mollie A. Minear, Ph.D.
Duke University, Institute for Genome Sciences & Policy,
Postdoctoral Associate,
Durham, NC USA
E-mail: mollie.minear@duke.edu

■ Cristina Kapustij,
Two Pore Guys, Inc.,
Director of External Affairs,
Santa Cruz, CA USA
E-mail: cristinakapustij@gmail.com

■ Kaeleen Boden,
Case Western Univ. and
Duke Univ. Inst. for
Genome Sciences & Policy,
Student and IGSP
Summer Fellow,
Cleveland, OH USA
E-mail: kab86@case.edu

■ Subhashini Chandrasekharan, Ph.D.
Duke University Institute
for Genome Sciences & Policy,
Research Asst. Prof.,
Durham, NC USA
E-mail: shubha.c@duke.edu

■ Robert Cook-Deegan, MD
Duke University, Institute for
Genome Sciences & Policy and
Stanford School of Public Policy,
Research Prof.,
Durham, NC USA
E-mail: bob.cd@duke.edu

- **Francis Collins, M.D., Ph.D.:** co-discoverer of the *CFTR* gene and its important $\Delta F508$ mutation that causes cystic fibrosis;
- **David Ritchie, Ph.D.:** Senior Technology Licensing Specialist at the University of Michigan Office of Technology Transfer (now retired) who managed the licensing agreements for the *CFTR* patents from 1998 to 2011;
- **Anne C. DiSante, MBA, CLP:** former Senior Technology Licensing Specialist at the University of Michigan's Technology Management Office (now the Office of Technology Transfer) who was present during the *CFTR* patent application filing and licensing discussions; and
- **Diana Wetmore, Ph.D.:** who was the Vice President of Development and Alliance Management for the Cystic Fibrosis Therapeutics Foundation at the time of the interview.

This paper summarizes what we learned from these interviews and offers suggestions for implementation of a similar licensing model for other gene patents. It begins with a brief overview of CF and the science exploring the genetic basis of a devastating disease.

Identifying the Genetic Basis of Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disorder long known to be inherited as an autosomal recessive character, and to be highly variable in its severity, duration, and spectrum of symptoms. It can be devastating, but treatment has improved dramatically in the past several decades. An early diagnosis is the first step in effectively managing the disease, and genetic testing has been used in carrier screening, prenatal genetic testing, and diagnosis.

CF affects an estimated 70,000 people worldwide,⁹ over 30,000 of whom are in the United States¹⁰ which makes this one of the most common genetic disorders in the United States. CF is most common among those of European descent, with an estimated 1/25 non-Hispanic Caucasians carrying a CF risk allele.¹¹ CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene on chromosome 7, which encodes a chloride ion channel. That is, mutations affect a large protein pore responsible for conducting negatively charged chloride atoms through the cell membrane. Mutated *CFTR* protein results in a buildup of thick, viscous mucus in the lungs, digestive tract, and reproductive system. This mucus makes it difficult for patients to clear

lung infections, which are the leading cause of death in CF. Indeed, improved management of pulmonary infections is one of the main reasons that mortality and morbidity of CF have dramatically fallen. Other symptoms include malnutrition caused by an inability to adequately absorb nutrients because pancreatic enzymes cannot reach the intestines, salty-tasting skin, wheezing and/or persistent cough, abnormal bowel movements, and infertility (especially in males).¹²

The most frequent mutation in CF is known as $\Delta F508$, which is a deletion of three nucleotides that removes a single amino acid, phenylalanine, from the *CFTR* protein. This single mutation is present on 67 percent of chromosomes of Caucasian patients with CF worldwide¹³ and patients with two copies of this mutation (about half of all patients) have a severe form of CF.¹⁴ Part of the variability in CF is due to a large number of genetic mutations that have variable effects on *CFTR* protein function. In July 2012, the Human Gene Mutation Database listed 1538 mutations in the *CFTR* gene¹⁵. Some variants do not cause CF symptoms; others are quite severe. Interaction with other genes and medical management of symptoms, like taking measures to prevent infections, add to mutational variability to make the clinical course of CF unpredictable.

The search for the genetic underpinning of CF began in the 1950s with unsuccessful attempts to identify linkage with known blood groups.^{16,17} As genetic mapping technologies improved, especially in the 1980s with the discovery and implementation of restriction fragment length polymorphisms, the pace of discovery rapidly increased. In 1987, Dr. Francis Collins, then at the University of Michigan (U of M), and Dr. Lap-Chee Tsui and Dr. John Riordan, both then at the Hospital for Sick Children (HSC) in Toronto, formed a “very intense” collaboration to speed up the pace of discovery by pooling their complementary approaches and skills.¹⁸ Two years later, in 1989, the collaboration paid off: discovery of the $\Delta F508$ mutation and *CFTR* gene was announced in three sequential papers in *Science* by Lap-Chee Tsui,¹⁹ John Riordan,²⁰ and Francis Collins.²¹

