UCSF TRACS™

ChemoFilter ®

By Dan Fost and Yan Cao, Ph.D

March 14, 2018

SUMMARY

ChemoFilter, Inc. was a California biotechnology startup established in 2013 by UCSF Prof. Steven Hetts, MD, Anand Patel, MD, a UCSF radiology resident, and Albert K. Chin, MD, a biotechnology inventor and entrepreneur. The company's main product, also known as ChemoFilter®, is a sponge-like device designed to attract and absorb excess drugs during intra-arterial delivery of chemotherapy for liver cancer, preventing all or most of those chemotherapeutics from entering the bloodstream and thereby improving outcomes while alleviating the worst side effects of chemotherapy.

Intra-arterial chemotherapy (IAC), which delivers high concentrations of drugs directly to tumors, represents a common strategy in fighting many different types of cancers. Current IAC methods do not eliminate side effects such as nausea, vomiting and bone marrow suppression, which limits the ability to use large concentrations of chemotherapeutic drugs to cure a particular cancer. The need to solve this persistent problem represents a large opportunity for innovation.

With guidance from UCSF's Catalyst Program, ChemoFilter, Inc. was established as a virtual company, and was acquired in 2015 by a global interventional therapies company that designs, manufactures and markets innovative medical devices.

Seeing a Problem, Seeking a Solution

Hetts first started investigating possible solutions to chemotherapy's side effects in 2011 when he was working in the narrowest of places—the eyeballs of infants. Hetts, an interventional radiologist, uses X-rays to navigate catheters inside the blood vessels of patients, a process known as inter-arterial chemotherapy (IAC). He started treating children as young as three months old who had retinoblastoma, a cancer of the eyeball.

"We would get tiny catheters all the way from the femoral artery up into the ophthalmic artery that goes to the eyeball," he said. Delivering the chemotherapy in this fashion was designed to prevent the medicine from spreading throughout the body, where it carried potentially devastating side effects such as toxicity for the bone marrow and a reduction in white blood cell counts.

Rather than that large intravenous dose, Hetts would administer a relatively small dose right to the eyeball. "We've seen very good responses with it in the children," he said. "But we would still see a couple of weeks later that some of the kids' white blood cell counts dropped. So not all of the chemo is absorbed in the eyeball; some of it will pass right through into the veins that drain the eyeball." The medicine would then make its way to the heart, which would then pump it through the body. [1]

Hetts started thinking: "If only we had a way to remove the excess chemotherapeutic agent from the veins draining an organ that you're giving inter-arterial chemotherapy to, then maybe we could reduce systemic toxicity. That idea was my initial entrée into this project—thinking about the small children I had treated for cancer."

He began looking to see what other clinicians and companies had tried. He looked at embolic filters—umbrella-like devices designed to catch blood clots or plaques during procedures such as angioplasty. "However, these were essentially just physical or mechanical devices," he said. "My notion was to design a filtering device with an active membrane that would bind specifically to a chemotherapeutic drug and sequester it."

Then, he said, at the end of the procedure, the filter could be removed from the patient's body, eliminating the chance that the drug could somehow seep back into the bloodstream from the membrane later on.

Teaming Up

Hetts filed an invention disclosure with UCSF's Office of Technology Management (OTM) on the concept and continued working on his device. At the time, Anand Patel, MD, was working as a resident in Hetts' department, and the two began

[1] REF-- Monroy 2014

collaborating. Patel then received a T32 grant from the National Institutes of Health to spend the 2012-13 academic year training as a researcher and working on the project.

Patel also had treated patients with liver cancer, which affects 40,000 to 100,000 people—a far greater number than the 300 people with retinoblastoma. Because of the size of the market and Patel's experience in the area, the team decided to focus its aim on liver cancer, specifically Hepatocellular carcinoma (HCC), the most common form of liver cancer.

That decision had another advantage: the drug most commonly used to treat liver cancer, doxorubicin, known as Dox, was relatively inexpensive and had been around since the 1970s.

"A parallel theme of our research was our goal of repurposing an older drug," Hetts said. "We wanted to use older, cheaper, yet well understood and effective drugs that were just too toxic to cure tumors, as opposed to designing brand new drugs, which can take up to 10 years and can cost billions of dollars. If we could find a way to make existing drugs more effective and less toxic, we knew that would be very valuable for patients."

