

The Fight to Flip the Master Switch: A Dispatch from the Battlefield of Discovery

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Imagine that you're ranked by your medical peers as one of the best cancer doctors in America* and you believe you have found a new way to fight the deadly disease. You would think you'd feel pretty great. Maybe not.

The following is the true-life account of Dr. Charles Brunicardi and the barriers he has faced since 2008 when he discovered a potential master switch for cancer. At the time he had served 12 years as the Michael DeBakey Chair in surgery at the Baylor College of Medicine in Houston, Texas where the National Institutes of Health authorized twenty years of funding for his research program in molecular physiology of the endocrine pancreas and pancreatic cancer. There Dr. Brunicardi received both national and international awards for his work: *"Pancreatic Cancer Treatment Using Surgery and Gene Therapy"* and *"Intraislet Communication in Surgically-Altered Pancreas."* In all, Dr. Brunicardi has received 129 awards and honors, including memberships in the Blue Key Honor Society at Johns Hopkins and the Royal College of Surgeons Fellowship. A prolific writer, Dr. Brunicardi has co-authored 275 publications, 127 abstracts and 32 book chapters. Since 2000, he has been editor-in-chief of the bible for surgeons: *Schwartz's Principles of Surgery* (now in its 10th edition). Charles Brunicardi is, perhaps, one of the last of a dying breed of the "isolated guy in the lab" on the threshold of discovery and his may be the big one. In 2002, Brunicardi found that a certain protein called PDX-1 was over-

expressed in all cancerous endocrine and pancreatic tumors. As Brunicardi followed his hunch, he found an over-expression of PDX-1 not just in pancreatic tumors, but tumors of the colon and the lung and ultimately in all solid malignant tumors. This new discovery began a bold and exciting scientific journey to see if turning off the production of PDX-1 could actually silence cancer.

His weapon of choice was RNA interference (RNAi) therapy for its ability to selectively interfere with the human body's production of proteins. At the time, the discovery of RNAi was considered one of the greatest scientific breakthroughs in the past 15 years, a true game-changer. In 2006, the Nobel Prize for Physics or Medicine was awarded to two scientists, Andrew Fire and Craig Mello, for their discovery of RNA interference. Back then, the Nobel Assembly at Karolinska Institutet (which selects the Nobel Prize) stated, "It was evident from the very beginning that the significance of the discovery of RNAi would be exceptional."

A QUICK REFRESHER

The human genome consists of approximately 30,000 genes, with only a fraction of them used in each cell. Our individual genetic information is carried by DNA (deoxyribonucleic acid), a self-replicating material which consists of two strands coiled around each other to form a double helix, a structure that is like a spiral staircase. The strands are called sense and anti-sense. RNA (ribonucleic acid) is the messenger that carries instructions from DNA to determine which genes are copied, which new proteins are expressed. The coding of DNA to RNA is called transcription which is found in most living things from bacteria to humans.

The genetic phenomenon now known as RNAi was first observed in plants around 1990 when bi-

*Charles Brunicardi was named to the "Top Cancer Doctors 2015" list by Castle Connolly Medical LTD and published by Newsweek Magazine July 2015. The Castle Connolly physician-led research team makes tens of thousands of phone calls each year, talking with leading specialists, chairs of clinical departments and vice presidents of medical affairs, seeking to gather further information on nearly 100,000 nominees.

ologists trying to increase the color intensity of purple petunia petals instead produced white petunias, petals with no color at all. This remained a scientific puzzle until Fire and Mello's studies of gene expression. Their work (in 1998) centered on nematode worms which twitched due to a lack of a specific muscle protein. They first tried to reproduce the twitching in other worms by injecting them with the sense sequence of the messenger RNA (mRNA). This produced no change. Injecting the genetic sequence from anti-sense also had no effect. But when Fire and Mello injected both strands of RNA together, the sense and anti-sense, the healthy worms suddenly displayed the peculiar twitching movements. In effect, the scientists discovered how to genetically interfere with the production of a specific protein. When sense and antisense RNA molecules meet, they bind to each other and form double-stranded RNA. Injecting the double-stranded RNA molecules, containing the genetic codes for muscle protein, silenced that gene.

Fire and Mello deduced that double-stranded RNA can silence genes, that this RNA interference is specific for the gene whose code matches that of the injected RNA molecule, and that RNA interference can spread between cells and even be inherited. It was enough to inject tiny amounts of double-stranded RNA to achieve an effect, and Fire and Mello therefore proposed that RNA interference (now commonly abbreviated to RNAi) is a catalytic process. Their findings clarified many puzzling observations (such as why the purple petunias turned white) and revealed nature's mechanism for controlling the flow of genetic information.