Initial Discussions on *CFTR* Patenting and Licensing Schemes

When the *CFTR* gene was discovered, Francis Collins called Anne DiSante at the University of Michigan (U of M) Technology Management Office (now the Office of Technology Transfer) to tell her the news; even 20+ years later, she still gets chills thinking about that phone call.²² While the initial plan was to file a patent application prior to the publication of the

findings, there was a news leak that the CF gene had been found so the technology licensing offices had to rush to file the application. DiSante recalls that they only had 2-3 days to complete the patent application so that it could be filed before they could publicly confirm that the gene had been identified. (In the United States, an inventor can publicize the discovery or invention before filing a patent application, but many other jurisdictions do not have such a grace period and any public announcement vitiates the subsequent ability to get worldwide patent protection.)

All of the interested stakeholders, including the U of M, the Toronto HSC, the Cystic Fibrosis Foundation (CFF) as represented through Robert Beall, and the Howard Hughes Medical Institute (which funded Dr. Collins as an HHMI Investigator), supported filing for a patent to protect this discovery. It was obvious that diagnostic and therapeutic applications might develop from understanding the molecular details of the gene mutated in CF. The development of therapeutics, in particular, would require substantial investments over long periods, and might benefit from patent incentives. Therefore, patenting made sense to the scientists, their nonprofit institutions, and disease advocacy groups.

In spite of the rush to file the patent application, considerable thought and attention were devoted to constructing an appropriate licensing strategy to allow use of the *CFTR* gene sequence in various applications, including carrier screening, diagnostics, therapeutics, and research. The primary issue considered during these deliberations was anticipating who the potential licensees might be as well as how they might use the technology. One group of potential licensees was clearly interested: clinics and hospital laboratories that wanted licenses to perform CF testing. The U of M and the HSC wanted to make a distinction between the companies and hospitals that would do in-house testing (so-called “homebrew diagnostics” or laboratory-developed tests) and companies that would manufacture and sell diagnostic kits. Broad access to diagnostics was important to the U of M, the HSC, and the CFF, and Anne DiSante recalls that they wanted to make sure that everyone who wanted to do “homebrew diagnostics” had the right to do so. This meant that the license had to be affordable to small nonprofit operations.²² Moreover, it was clear that although the $\Delta F508$ mutation was present in 70 percent of CF cases, there were an unknown number of additional mutations that would be discovered in the future that would also need to be screened for diagnostic and carrier screening purposes. The optimal test approach might depend in part on mutational complexity that

was not known when the patent application was filed. Francis Collins recounts that “it was not clear over the long term what the actual diagnostic platform would be that would be most appropriate for getting the highest sensitivity for detecting CF carriers.”¹⁸ If the $\Delta F508$ mutation was exclusively licensed to a single entity, the platform for detecting CF mutations might not evolve as rapidly as technological changes would, thereby potentially “squash[ing] the field in the long run by tying yourself to one company that might not have the best technology...[to] reduc[e] cost and improv[e] accuracy.”¹⁸

Licensing the *CFTR* patents was also a tool for managing the quality of genetic testing on at least one occasion.² In that instance, the U of M was informed that a laboratory was advertising CF testing, while not adhering to quality control standards or the professional medical guidelines for testing and counseling. David Richie from the U of M called the laboratory, letting them know about the U of M’s patent rights and suggesting they get a nonexclusive license, but also noting that such licensing came with commitments to abide by professional standards.²³ No notification letter was sent, and apparently the laboratory quietly withdrew from the market, or at least stopped advertising its CF testing service so publicly. Discussions with several other non-licensed companies are currently ongoing, suggesting that enforcement issues are always present with any patented technology.

Considerations for therapeutics were entirely different. Companies wanting to develop CF therapeutics would face a long slog. Not much was known about whether a potential protein-based therapeutic could be developed, since the function of the *CFTR* gene was not yet known, other than hints it was an ion channel for chloride. However, gene transfer was a very hot technology in the late 1980s and hopes were high that gene transfer could become gene therapy, a “cure” for CF, by replacing the defective *CFTR* gene in mucus-secreting cells of the lung epithelium and other tissues. Because the development of any therapeutic would require significant investment from a biotechnology or pharmaceutical company to bring a product through proof of clinical mechanism, clinical testing, and U.S. Food and Drug Administration (FDA) approval, companies researching therapeutic options would want some form of exclusivity to protect those long-term, large investments. However, the main challenge posed by conferring exclusivity to a gene therapy company was that there were several potential venues through which exclusivity could be granted: (1) the *CFTR* gene sequence itself that