Dox was typically applied during Trans-arterial Chemoembolization (TACE), an inter-arterial infusion of chemotherapy into the hepatic artery to treat liver cancer. Although studies indicated that larger doses of Dox could be more effective in treating cancer, large doses of Dox (above 360 mg) also had the potential to cause irreversible heart failure. Even a standard dose of Dox (50 to 75 mg) could cause bone marrow suppression, alopecia, gastrointestinal toxicity, and heart failure.[2] The trick would be finding a way to deliver higher doses of Dox locally while minimizing systemic exposure.[3]

At this point, Dr. Mark Wilson, chief of interventional radiology at the San Francisco General Hospital, joined the collaborative team, bringing deep knowledge of HCC and experience delivering IAC to patients with liver cancer.

Patel began working on prototypes. Because the team knew that Dox bonded to ion-exchange resins[4], they began to test models that simulated IAC using resin immobilized in mesh filters.

"Our goal in developing a chemotherapy filter device was to trap Dox before it could make its way to the heart," Hetts said. "After demonstrating reduced toxicity with this system, we might be confident in giving higher doses of Dox in the hopes of curing tumors as well."

---

[2] REF -Doroshaw 1996
[3] REF- Patel 2014
[4] REF- Patel 2014

Developing Intellectual Property

Hetts and Patel worked with OTM to protect the intellectual property behind the device. Hetts had filed his invention disclosure form with OTM early on in the process, when it was too early to file a provisional patent application. OTM senior licensing officer David Fung, PhD, advised Hetts and Patel on intellectual property strategy.

Fung cautioned the team to exercise restraint in talking publicly about their work, at least until they had the proper paperwork filed.

"Being an academic institution, we are all for dissemination of knowledge," said David Fung. "Our scientists are presenting all the time at conferences, but before an inventor discusses a proprietary idea, they should talk with us."

Whenever possible, OTM tries to file a provisional patent application before an invention is publicly disclosed. "If you tell the world about your invention without first filing a patent application, then you lose certain patent rights," Fung said, such as the ability to get a European patent.

One key in the patent application process is differentiating a product or idea from others. In the case of ChemoFilter®, two other similar technologies were also in the works that could be considered competitors, but Hetts said they were different enough from ChemoFilter that they wouldn't stand in the way of a patent.

One involved removing a patient's blood from their body and filtering it, much like a dialysis machine does for the kidneys. This process is risky and had yet to win FDA approval, Hetts said. The other method used beads that would be implanted in the body and gradually release the drug over time. The beads could also impede blood flow, Hetts said, making them less than ideal.

Through OTM, UCSF filed a provisional patent application in 2012. At roughly the same time, the team discovered the recently established Catalyst program at UCSF—a fortunate development, since the team was at a critical stage of prototyping and in need of money as well as industry guidance.

The Catalyst Effect

UCSF, one of the birthplaces of the biotechnology industry in the 1970s, is increasingly working to team scientists with venture capitalists, seasoned biopharma executives and entrepreneurs—many of them neighbors in Silicon Valley—as a way to speed the translation of research innovations into projects that serve patients, part of the University's mission of "advancing health worldwide." UCSF launched the Catalyst program in 2010 for this purpose, providing both funding and mentorship to scientists with promising ideas. Catalyst offers awards of

up to $100,000 and, just as importantly, it connects UCSF's renowned academic scientists with experts from business, technology, and the biopharmaceutical industry and to aid in the commercialization of laboratory innovations. Catalyst started out as part of UCSF's Clinical and Translational Science Institute, and now is part of UCSF's newly formed Innovation Ventures.

Hetts and Patel applied to Catalyst in 2012 and received a consultation award. "We had enough promising preliminary data that I was able to write up not only an entire scientific plan but also a business plan," Patel said. "Catalyst required us to demonstrate market potential as well as scientific potential."

Catalyst also offered introductions to experts from the life sciences industry, which proved particularly useful for ChemoFilter. The program connected ChemoFilter's team to Albert K. Chin, MD, a former surgeon and prominent medical device inventor, a co-founding partner and chief innovation officer at Pavilion Medical Innovations. During his career, Chin has been issued more than 180 patents and developed commercialized products for use in cardiac, vascular, orthopedic, gynecologic, urologic and general surgery. His products have generated more than $3 billion and have benefited millions of patients.