In 2008 Charles Brunicaudi used RNAi technology to suppress production of PDX-1 and was able to silence pancreatic cancer in his lab at Baylor. As is the very definition of science, he repeated his experiments, all with the same remarkable results. He quickly asked Baylor College of Medicine to apply for a patent for his discovery as without a patent there is little hope of translating the therapy into clinical practice. Shockingly, administrators chose not to pursue a patent. Brunicaudi recalls being told, "Big pharma owns rights to all of RNAi technology."

Where there is discovery, there is litigation and lawsuits over the RNAi patent began in June 2009 involving several universities, pharmaceutical companies and countries. By March 2011, on the eve of a trial set for a federal court in Boston, a settlement deal was agreed involving the University of Massa-

chusetts, the Whitehead Institute for Biomedical Research, MIT (a former party to the litigation), plus the pharmaceutical company, Alnylam, which had been developing RNAi treatments for respiratory syncytial virus, liver cancers, and Huntington's disease. The groups agreed to give control of the negotiation for the grant of the patent called *the prosecution of the patent*, to Germany's Max Planck Institute where, in 2001 a scientist named Thomas Tuschl became the first scientist to induce RNA interference in mammals, a discovery which led to the surge in interest in harnessing RNAi for biomedical research and drug development. By 2002, Tuschl co-founded Alnylam Pharmaceuticals, Inc., which has enjoyed exclusive licensing of RNAi technology from his discoveries at the Max Planck Institute. Alnylam (NYSE:ALNY) has brought in millions of dollars in revenue from licensing and partnership deals with major drug makers such as Novartis, Roche, and Takeda. Analysts have described the business as such: every discovery that uses RNAi will have to pass through the doors of Alnylam. It is, in fact, a toll booth for discovery.

What this meant for Charles Brunicaudi who had (and still has) every reason to believe he has found the master switch for cancer: his discovery would not be worthwhile for Baylor. To this day, Alnylam battles endless patent lawsuits including one they settled for \$65 million and another from a University of Utah scientist who claims she played a part in the original discovery.

Charles Brunicaudi left Baylor for UCLA in 2011 and has continued in his research into curing cancer. At UCLA he is the UCLA Moss Foundation Professor of Gastrointestinal and Personalized Surgery and Chief of General Surgery at the UCLA Santa Monica Medical Center plus Vice Chairman of the Department of Surgery at the David Geffen School of Medicine, UCLA. His current research focuses on translational genomic medicine and surgery for diabetes and pancreatic cancer. He coordinates his laboratory efforts with experts in clinical trials so he can eventually be granted permission for human trials. He describes translating laboratory findings into clinical trials as "entering death valley," named for a journey many scientists begin but very few ever finish.

Brunicaudi, like many scientists, works on average 90 hours a week. Half that time is operating on and taking care of patients, plus teaching. The other half is spent on cancer research which includes creatively thinking, designing experiments, analyzing data, participating in countless meetings of collaboration and the frustrating part: writing papers to seek

grants. “It’s a painful, arduous process if you believe there are better treatments for people who you watch suffer or die in front of you. It’s not enough to tell them, ‘okay, I’m going to dedicate my life to finding a better treatment.’”

On the way to FDA approval for human trials, he first had to show his treatment would silence cancer in various cell lines and then human pancreatic tumors grown in three different mouse models. All told, these preclinical studies cost \$5.2 million which he raised with two NIH grants, two foundation awards (M.D. Anderson Foundation and Vivian L. Smith Foundation in Houston) plus addition help from grateful patients.

We have a new oncogenic target, PDX-1, which is a master switch; if we turn it off and disable it, the cancers disappear.

“The frustration is to have all these scientists spending their time writing grants trying to keep their labs afloat, but many labs are closing due to the current funding rate being less than 10%. These are enormous hurdles,” he says, “it is a wonder how anyone does it!”

In his 30 years as a researcher, he says fundraising has never been more difficult. While he’s received many NIH grants over the years, he says they are only funding less than ten per cent of requests that come in, down from a traditional one in four. At times, the fundraising efforts are overwhelming, especially as Dr. Brunicardi continues to witness great suffering in his patients who are battling pancreatic cancer. He says current available chemotherapy drugs do not work well on pancreatic cancer and almost all patients succumb within months of diagnosis. One patient pleaded with him to try his new treatment and Brunicardi applied to the FDA for an IND, permission to treat an individual patient with an investigational new drug.

The mountain of paperwork begins with FDA form 1571. He files the patient’s clinical history – diagnosis, treatment, response to prior therapies, the rationale for requesting the proposed treatment, including a list of available therapeutic options that would ordinarily be tried before the investigational drug or an explanation of why use of the investigational drug is preferable to use of available therapeutic options. And he files his proposed treatment plan. There is approximately 100 hours of paperwork involved.