would be inserted into a CF patient, (2) the vector or other delivery vehicle that would deliver and insert the new gene into cells, or (3) the CFTR protein. There were many different biotech companies at the time, exploring different delivery vehicles and with different technical approaches, and some U of M/Toronto patents were potentially relevant to these approaches. The U of M and the HSC had no way of knowing which of these approaches had the best chance of treatment success—Anne DiSante recalls that she asked Francis Collins which of the companies had the “right vector” and he didn’t know, so she thought “...well if Francis can’t figure it out, then how the heck am I going to figure it out?”²² Since different companies were pursuing their own delivery vehicles and vector control mechanisms, the expertise each company had with their vehicle gave them a “*de facto* exclusivity”²² that didn’t seem to warrant an exclusive licensing agreement on the gene sequence. As DiSante recalled, “We felt the exclusivity [with respect to gene therapy] would come [with] the delivery vehicle.”²² There was one exception, a patent that was exclusively licensed. It was a U of M patent (U.S. patent, 5,240,846) stemming from the original August 22, 1989 patent, but as granted it only included James Wilson and Francis Collins as inventors, both from the U of M. It was exclusively licensed to Wilson’s startup firm when he moved to the University of Pennsylvania. Exclusive licensing is quite common as an incentive to startups, and in this case a particular vector system was covered. But the U of M did not want to exclusively license the gene itself, because that would block development of alternative delivery and insertion systems for gene transfer, as well as using the *CFTR* gene or CFTR protein as therapeutic targets.

The inclusion and active participation of the CFF patient advocacy organization was another important factor in the initial patenting and licensing discussions. It distinguished the CF licensing process from patenting and licensing of Canavan Disease⁴ and *BRCA*⁵ patents for genetic testing, where patent-related controversy dogged the history of genetic diagnostics. CFF’s Diana Wetmore said that the foundation felt very strongly about non-exclusive licensing for the *CFTR* gene patents, a message relayed back to the U of M through Francis Collins, who advocated on behalf of the CFF.²⁴ DiSante recalls that even though the final decision was not up to Collins, “his thoughts, his feelings, his concerns were very important to us, so we listened to those.”^{22,25†} Wetmore notes that

the CFF was at the table during all of the important discussions about how to license the patent, and U of M “listen[ed] to us when we said that we felt strongly that [the license] needed to be non-exclusive.”²⁴ Anne DiSante of the U of M also recalls that the CFF was “very active in the licensing process.”²² When asked whether she thought the licensing scheme would have ultimately had a non-exclusive component had the CFF not expressed its position, Wetmore responded “I don’t think that’s a given.”²⁴

One further, somewhat surprising, feature of the CF licensing scheme was the humanitarian licensing of some of the same patents for developing ways to prevent or manage diarrheal diseases. Diarrheal disease is a major cause of mortality in resource-poor regions, killing an estimated 1.5 million children each year.²⁶ It turns out that chloride channel biology may be relevant to some common diarrheal diseases, and inhibiting the CFTR ion channel’s action might help manage symptoms, even when caused by infectious agents. The U of M licensed some *CFTR* patents to OneWorld Health, a nongovernment organization focused on fostering products and services for developing countries.² The U of M gets a small payment if OneWorld Health sub-licenses to a developer, but gets no running royalties on products or services. One result of this was a three-year development agreement that Novartis and OneWorld Health signed in 2009 to develop anti-diarrheal therapies.²⁷ From the perspective of the U of M’s technology licensing office, this left management of *CFTR* licensing to a trusted nonprofit entity with much greater expertise in global health, while promoting the U of M’s goal of ensuring worldwide use of the technology. This comported with Point 9 of the “Nine Points to Consider” document,²⁸ and in the spirit of global health technology licensing for humanitarian purposes proposed in many guidance documents by the University of California, Berkeley; University of British Columbia; Technology Managers for Global Health; Universities Allied for Essential Medicines (UAEM)²⁹; the Association of University Technology Managers (AUTM)^{30,31}; the “ipHandbook of Best Practices”³² assembled by the Centre for Management of Intellectual Property (MIHR) and Public Intellectual Property Resource for Agriculture (PIPRA) and other groups wanting to promote global health through sophisticated use of intellectual property.

A final important factor that played into the licensing discussions was the mission of the U of M Technology Management Office. DiSante recalls that

† Dr. Collins also donated all of his patent royalties to the CFF, rather than accepting them as personal income. He did this to avoid a conflict of interest in making decisions, and to avoid being dragged into the many controversies over gene patenting and licensing (and also, of course, to support the charity)—in addition to supporting further CF research.

their office's primary mission was not to maximize revenues for the U of M, but rather to benefit the public. Since the U of M is a public university, the main goal was to get the gene sequence and associated technology out so that it could reduce the health toll of CF for the public's benefit. If the technologies were successful, then the university would benefit in other areas, through advancing and enhancing its reputation and providing a royalty stream to support education and research. DiSante recalls that there wasn't a particular individual or institution that they were trying to target with their licensing strategy; the main thing was to help the public and CF patients.²²