"When I read through all of the proposals for the Catalyst Awards Program," Chin said, "the ChemoFilter project struck me because I have always liked the simplest design possible—one that really has a lot of clinical utility. Simplicity in design makes it easier for the device to function and easier for practitioners to learn how to use. The team's filtering device had a truly simple design."

Chin was also impressed with Patel's bench tests that successfully filtered the doxorubicin. "I was impressed," Chin said. "Not only had he come up with some ideas, but he also had actually made some filters and demonstrated that the device would work. So I started mentoring the group."

Beyond providing valuable advice, Chin brought to the team extensive personal experience in making prototypes. He assisted in some of the prototyping, supporting the team in areas where they lacked capability. Chin has a machine shop where he tinkers with different materials.

"When it came down to the practical making of the early prototypes, Al Chin had a lot of know-how," Hetts said. "He was able to walk us through the specifics. Then he could go to his lab and make one and show it to us. That was a huge help."

A team from Catalyst consisting of medical device and product development experts, venture capital representatives, and IP experts offered feedback on the preliminary ChemoFilter device. The Catalyst panel raised questions about the market opportunity, safety concerns, and regulatory issues that might arise. It also helped them realize the device's broader potential. If the filter worked for HCC, the team members anticipated studying the filter's effect for other liver tumors, and could

eventually expand their work to treat nearly any solid organ tumor. By the same token, if the filter kept Dox from entering the bloodstream, similarly targeted filters might be used in the same fashion with a range of other chemotherapeutic drugs.

Patel and Hetts worked with Chin to address the gaps identified by the review panel and prepare a final pitch presentation. The team was granted a Catalyst Award of $50,000 in March of 2013.

A Virtual Company

Catalyst also spurred the ChemoFilter team to apply for a Small Business Innovation Research (SBIR) grant and a Small Business Technology Transfer (STTR) grant from the National Institutes of Health in the spring of 2013.

As part of the application, Patel said, "we were required to start a small virtual company. The address for ChemoFilter, Inc. was basically Steve's house. There was no real office. We weren't required to have a dedicated space and address, so our office was wherever we were. That is common with this kind of start-up, and it enables you to proceed without a lot of overhead, because you aren't required to buy or rent a building." ChemoFilter was established by three co-founders, Hetts, Patel and Chin.

By the summer of 2014, the company had finalized an exclusive license from UCSF to commercialize the technology. It was awarded an SBIR-STTR grant of $249,995, which enabled it to proceed with critical animal testing. When they tested the device in pigs, the ChemoFilter removed much of the Dox from the bloodstream, Hetts said.

The company was nominated for Medical Device Startup Company of the Year in the First Annual California Quantitative Biology Awards in 2015.

Catalyst also connected the team with "a range of other people who provided us with valuable advice," Hetts said, citing the Rosenman Institute, QB3 (the Institute for Quantitative Biosciences), and Bob Tillman, who Hetts said had experience in the financing of very early companies. "Ultimately, if we had pursued the approach of building ChemoFilter into a 'real' company, as opposed to a virtual company that was invested in IP, then those people would have become even more instrumental," Hetts said.

Getting to the Exit

With many medical devices, a window of time exists to release a product to market. If this window of opportunity is missed, a competitor will become the first to market and gain dominance. The window of opportunity is still open for ChemoFilter, as there is still no viable solution for this significant clinical need.

But building a brick-and-mortar company carries many other challenges, which ChemoFilter wasn't sure it wanted to assume.

"We wanted to move up to the next phase, the commercialization phase," Patel said. "To do that, we would have to transfer this from a growing virtual company to a real company, with a real factory, and employees, and other expenses."

Such an endeavor would have required $1 to $2 million in venture capital just to get going, Chin estimated. "You really have to have the structure in place," he said. It takes a tremendous amount of effort just to turn a prototype—even one that works—into an actual product.

To do so, the company would need a full engineering team, with systems in place to document and validate everything in order to meet FDA requirements. "All that takes a lot of testing," Chin said. The regulatory path for this product would be via a 510(k) submission or a de novo 510(k) route. Chin believed the ChemoFilter product could reach the market in12 to 18 months after completion of a $2 million round of fundraising, providing that it ran in lean startup mode. The company would have to perform an initial market release with a simple version, even the "tea-bag" design used in pre-clinical studies, and follow up later with more sophisticated next-generation devices.

