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Second Sight Shows The Way

by Tom Salemi

Second Sight secured FDA approval for the Argus II Retinal Prosthesis System in 2013 and followed it with an IPO, giving the company the capital necessary to expand the commercial launch of its system to restore the vision of patients blinded by retinitis pigmentosa while also developing a new system that might restore the vision of anyone who has lost their sight to disease. An interview with CEO Robert Greenberg, MD.

- CEO Bob Greenberg knew what he wanted to do with his life the instant he saw electrical stimulation of a blind man's retina produce flashes of light.
- What Greenberg initially saw as an “engineering” challenge turned into a 15-year campaign to create a device capable of restoring vision in those people with late-stage retinitis pigmentosa.
- The effort culminated in the FDA approving Second Sight’s Argus II Retinal Prosthesis System in 2013.
- After the company had raised more than $150 million in private capital, Second Sight staged an IPO that wiped out its debt and left a sizable pool of capital.
- Now the company is working toward a new treatment that could restore the vision of anyone who has lost their sight to disease.

In recent years, mounting pressures from regulators, insurers, and public investors have kept medtech off stride. The sector has steadily lost ground – and venture dollars – to the IPO-rich biopharmaceutical or the hype-heavy digital health sectors. But the past year has been increasingly kind to medtech, giving the industry hope as companies find success on public markets and forge warmer relations with payors and providers.

Few, if any, ventures represent the surge better than *Second Sight Medical Products Inc.* In the past two years, the company secured FDA approval for its *Argus II Retinal Prosthesis System* and used the good news to stage an IPO late last year. *[See Deal]* The transformative two years have

Second Sight on pace to create the market of vision restoration for people who suffer from late-stage retinitis pigmentosa. The IPO offering also positions the company to move forward with the development of the *Orion I* visual prosthesis, a device that stimulates the region of the brain that should restore vision of those who have lost their sight from other diseases.

Second Sight was founded in 1998 when medtech investors still swung for the fences with vigor. The kernel of the company's creation came a few year earlier when Second Sight CEO Robert Greenberg, MD, stood in an operating room with ophthalmologists Eugene de Juan, MD, and Mark Humayun, MD, PhD, watching them test a hypothesis that electrical impulses on the retina could create flashes of light in patients blinded by retinitis pigmentosa.

The procedure proved the hypothesis was sound, but the route to the creation of Second Sight followed a few detours that connected Greenberg with Al Mann, perhaps one of the few medtech stalwarts whose persistence could keep the development of the technology moving forward. But the task of shepherding the project fell to Greenberg, whose only prior entrepreneurial experience involved creating and selling a software program while he was still a high school student. He also created and sold a card-reading security device while he was in college. (*See sidebar, "The Making Of A CEO: Robert Greenberg, MD.*") "This was obviously a golden opportunity for me as a young engineer-physician to grab ahold of what I knew would be a big project," Greenberg recalls. "Over the years, I had the fortunate support and backing of some great people that really allowed me to grow with the company."

Today, Second Sight has implanted more than 100 systems in patients in the US, Canada, and Europe, where the Argus is gaining traction. In March, the company reported ending 2014 with 18 active implanting centers, with discussions ongoing with another 25 centers worldwide.

IN VIVO: Let's just start at the beginning where good stories always start. Can you share the "Ah Hah!" moment that you had with Gene de Juan, in the operating room at Johns Hopkins?

Robert Greenberg: I was in the MD-PhD program at Johns Hopkins. My PhD thesis advisor at the time [Richard Johns, MD] was the founder of Biomedical Engineering at Johns Hopkins back in the 1960s, a really amazing guy. He was nearing retirement and introduced me to Gene de Juan. My advisor knew of my background in electrical engineering. He

The Making Of A CEO: Robert Greenberg, MD

By Tom Salemi

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Robert Greenberg, MD, hadn't served as a CEO prior to taking the post at Second Sight, didn't even post any significant executive experience. But he did have some success as an entrepreneur prior to joining the company.

Read the full article here

knew of Gene's interest in electrically stimulating the retina and thought there might be some mutual interest there. Gene and I met at the Tower restaurant. We talked about his work. Literally, the next day, he was getting ready to do an experiment in the operating room where he was going to electrically stimulate a blind patient's eye for the first time. He asked me if I'd like to come to the operating room.