Licensing Strategy Developed for the *CFTR* Gene Patent

The licensing strategy developed by the U of M and the HSC had a three-pronged approach intended to satisfy the needs of key stakeholders. A single exclusive license would be issued for the vector and for therapeutics developed from it to James Wilson's startup firm, non-exclusive licensing would be done for gene therapy (for many delivery systems and vectors and for the gene sequence itself) and other therapeutics development, and non-exclusive licensing would be used for diagnostic purposes with different fees applying to in-house use and kit manufacture. In addition, a "most favored nation" clause was added to the non-exclusive licensing terms, so that licensees would be assured they would get the same deal as others if licensing terms changed. The U of M holds all licenses within the U.S. and the HSC holds the licenses for the rest of the world. However, because the $\Delta F508$ licenses are executed by both institutions, both institutions share their royalty streams from these particular license agreements with one another. The patent landscape is complex and includes many other patents jointly held by the HSC and the U of M, a few patents only assigned to the HSC or the U of M, and patents awarded to Third Wave Technologies, Johns Hopkins, and others (see Appendix 1 of Chandrasekharan, *et al.*, 2010²). While the U of M administers all U.S. $\Delta F508$ licenses, the U of M granted the CFF a license allowing the CFF to sub-license limited fields of the technology to interested parties.

DiSante was flooded with phone calls from companies interested in securing an exclusive license from the U of M. There was pressure to select one of these companies for an exclusive agreement, in part because it would have been more lucrative initially. Yet in spite of this pressure, only one exclusive license was ever issued, to James Wilson's startup firm for use of a particular adenovirus vector that carried the

CFTR gene, for a particular approach to gene therapy. This was largely because the vector's inventor moved from Michigan to Pennsylvania and wanted to start a biotech firm.²³ If successful, this would have been a very expensive product to develop and test for safety and effectiveness, and so exclusive licensing made sense, while it did not block others from developing alternative vector systems or doing research on *CFTR* as a therapeutic target. Beyond this single exclusive license, DiSante does not recall "ever exploring the terms and conditions of an exclusive arrangement."²² All other license agreements for gene therapy research, three in total, were non-exclusive for the use of DNA to be incorporated into a vector.²³

Diagnostics

The U of M developed two license agreements for diagnostic purposes, one for hospitals, clinics, and diagnostic companies for in-house genetic testing, and the other for companies to manufacture and sell diagnostic kits. The terms for these two agreements were different: the overall price of an in-house testing license was less than a kit license, and this made entry into CF diagnostics less expensive,²³ thereby making CF genetic testing more readily accessible to patients. The up-front payment for kits was \$25,000, and for laboratory-developed tests was \$15,000 (and could be negotiated); the standard royalty for laboratory developed tests was 6 percent depending on volume and other factors, the actual royalty rate was often in the range of 3.6 percent. Ritchie and Wetmore both believe that making this distinction between laboratory-developed tests and commercial test kits was a crucial decision; Wetmore "suspect[ed] that the CFF would have tried to advocate for more reasonable pricing"²⁴ if the in-house diagnostic license fees were prohibitive; however, the price appeared to be reasonable since several companies took out diagnostic license agreements with the U of M.² Several firms also developed different multi-allele or full gene sequence-based tests or test kits that became available commercially. The patents did not therefore produce a single-source testing service, the business model adopted by Athena Diagnostics, Myriad Genetics, and others that has been accompanied by intense controversy (see case studies on genetic testing for long-QT and other cardiac channelopathies¹, breast and ovarian vs. colorectal cancer,⁵ and Canavan vs. Tay-Sachs disease⁴).

The licensing practices used for *CFTR* patents followed the "Best Practices" suggested by NIH's Office of Technology Licensing. The U of M licensing officials were familiar with discussions at NIH. Many of the licenses predated the 2003-2004 development

of “Best Practices Guidelines” that were eventually published in the *Federal Register*. The *CFTR* licensing scheme is an illustration that some of the ideas later promulgated by NIH’s Office of Technology Transfer were already in the air. The nonexclusive licensing for *CFTR* genetic testing comported well with recommendations of the Nuffield Council on Ethics in its 2002 report on “The ethics of patenting DNA,”²³ as well as the 2006 “Guidelines for the Licensing of Genetic Inventions”²⁴ developed by the Organization for Economic Cooperation and Development in Paris, and with Point 2 of the “Nine Points.”