Raising the money to get to that point would probably take a year, Chin said. Yet Chin saw enough promise in the idea that he helped the team start down the fund raising road.

"I went with Dr. Patel to groups of VCs and angel investors and gave presentations," Chin said.

While Chin and Patel participated in those pitch sessions, Hetts kept up his regular schedule, which included giving a presentation on the device at a national neuro-interventional meeting in 2015. That presentation proved more effective than Chin and Patel's journeys along Sand Hill Road.

After Hetts' talk, someone he knew from his clinical work approached: the chief executive of a global device company. "Shortly afterward, we signed a purchase agreement between our little ChemoFilter company, which we had spun out of our lab, and this device compny," Hetts said.

Rather than ChemoFilter needing to raise money, taking on rent and employees and building a factory, this device company "already had all these resources and everything that we needed," Patel said. "Everything was very fortuitous."

Soon after, the company had a successful initial public offering (IPO). The following year, the Wall Street Journal highlighted ChemoFilter in an article about the promise of improved chemotherapy for cancer patients.[5]

Meanwhile, back in his lab at UCSF, Hetts continues to work on the problem of keeping toxic chemotherapy drugs out of the bloodstream, now with a new cast of collaborators, and he has filed two new patents since 2014. In addition, Hetts said, "we applied for and received R01 funding of $2,595,272 from NIH along with collaborators including Nitash Balsara, PhD, from UC Berkeley, Julia Greer, PhD, and Nobel laureate Robert Grubbs, PhD, from Caltech, and Vitaliy Rayz, PhD, from Purdue."

Lessons Learned

Hetts and Patel received a valuable education in their journey from academics to entrepreneurs.

First, they saw the importance of defining a market. The move to apply their device to liver cancer was critical, as it established a large market that ultimately interested a big device company. They also kept their focus on liver cancer, even though they might have been tempted to target many different types of cancers.

Funding was also a critical component of ChemoFilter's success.

"There were many milestones that we had to make with very limited funding, even before we applied for the Catalyst Award," Patel said. "The Catalyst money was a very big piece of funding for us; however, even after we received that money, I continued to apply for every grant I found."

These early funding sources were vital, he said, in getting some of the early basic experiments done. "This is one of the most important lessons for any inventor: that you have to be persistent," Patel said. "If you don't get funding the first time around, keep applying, and keep showing people that you are making progress. You want people to see that this researcher keeps applying, keeps making more steps, keeps refining the application and the idea. You end up with a higher chance of getting the funding you need." The Society of Interventional Radiology had a resident grant for about $5,000, He didn't get that until a year after he first applied.

It was also important for the team members to know their own strengths and weaknesses, and thereby set a goal for their exit strategy. Hetts and Patel are clinicians at heart, and ultimately did not want to leave to run a startup.

If they had decided to proceed to the commercialization phase of development, they would have had to transform their fledgling virtual company into a real company,

[5] https://www.wsj.com/articles/making-chemo-more-tolerable-1467045528

with real manufacturing capabilities, which would require significant venture capital funding.

“Both Dr. Hetts and Dr. Patel are clinicians,” Chin said. “They do a lot of research, but in order to get something onto the market, that’s a completely different animal.”

Spending a year raising up to $2 million and then obtaining office space, hiring a team, continuing experiments, and going through the regulatory process would have required even more time and money, with no guarantee of success.

“It was very fortuitous that this company got interested in acquiring us, because they already have all of the structure in place. They’ve got a full team of engineers,” Chin said. “I believe that was the best outcome for ChemoFilter.”

Hetts agreed. “Being acquired was a route that I was comfortable with,” he said. “I am a clinical faculty member and I can’t spend all of my time running a company.” Patel is a full-time doctor as well, and Chin has a hand in many companies. “All of us were very comfortable with getting acquired, and taking advantage of the company’s resources and expertise to get this to market,” Hetts said.

In selling any technology to a larger company, founders also need to know that they are surrendering control. They have no guarantee that the product will make it to clinical trials. For the ChemoFilter team, the deal made sense, since they didn’t want to run a company themselves. Other founders might consider other options, such as working with a motivated entrepreneur who does want to start a small company dedicated to the specific idea that started in their lab.