Brunicardi’s patient and her husband stood strong in wanting to try his experimental therapy. As the clock ticked down more letters were exchanged. The wait continued for months while the FDA reviewed her case. NIH reviewers have ex-

pressed concern in a letter to Brunicardi that his treatment may be harmful or toxic to the pancreas, possibly causing mild diabetes. Brunicardi finds it beyond baffling that reviewers don’t realize any patient dying of pancreatic cancer would willingly swap this terrible fatal disease for a risk of mild diabetes. Permission for compassionate use of the therapy was granted for the patient to become the first human to test Dr. Brunicardi’s new treatment. In a cruel twist, the patient died the very day the FDA granted its approval.

“I am happy to learn the FDA is now streamlining the process for “compassionate use” and the new paperwork for informed consent by a patient will take only 45 minutes to fill out. Hopefully, it will become the new standard operating procedure. The public has also spoken. Thirteen states now have passed a “right to try” law for access to experimental drugs. Seven more have legislation ready to go.”

Dr. Brunicardi has now proved that by turning off the PDX-1, he can silence cancer in the human pancreatic tumors grown in mice and he’s shown the treatment does not cause diabetes or other toxic effects in the first trial of 10 pigs. Although side effects were minimal, the FDA has recently requested tests on fifty more pigs. During this long process too many of his patients have died from the disease he is trying to cure. Not one patient has been able to enter a clinical trial. Although he still sees the promise of turning off PDX-1, Dr. Brunicardi has moved on to a different concept he has to tackle pancreatic cancer.

In the meantime, Alnylam has not had much success with RNAi. According to an article in *MIT Review* (September 14, 2014):

“By 2010, some of the major drug companies that were working with and investing in Alnylam lost patience. Novartis decided not to extend a partnership with Alnylam; Roche gave up on RNAi altogether. Alnylam laid off about a quarter of its workers, and by mid-2011, its stock price had plunged by 80 percent from its peak.”

Alnylam is hoping to stage a comeback. After a decade, the company is in advanced trials for an RNAi treatment of a disease known as familial amyloid polyneuropathy, or FAP, which impairs a person’s ability to walk or perform delicate tasks with their hands. Most patients die within 10 to 15 years of the first symptoms. Eleven more drugs are in the pipeline to treat other diseases.

Is this a case where broad knowledge-sharing among scientists would have accelerated discovery? Would progress have been different if Alnylam not served (inadvertently or not) as a “toll booth” for scientists?

Brunicardi knows, as do all scientists, discovery can happen in an instant, or can be a road with an unforeseen detour. He believes strongly in the oath he took: first do no harm, but he is determined to convert his scientific discovery into a reality for patients.

“We have to get our treatments through the FDA much faster and test them in humans. I don’t want to harm a patient, but if a new treatment looks like it’s safe in animal models and the person is going to die within a couple of months of their disease, why shouldn’t the patient be able to try the experimental therapy? The system needs to be streamlined so it doesn’t take ten or 15 years and over a billion dollars to get the therapy through the FDA.

“If you go back a hundred years, people died of simple bone fractures, infections, appendicitis. It’s clear if you invest more money into treatments, you get better treatments. When I was a med student, AIDS was a death sentence. Now it’s a chronic disease that people can live with because the government invested billions of dollars of research into this disease. So why are people like Steve Jobs dying of pancreatic neuroendocrine tumors? If the government invested more money, we’d have better treatments. Brunicardi calls the NIH “one of the greatest gifts Congress has ever given Americans.” He says great strides have been made in cancer treatments in the last 20 years, especially in targeted therapies.

And he applauds their investment in genomics and the National Institute of Cancer (NCI). He says they just now need to prioritize the investment of more of our tax dollars towards the goal of a better quality of life through better treatments, hopefully cures of the diseases we get.

Brunicardi says the 21st Century Cures Act and the \$10 billion pledged to NIH is vital. It is also important that the panel which disburses the funding has a “disrupter” among them, someone who will challenge the obvious, like Henry Ford who once said, “If you ask the public what they want, they’ll tell you ‘a faster horse.’”

Hopefully, the issue of over-reaching patents will be addressed in any final bill. Should patents be approved which are so broad, they block the discoveries of others? Should there be a time limit on unused patents that could be put to use for ending human suffering? Shall we challenge more existing patents that interfere with discoveries related to the human genome, like the U.S. Supreme Court case in 2013 which ruled the BRCA gene test patent invalid? Should government-funded research results be open-sourced for all to share? Re-setting patent laws and knowledge sharing are two important considerations in final legislation of a 21st Century Cures Act for America.

Charles Brunicardi is a board member of The Cure Alliance, a non-profit group of leading scientists, researchers, medical doctors and innovators plus those who support their efforts to end suffering by developing cures for chronic, debilitating and fatal diseases. Its #1 goal is to help accelerate potential cures from the laboratory to the bedside.