“Most Favored Nation” Clause

A “most favored nation” clause states that the licensor (here, the U of M/HSC) agrees to give a licensee (here, a biotech company or other institution) the best terms it makes available to other licensees. Although such a clause was not initially written into the non-exclusive license, the first licensee insisted that such a clause be added to the terms of the license agreement. The clause was incorporated into every license the U of M has issued since. Ritchie argues that this clause helped maintain the long-term viability of the *CFTR* licensing structure by serving as a valuable tool during negotiations with companies. Although a company may try to argue for better licensing terms by using arguments like “the technology is over 15 years old and therefore is not worth much,” or “the $\Delta F508$ mutation is just one of thousands of mutations that can cause CF and therefore should be worth a smaller percentage of the overall royalty stream,” Ritchie counters with the fact that the “most favored nation” clause has been a part of all of their licensing agreements and that the U of M is not willing to change that because it would require a cascade of changes for all licensees.²³ However, this clause is only present in the diagnostic kit manufacturing license agreement; it is absent from the in-house diagnostics license, which means that the upfront license fee and royalty rates can be more easily adjusted for in-house diagnostic purposes to make it easier for hospitals and companies to offer CF genetic testing services.²³

Sub-Licensing Through the CFF

According to Wetmore, the CFF holds a license from the U of M and HSC that gives CFF the right to sub-license to entities that wish to create reagents using the *CFTR* gene and for the application of a cell line that contains the *CFTR* $\Delta F508$ mutation to identify modulators of *CFTR* activity. This license is for research purposes only; the CFF license is not for diagnostic purposes. Wetmore says that there was “no need” for the CFF to hold a diagnostic license²⁴ since the non-exclusive diagnostic license agree-

ments developed by the U of M enabled companies to compete in the diagnostic market, thus preventing a monopoly that might have driven up the price of diagnostic testing. This lower diagnostic testing price has had the additional benefit of enabling many states to implement CF screening into newborn screening programs.

Part of the CFF’s goal of developing better treatments and cures for CF patients is to fund basic research. The cell line that carries the $\Delta F508$ *CFTR* mutation can be used as a tool to help screen small molecules so that those with the ability to correct the CF ion transport defect can be identified and pushed into further clinical testing. This cell line is covered by a U of M patent, so if the CFF funded this type of research without sub-licensing rights, the funded company would have to apply for a license with the U of M to do their research. Instead, because the U of M gave the CFF the right to sub-license, companies only need to deal with the CFF, thereby reducing the amount of time they have to deal with obtaining a license from the U of M and expediting their research by a few months. Furthermore, as a part of their agreement with the U of M, the CFF pays an up-front fee for each sub-license it grants; this earns a small royalty stream for U of M but does not limit CFF’s freedom to operate, and its licensing costs are small and predictable. Thus, CFF research funding can be directly used for research purposes without concern for downstream licensing risks. The CFF, in turn, gives the U of M an annual report detailing its active licensees. Other *CFTR* licenses from the U of M, beyond the CFF and OneWorld Health examples cited in this report, do not have sub-licensing rights; additionally, the license agreement between the U of M and the CFF is not exclusive, meaning the U of M can issue additional non-exclusive licenses to other entities.^{23,24}

One of the benefits of this arrangement for the U of M is that the CFF handles all the administrative aspects of non-exclusive licenses for CFF research collaborations. Although a few companies have gone directly to the U of M for a non-exclusive research license, the university prefers that companies work through the CFF.²⁴ Because the university wants to benefit the public by helping the CFF achieve their mission of helping CF patients, they have a lower licensing fee for the CFF license than they otherwise might have obtained because keeping costs low helps the CFF fund research projects to which they then offer sub-licenses. The sub-license fees are paid by the CFF on an annual basis, which gives them an opportunity to make sure that sub-licensees

are actively working on the research project; if work ceases then the CFF stops paying the sub-license fee for that company. In addition, when working with a company the CFF is able to offer an enticing deal—a license that will be needed for research on *CFTR* that will be “free” to the company since the CFF will pay for it, the CFF will handle the administrative burden of obtaining that license, and the CFF will fund the research project.²⁴

The Diagnostic-Therapeutic Nexus

The recent development of the drug ivacaftor (Kalydeco®, Vertex Pharmaceuticals) is worth noting, because it illustrates the tight linkage that is emerging between some genetic subtypes and treatment. It is also a major success in the two-decade quest for better CF therapeutics building on the *CFTR* gene discovery. In January 2012, the Food and Drug Administration approved ivacaftor to treat the roughly four percent of CF patients with the G551D mutation in the *CFTR* gene.³⁵ This is one of several mutations clustered in exon 11 of *CFTR* that was covered by a patent (U.S. 5,407,796) held by Johns Hopkins University (JHU) on mutations discovered several years after the more common $\Delta F508$ mutation. The Hopkins patent expired in April 2012. The drug has only been approved for those with a G551D mutation who are over 6 years old, although it is now being tested for other uses and in children as young as 2.