I was a second-year medical student and had never been to the operating room. So the chance to go to the OR and see what ended up being a historic experiment was pretty exciting. He had the patient, Harold Churchey, lay down on the table and he put him under a little bit of local sedation. Since Harold was awake, his eye was moving, and Gene is trying to hold this wire close to his retina without touching it. Harold was blind already, so the consequences of touching the retina weren't dire. But still, Gene knew he would damage the retina if he touched it, so he was trying as best he could to get close.

Mark Humayun [then a resident at Duke], turned up the current and Harold saw a spot of light. Then, Gene put a second wire in Harold's eye, and Harold saw two spots of light. At that moment, I was hooked because I knew that if you could create two spots of light, the rest was just engineering. You could do hundreds of electrodes and create images like the pixels on your monitor or lights on a scoreboard. So, that was kind of the first "Ah Hah!" moment that I had and I went back to my now wife, then girlfriend, and said, "I think I know what I'm going to do for the next 25 years."

Robert Greenberg, MD

Prior to that moment, what were the next 25 years looking like for you? What were you striving f

] who headed Al Mann's research foundation at the time. When I met Joe, he told me he'd give me a job after graduation. But I never followed up. Joe called me while I was working at the FDA and told me Al Mann was coming to DC to give a talk. He thought Al and I should meet. I agreed, of course. So we met and Al told me, "You don't want to work for the government for the rest of your life. Come out to LA and see what we're doing. I think you'll enjoy it." I loved it and accepted a job at his research foundation working with Joe on his other engineering projects: implantable batteries, micro-stimulators that helped paralyzed people walk, cochlear implants to improve hearing. It was a fascinating area. I always hoped that maybe someday, we'd get back to the electrical stimulation of the retina.

Was the retinal prosthesis seen immediately as a viable venture?

Initially, I wasn't sure if it was ever going to be a major project. We obviously needed to do a lot of work on it to see it to fruition. I hadn't given up hope of being able to do that someday. Even though I wasn't working on the retina, I knew I was having a really great experience learning about a variety of implantable electronic devices. Joe Schulman had been working in the field for 40 years and was certainly one of the thought leaders in this area of technology. He had developed one of the first rechargeable pacemakers and one of the first cochlear implants and one of the first closed-loop insulin pumps. These were all multiple major projects that he did with Al Mann. Joe was actually Al's very first employee at Pacesetter back in the 1960s.

So what finally gave Second Sight life?

A lot of the credit belongs to Sam Williams, who was an investor in one of Al's other companies. Sam was blind and he had met Gene before. Sam was a fairly large donor to academic research projects in the field of retinitis pigmentosa. He was really the one who said, "I'd like this to happen in my lifetime and I think we ought to form a company to do it." So, Al said, "Well, there's this guy in my research foundation, Bob Greenberg, who worked with Gene de Juan back at Hopkins. Why don't you talk to him?" So, I met with Sam. The next day, Sam called Al and said, "I think we should do this." Al said okay.

How did things play out after that decision?

Initially, Al thought he would fund it as a project within the foundation because it was really early science at that point. Sam, who was an entrepreneur, really thought this needed to be a separate company. Al agreed, so then, they asked me if I would like to run it and that was how we started Second Sight.

The capital came from Sam, Al, Gunnar Bjorg, and Aaron Mendelsohn, who really brought everyone together. Al, Sam, Aaron and I formed the board, with me as CEO. Then we licensed the technology that we had developed at Hopkins and some earlier research at Duke.

What is the origin of the name?

I suggested the name, Second Sight, because we tried the device on a patient who had been blind his entire life. He sat up during the procedure and described a "retinal storm." It was a very emotional moment, experiencing a sense he had never had before. It would be like giving you or me ESP. We realized that, like with the cochlear implants, it was probably going to work better in people who had lost their vision. Or you would have to implant it in a young patient who could learn to see with the device like they're doing today with cochlear implants, which are implanted in kids under two so they actually learn to hear with the device. Anyway, that's how the name Second Sight came about. The idea was that these patients had all seen before and this is their second chance of seeing again. The board loved it.

Second Sight Timeline

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What was the process of starting such a unique venture, a development of technology that had never before been used in this fashion?

I think we understood – I certainly understood at the time – that it would work. Then, as we framed the challenges, there were several engineering problems that had to be solved to make it work and to make it practical. So, as we set about outlining what those were and began working on each of those in parallel, it was kind of a step-by-step approach. Then, we put together both near- and longer-term business plans and we outlined what types of expertise would be needed to solve some of those engineering problems.