The drug developed from a long collaboration between the CFF and Vertex, including funding from both institutions. Use of the drug is tied directly to subtyping through genetic testing. This story has a successful ending, but it also shows how the complex patent landscape could have thwarted its development, because the final treatment necessarily involves several patented technologies. The original *CFTR* patents held by the HSC and the U of M, the exon 11 *CFTR* patents from JHU, and the patent on the inhibitory drug itself (US patent 7,495,103, expiring May 20, 2027) are all embodied in the clinical decision pathway. The final therapeutic patent is exclusively controlled by Vertex (with a royalty agreement to CFF), but if the *CFTR* DNA sequence, method, and mutation patents had been exclusively licensed, developing and using ivacaftor would have been contingent on clearing diagnostic rights, making the situation more complex. Such multi-lateral licensing schemes are possible, indeed they are becoming more common, but they also require negotiation, additional cost, and a risk of failure.

It is also worth noting that the drug resulted from a partnership between a disease advocacy organization and a for-profit firm, and the three-month priority

approval process at FDA was expedited by trials that involved 213 patients, ages 6 to 11. Only 1,200 total U.S. patients are estimated to have the requisite mutations. The two clinical trials thus required access to patients and their families, a drug-development team, and rigorous clinical efficacy and safety trials that drew heavily on the resources and organization of the collaborating partners, as well as illustrating the new model of therapeutics developed for genomic subtypes. The story of ivacaftor development has been detailed by Feldman & Graddy Reed, in a paper presented at the “Making Quantum Leaps in University Technology Transfer” Workshop held at Johns Hopkins University, Baltimore, MD on April 19, 2012.

Long-Term Success of the *CFTR* Licensing Strategy

As of 2009, the U of M was issuing about 1-2 license agreements each year, a rate that has stayed constant since 1998 when David Ritchie joined the U of M’s Office of Technology Transfer. There were 18-20 active licenses at the time of our 2009 interview. Three or four licenses had lapsed because research on gene therapy failed to progress to market.²³ The CFF had six active sub-licenses in 2009, five of which were for therapeutic research and the sixth for generating a cell line.²⁴ The nonexclusive terms of the license also avoid the potential problem of patents on individual genes hindering whole-genome or all-exome analysis, a topic of current concern for genes that have been exclusively licensed.

After ten years of working with the *CFTR* licensing strategy, Ritchie thinks that there is very little, if anything, that he would change about it, and that this strategy would be suitable for other universities and institutions to use:

“...the fact is that this was a well-designed license agreement. It’s held up well over these years through maybe 20 different negotiations with different companies, and companies end up doing the license agreement with it. A lot of times they’ll want to come back and will want to change multiple aspects of it, but in the end after sometimes six months of negotiations we end up with kind of the same language. ... [I]t’s done its job well.”²³

Although this particular licensing strategy is currently only used by the U of M with respect to the *CFTR* patent, Ritchie does draw from it to help draft other licensing agreements with other entities:

“There are often times situations that arise during negotiations that I may have with another company where...my mind will immediately

revert to certain terms in the CF license. And I can use that license as kind of a separate template to carry on further discussions in terms of offering the company here's an alternative to the licensing design for the agreement we've been talking about, 'Let's try this other thing, okay?' One example is that sometimes companies will want to do both in-house testing as well as make products and so I'll immediately suggest that we do two separate licenses for that, when they initially want to come in and do one license. We don't use CF as a template for all other agreements, but we take bits and pieces out of it here and there to fit into our standard agreement if, in fact, a situation warrants."²³

Applicability of the *CFTR* Licensing Strategy to Other Gene Patents

Although the licensing strategy developed by the U of M, the HSC, and the CFF has worked well for CF and the *CFTR* gene patent, this strategy would not necessarily be successful when applied to other diseases or other gene patents. A major factor in the strategy's success is the involvement of the CFF, a patient advocacy organization that took on some of the administrative aspects of licensing to make this process more streamlined for companies engaging in therapeutics research. The CFF was founded in 1955 and has grown to become a savvy non-profit organization with the staff and resources required to take on the administrative burden of sub-licensing; not all diseases have such sophisticated patient advocacy organizations with the resources to take on this burden. Additionally, the CFF was able to attract more interest in therapeutics research by performing a market analysis to predict how much a pharmaceutical company might expect to make if it were to develop a successful CF treatment.²⁴ Another factor is the prevalence of CF. It is common enough to attract attention, and indeed the success of ivacaftor shows there was sufficient commercial interest to develop a therapeutic for a genetic subtype of low prevalence (earning Orphan Drug designation). Prior to this analysis, there was an assumption that with CF being a rare, orphan disease that any CF treatment would not generate much revenue. However, by showing that there were enough patients, that CF would require a chronic therapy (as opposed to a one-time therapy or one used just when symptoms are exacerbated), and that a therapy would add to CF patients' life expectancy, an estimated \$200-800 million per year could be generated by a CF treatment.²⁴ Not all of these factors will hold true for rarer diseases or for diseases that would not require a chronic therapy.