What was step one?

The first six months of the company, I probably spent 90% of my time flying around the world recruiting the best scientists we could find. Many of those folks are still with the company today, 16 years later. I think a really important part of the early founding of the company was getting the right people to solve these really tough engineering problems.

So you had the core team in place, what was next?

There were some problems that we knew that were tough and then, there were some that we didn't appreciate how tough they were until we actually got into it. We knew, for instance, making a very small hermetic cam was going to be difficult and so we started working on that

day-one and went down a number of dead ends that didn't work before we hit on the current product. Then there were other challenges like the fragility of the retina. We under-appreciated how challenging that was going to be from an engineering standpoint. Interfacing something to this very delicate, one-ply, wet tissue paper-type surface in the moving eye was tough. There were some very hard problems, so I think we really did need all the time that we had set aside for them to solve the tough engineering problems.

You had early success with Argus I. Was that the proof that this concept would work? Was it just a matter of refining this achievement or was there still a lot of uncertainty?

Argus I was really critical. We actually argued about whether or not we should pursue an Argus I because we knew it wasn't going to be the commercial product. We knew from those early experiments that we had done at Hopkins that the concept worked. The patients were able to see spots of light. But we didn't really know that you could create a product that the patient could wear and that would last in the body. We also didn't know if the electrical stimulation would somehow damage the retina over time. So, there really were still a lot of unanswered questions before we did the Argus I.

So that device really answered a lot of those questions. It proved that you could actually build a device, however crude it was, and that you could chronically stimulate the retina without damaging it. So we confirmed a lot of what we knew and we refined some of our ideas. We then were able to work on the software that helped us develop the Argus II, which is a much more sophisticated device that requires a much shorter surgery that is far less invasive.

Equally important, Argus I gave our investors the confidence that we weren't going down a dead end. I wonder if we didn't have that proof that it really did work, if our investors would have lost patience along the way.

"I think a lot of companies fail in those moments where there's kind of a failure of nerve, if you will, where people get skittish at exactly the wrong time. Had we stopped, at that point, we were within weeks of solving the problem." – Robert Greenberg, MD

Was there ever a point where it was decided this was not going to work?

I think there were certainly many points along the way where it looked like the engineering problems were perhaps too challenging. This was one of the areas where I really credit Al Mann in recognizing the difference between a difficult engineering problem and an impossible one. One day we were sitting around the boardroom after spending a couple of years trying to develop this retinal interface. We had to solve the engineering problem of attaching something to the retina, and we were asking ourselves whether it was possibly too hard a problem. He was the one who said, "No, this is an engineering problem. It's solvable. Go back to the lab and solve it." With

that encouragement and, of course, with the funding necessary to continue to work on those problems, we were able to get over that hump.

I think a lot of companies fail in those moments where there's kind of a failure of nerve, if you will, where people get skittish at exactly the wrong time. Had we stopped, at that point, we were within weeks of solving the problem. Of course, we didn't know that. You can only know that in retrospect, but those moments really test you. I think a big part of Al Mann's success in his career is tackling hard problems that other people gave up on and thought were too difficult.

What were the challenges that were unique in getting this through clinical trials and obtaining regulatory approval?

There were a number of challenges in setting up the Argus II clinical trials. One of them was that retinitis pigmentosa is a relatively rare disease and so just finding the patients was one of the challenges. We also had to find hospitals that had access to patients who were willing to try something like this before anybody knew whether it would work or not. Finding patients to enroll in a trial is one challenge that is a common problem with clinical trials, but it's made worse if the population is relatively small.

I think the other, more vexing problem was that there are no established endpoints for measuring levels of low vision. We really had to reach out to the low-vision community, working with optometrists and ophthalmologists to develop measures from scratch. Then, once we came up with them, the challenge was getting the FDA to buy into those tools and to agree on what the metrics would be. We were creating not only a device, but at the same time, we were creating the tools and criteria with which we were going to measure the device. So, doing those in parallel was a challenge that hopefully future generations of visual prosthetics will benefit from.

Was the low-vision community receptive to a device like this? Were they equipped to help you with clinical testing, or did it require a great deal of learning?

We were fortunate that we were working in a space where everyone we came in contact with had always hoped that there would be some therapy for blind patients. For anyone who has ever met or worked with a blind individual, the Holy Grail was to try to restore some vision. We received very enthusiastic support from nearly everyone.