And indeed the ivacaftor model will be held up as a success only if it generates sufficient revenue to warrant similar future investments, and if its high cost does not hinder utilization. Furthermore, if a patient advocacy organization lacks the monetary resources required to fully fund the initial stages of therapeutic research and to cover the cost of sub-licensing, then this licensing strategy might not be as successful as it has been for the *CFTR* patents.

Conclusions

Discovery of the *CFTR* gene and its CF-causing $\Delta F508$ mutation in 1989 culminated an intense years-long "race" to find the gene mutated in those with cystic fibrosis. Despite the rush to publicize an important discovery and a news leak that forced quick action to preserve worldwide patent rights, careful deliberation and engagement of key stakeholders enabled the U of M and the HSC to develop a licensing strategy that held up well over time. It enabled continuing research, wide-spread CF diagnostic testing and newborn and carrier screening, and facilitated development of CF therapeutics. One vital aspect of this licensing strategy was the engagement of the CFF, a patient advocacy organization that reached a licensing agreement with the U of M that enabled it to offer sub-licenses to companies that wish to pursue CF therapeutic research, with the caveat that the CFF fully fund the initial stages of such research. This agreement benefits the U of M since the CFF takes over the administrative burden of handling non-exclusive licenses, and it benefits the CFF by having a low sub-licensing fee agreement with the U of M. Different license agreements between in-house diagnostic testing and kit manufacture and sale make it possible for many hospitals and clinics to offer in-house CF genetic testing by removing the large financial barrier imposed by a high licensing fee. The patent royalties received by one patent inventor, Francis Collins, are donated to the CFF and have provided the CFF with a revenue stream that helps fund therapeutic development, as highlighted by the recent success of the drug Kalydeco[®]. Although this model may not be successful when applied to patents that cover genetic mutations that influence rare diseases or diseases without a stable and savvy patient advocacy organization, it has held up well over the past two decades through negotiations with a variety of companies.

Perhaps the most impressive detail to emerge from this case study is the change in CF patients' life expectancy. When the CFF was founded in 1955, a child born with CF was not expected to survive until elementary school; in contrast, the life expectancy

today is over 37 years, and is increasing at the rate of about one year per year.²⁴ Obviously, many factors contribute to this progress, but the successful licensing structure developed for the *CFTR* gene may have contributed to this advance, and at the least it has not apparently hindered advances in screening, diagnostics, or therapeutics.

The precise molecular definition of CF led to genetic subtyping; to earlier and much more precise diagnosis, and thus improved medical management; and to the first genotype-specific treatment. Wide access to genetic testing and screening made it easier for states and hospitals to implement newborn screening programs; earlier detection of CF meant that patients could be started on nutritional supplementation sooner; and medical care providers could more aggressively intervene to prevent lung infections, a leading cause of death among CF patients. Had CF diagnostic testing not become as accessible as it was, these life expectancy improvements may have been less impressive or happened later. Patenting and licensing are only a small part of the story. They are perhaps most important for how they managed to keep out of the way—how the licensing strategy retained freedom to do research and creative use of the patent incentive to promote promising therapeutics while also permitting many approaches to screening and diagnosis by many providers and generating modest revenue for further research and education. ■

References

1. Angrist M, Chandrasekharan S, Heaney C, Cook-Deegan R. Impact of gene patents and licensing practices on access to genetic testing for long QT syndrome. *Genetics in medicine: official journal of the American College of Medical Genetics*. Apr 2010;12(4 Suppl):S111-154.
2. Chandrasekharan S, Heaney C, James T, Conover C, Cook-Deegan R. Impact of gene patents and licensing practices on access to genetic testing for cystic fibrosis. *Genetics in medicine: official journal of the American College of Medical Genetics*. Apr 2010;12(4 Suppl):S194-211.
3. Chandrasekharan S, Pitlick E, Heaney C, Cook-Deegan R. Impact of gene patents and licensing practices on access to genetic testing for hereditary hemochromatosis. *Genetics in medicine: official journal of the American College of Medical Genetics*. Apr 2010;12(4 Suppl):S155-170.
4. Colaianni A, Chandrasekharan S, Cook-Deegan R. Impact of gene patents and licensing practices on access to genetic testing and carrier screening for Tay-Sachs and Canavan disease. *Genetics in medicine: official journal of the American College of Medical Genetics*. Apr 2010;12(4 Suppl):S5-S14.
5. Cook-Deegan R, DeRienzo C, Carbone J, Chandrasekharan S, Heaney C, Conover C. Impact of gene patents and licensing practices on access to genetic testing for inherited susceptibility to cancer: comparing breast and ovarian cancers with colon cancers. *Genetics in medicine: official journal of the American College of Medical Genetics*. Apr 2010;12(4 Suppl):S15-38.
6. Cook-Deegan R, Heaney C. Gene patents and licensing: case studies prepared for the Secretary's Advisory Committee on Genetics, Health, and Society. *Genetics in medicine: official journal of the American College of Medical Genetics*. Apr 2010;12(4 Suppl):S1-2.
7. Powell A, Chandrasekharan S, Cook-Deegan R. Spinocerebellar ataxia: patient and health professional perspectives on whether and how patents affect access to clinical genetic testing. *Genetics in medicine: official journal of the American College of Medical Genetics*. Apr 2010;12(4 Suppl):S83-S110.
8. Skeehan K, Heaney C, Cook-Deegan R. Impact of gene patents and licensing practices on access to genetic testing for Alzheimer disease. *Genetics in medicine: official journal of the American College of Medical Genetics*. Apr 2010;12(4 Suppl):S71-82.
9. Cystic Fibrosis Foundation: About Cystic Fibrosis, What You Need to Know. <http://www.cff.org/AboutCF/>. Accessed July 9, 2012.
10. Cutting GR. Modifier genetics: cystic fibrosis. *Annu Rev Genomics Hum Genet*. 2005;6:237-260.
11. ACOG Committee Opinion. Number 325, December 2005. Update on carrier screening for cystic fibrosis. *Obstet Gynecol*. Dec 2005;106(6):1465-1468.
12. Association AL. American Lung Association Lung Disease Data 2008: Cystic Fibrosis. 2008; <http://www.lung.org/assets/documents/publications/lung-disease-data/lld08-chapters/LDD-08-CF.pdf>. Accessed July 6, 2012.
13. Population variation of common cystic fibrosis mutations. The Cystic Fibrosis Genetic Analysis Consortium. *Human mutation*. 1994;4(3):167-177.
14. Johansen HK, Nir M, Hoiby N, Koch C, Schwartz M. Severity of cystic fibrosis in patients homozygous and heterozygous for delta F508 mutation. *Lancet*. Mar 16 1991;337(8742):631-634.
15. The Human Gene Mutation Database. 2012; <http://www.hgmd.cf.ac.uk/ac/index.php>. Accessed July 7, 2012.

16. Morton NE, Steinberg AG. Sequential test for linkage between cystic fibrosis of the pancreas and the MNS locus. *Am J Hum Genet.* Sep 1956;8(3):177-189.
17. Allen FH, Jr., Dooley RR, Shwachman H, Steinberg AG. Linkage studies with cystic fibrosis of the pancreas. *Am J Hum Genet.* Sep 1956;8(3):162-176.
18. Collins FS. Interview 2008.
19. Kerem B, Rommens JM, Buchanan JA, *et al.* Identification of the cystic fibrosis gene: genetic analysis. *Science.* Sep 8 1989;245(4922):1073-1080.
20. Riordan JR, Rommens JM, Kerem B, *et al.* Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science.* Sep 8 1989;245(4922):1066-1073.
21. Rommens JM, Iannuzzi MC, Kerem B, *et al.* Identification of the cystic fibrosis gene: chromosome walking and jumping. *Science.* Sep 8 1989;245(4922):1059-1065.
22. DiSante A. Interview 2009.
23. Ritchie D. Interview 2009.
24. Wetmore D. Interview 2009.
25. Collins FS. *The Language of Life: DNA and the Revolution in Personalized Medicine.* New York: HarperCollins Publishers; 2010; p. 113.
26. World Health Organization: Diarrhoeal disease, Fact Sheet N°330. 2009; <http://www.who.int/mediacentre/factsheets/fs330/en/index.html>. Accessed July 9, 2012.
27. Institute for OneWorld Health and Novartis Launch Innovative Collaboration to Discover and Develop Novel Therapy to Combat Diarrheal Disease. 2009; http://www.oneworldhealth.org/press_releases/view/pr_1247597701. Accessed July 8, 2012.
28. *In the Public Interest: Nine Points to Consider in Licensing University Technology.* Stanford University 2007.
29. Universities Allied for Essential Medicines: Philadelphia Consensus Statement. 2010; <http://essentialmedicine.org/cs/>. Accessed July 9, 2012.
30. The Association of University Technology Managers Global Health Toolkit. 2012; http://www.autm.net/Global_Health.htm. Accessed July 9, 2012.
31. Effort AE, Stevens AJ. *The Critical Role of Academic Licensing in Promoting Global Social Responsibility.* Boston, MA.
32. ipHandbook of Best Practices: Managing Innovation for a Better World. <http://www.iphandbook.org/index.html>. Accessed July 9, 2012.
33. *Nuffield Council on Bioethics: The ethics of patenting DNA.* London 2002.
34. *Guideline for the Licensing of Genetic Inventions* 2006.
35. News Release: FDA approves Kalydeco to treat rare form of cystic fibrosis. 2012; <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289633.htm>. Accessed July 8, 2012.