Finding a method of measuring performance was tougher. People didn't really know how to approach that problem. Everybody knew and was familiar with the ETDRS chart, where you could read the letters on a chart and assess the high levels of acuity. But no one really had agreement on how do you measure low levels of acuity.

There was never any reason to measure low levels of acuity because there were never any

therapies that could restore vision from no vision. This was really the first attempt at that. We've since seen a number of research efforts to take our work to the next level and refine the assessment methods even further. As we move forward, there'll be an increased need for assessing devices on a uniform playing field, but getting people to agree on these issues is not always easy.

What have the challenges been on the reimbursement side?

We've had mostly positive – but not universally positive – responses from payors. In the US, half a dozen private insurers are currently covering the device. We're fortunate to have had the AMA and Medicare issue codes for the device and the procedure. We've also been issued a New Tech Add-on Payment for the device. Coverage determination comes from the Regional Medicare Administrative Contractors [MACs]. Of the eight regional MACs, we have coverage policy from one so far. Reimbursement from the regionals has come a little bit slower than I would have expected given the strong support from private insurers and the federal Medicare group. We got FDA approval in April of 2013 and by October of that year, national Medicare had agreed to the payment for the Argus II. It's interesting because I think people assume national government moves slowly. But we've actually seen the reverse.

Had you focused more attention on the national scale to push for approval there?

I don't know that it's been a different focus. Maybe it's a quirk of the way the system is set up, but as we've gotten into this more, we've discovered that we're not alone in this and that there are other companies facing similar sorts of delays.

Second Sight – By The Numbers

Capital Raised: Over $120 million, not including $29 million of direct grants.

Employees: Over 100 people.

IP: 294 granted patents and 173 patent applications on a worldwide basis.

Market Size: Worldwide, an estimated 1.5 million people suffer from retinitis pigementosa, including 100,000 in the US and the 167,000 in the 28 EU countries. Company estimates approximately 25% of people with RP in the US have vision that is 20/200 or worse (legally blind).

SOURCE: Second Sight S-1

What is next for Second Sight? Are you well capitalized? Do you see yourself raising money from some other sources in the foreseeable future?

We are well capitalized. We listed on the NASDAQ exchange last November. The company went that day from being $36 million in debt to $34-some-odd million positive cash in the bank. So, about a $70 million one-day swing for the company, so that was very significant. Today, the company is completely debt free and is well capitalized and we don't have any immediate plans to do another fundraising.

As we expand and get into our clinical trials for Orion, the brain implant that will allow us to treat nearly all forms of blindness and as we expand those trials toward market approval, it's likely that we'll want to fund that work through additional fundraising of some sort, but we haven't made any decisions about how we're going to approach that and we don't expect it to be very dilutive.

Where are you with the development of Orion?

Our plans are to begin animal studies shortly. We'd like to be in patients within a couple of years. We should have proof-of-principle well within a couple of years and we're working to beat that schedule.

How different is the Orion approach from the Argus approach?

It's actually surprisingly similar. The technology is actually the same technology, so the externals are effectively the same and the implant is quite similar, as well. Essentially we're taking our electrical stimulator and instead of stimulating the retina with electrodes, we're putting a different electrode array on the device and bypassing the optic nerve and directly stimulating the visual part of the brain. Fundamentally, it's quite similar because we're electrically stimulating neurons and producing the perception of spots of light for the patient, whether it's in the retina or the visual cortex. It doesn't make that much difference.

Both are mapped spatially. Earlier studies have actually shown that it is possible to produce phosphenes by stimulating the visual cortex in much the same way the Argus II produces phosphenes by stimulating the retina. A fellow named Charles Brindley did some work in the 1960s and William Dobelle followed up with some feasibility work just over a decade ago. Neither one of them had the technology that we have today. They had issues with wires breaking over time, but we're pretty excited about using today's Argus technology to be able to treat essentially all forms of blindness in nearly eight million patients worldwide.

Final question, a Mann fund recently gave $4 million to John Hopkins University Applied Physics Laboratory. They'll be working with you on other implantable visual prosthetics. Is that related to Orion or is this something completely different?

It's more related to the external glasses and video processor, which is a shared platform for Argus

and Orion. Research from this grant will allow us to enhance the external software of the device. So, just like you can upgrade the operating system on your *iPhone*, we plan to upgrade the software on the Argus and then, later on the Orion, and add new functionality, so even once somebody gets an implant today, they should be able to benefit from future research through external software and hardware upgrades.