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Paving A Path To A Regenerative Medicine Industry

A Conversation With Tengion CEO Steven Nichtberger

Tengion is not a device firm. It is not a biotech or drug company either, although CEO Steven Nichtberger says his company needs to draw on the models of each.

No, Tengion describes itself as a regenerative medicine company. It makes "neo-organs."

Last year, the East Norriton, Pa.-based company's product drew worldwide attention when researchers at the Wake Forest Institute for Regenerative Medicine, lead by Anthony Atala, M.D., reported results from seven bladder disease patients implanted with a partially formed bioengineered bladder made from a biodegradable scaffold and the patients' own cells ("The Gray Sheet" April 10, 2006, p. 15).

Typically, these patients would be treated with a procedure involving part of their bowel being grafted onto their bladder, which comes with significant adverse side effects.

The study - in which the patients showed improved bladder functioning and the implanted neo-bladder became virtually indistinguishable from the patients' native bladder tissue - provided the first published human data for a complex internal bioengineered organ and, in a way, was the coming-out party for Tengion, which has a multimillion-dollar sponsored research agreement with the Wake Forest Institute.

Since then the firm has completed enrollment for a Phase II study, implanting neo-bladders in 10 children with spina bifida, a neurological condition that affects bladder function. And it has initiated a second ten-patient Phase II trial in adults with malfunctioning bladders due to spinal cord injury.

Tengion is also looking to start similar trials for severe urge incontinence and bladder cancer. The company is in talks about a pivotal Phase III trial design with FDA, where the biologics center is taking the regulatory lead and CDRH is playing a consulting role.

Looking further down the road, Tengion is working with the Wake Forest scientists on vessel and renal neo-organ programs.

Regenerative medicine is a hot topic, but it is not yet an industry in its own right. Some of the most publicized aspects of the field, including embryonic stem cell technology, could be decades away from commercial reality.

Tengion's goal, Nichtberger says, is to establish itself as the commercial integrator at the center of the nascent field, bringing together the diverse expertise needed to make regenerative medicine a business success, much like IBM and Apple did for personal computers decades ago.

He says the company is gaining the experience needed to meet this goal not by focusing on the outermost edge of the field, but instead on a product based on science, that, because it relies on using patients' own cells, is ready now (*see chart: "How To Build A Neo-Organ"*).

Nichtberger recently sat down with “*The Gray Sheet*” in Winston-Salem, N.C., nearby the firm’s pilot neo-organ manufacturing facility, to discuss the state of his company and regenerative medicine.

Q&A With Steven Nichtberger

“The Gray Sheet”: Neo-organs are a completely new class of products. How big a challenge has that been so far on the regulatory front, in getting a clear picture from FDA about the path ahead?

Steven Nichtberger: We are at the point in development where the regulatory pathway is not only being clarified but is being pursued. I’ve paid a lot of attention to not assuming anything along the regulatory pathway. So rather than submit an application to either CBER or CDRH, we went to the Office of Combination Products and we asked, “How would you prefer to regulate this?”

It was a very effective thing to do, because it gave the FDA a chance to have their experts look at this from both sides and to make a determination based on their criteria. Following their advice has, I think, born a lot of fruit. From 2004 until now, we’re three and a half years young and in mid-stage clinical testing, with all of the boxes checked along the way.

TGS: Concerns have been raised in some quarters about expertise and resources at FDA and whether agency staffers have the right experience to respond to issues raised by next-generation technologies like Tengion’s. Does FDA have the needed expertise for neo-organs?

Nichtberger: Yes.

TGS: That is not just the politically expedient answer?

Nichtberger: No, because they’ve invested the time to understand the technology. And our manufacturing processes have 120 standard operating procedures that allow for even a recent college graduate with technical school training to be at the front lines of our manufacturing capabilities. Our standard operating procedures take what is otherwise a complex process and reduce it to something that is reliably reproducible.

So we work with FDA and reduce our technology to its component parts and share with FDA our view on what’s going on in the regenerative process to help them appreciate the nuances.

TGS: You are conducting two Phase II trials with the neo-bladder and are in talks about a larger Phase III study. Are there any big-ticket issues that FDA has brought up that have challenged your ability come to an agreement on trial designs?

Nichtberger: [No] I think part of the success we’ve had is due to the approach we’ve taken with FDA. And I think the other necessary component is that our technology is nothing more than minimal manipulation of the cells. This isn’t a technology where one fears adverse outcomes for the patient in the long run because the cells do something they shouldn’t do.

How To Build A Neo-Organ

1. **Biopsy:** Surgeon takes a sample of a patient’s bladder and sends it to the Tengion facility.
2. **Isolate:** Tengion scientists isolate urothelial and smooth muscle cells that are capable of regeneration.
3. **Culture:** The cells are cultured to make a larger quantity.
4. **Seeding:** The cells are seeded throughout a pre-made biodegradable scaffold shaped like a bladder.
5. **Neo-organ:** Cells are allowed to grow on the scaffold for eight weeks. The result is a “neo-organ,” which is not a fully functioning organ because it lacks components like vessels and nerves.
6. **Implantation:** Neo-bladder is sent to the surgeon for implantation.
7. **Regeneration:** The body uses the neo-bladder to regenerate and integrate new tissue to restore bladder function. The biodegradable scaffold eventually dissolves, presumably leaving a working bladder in its place.

Source: Tengion

The comfort in that regard comes from the extensive preclinical testing we did. It comes from the existing human clinical experience from the academic setting. And it comes from the very rigorous approach that our scientists take. [Senior VP-Science and Technology] Tim Bertram used to run preclinical safety assessment for Pfizer. He has extensive experience and knows what it takes to get into the clinic and ultimately to get approved.

TGS: Do you have a timeline of when a larger Phase III study might begin?

Nichtberger: As soon as we have clarity with FDA on what Phase III should look like and we’ve got sufficient Phase II data to demonstrate all of the safety elements that we can understand from Phase II data, we will work with FDA to advance. Without FDA’s agreement, I can’t tell you [a date]. We are actively dialoging with FDA about what it will take to get to the next step.

TGS: I believe you have built or are building a launch-capacity manufacturing facility in Pennsylvania. Can you tell me more about that and what a neo-organ facility looks like?

Nichtberger: We built two facilities. The first one is our science and technology laboratories in Winston-Salem, where we have about 28 scientists working under Tim’s direction. And at the core of that facility is a GMP manufacturing suite that has full capability to manufacture the human neo-organs that are being implanted by surgeons today into patients.

The Phase III program and our launch manufacturing facility is in Pennsylvania, and it is fully built and being validated in preparation for Phase III.

TGS: And what does this facility look like?

Nichtberger: It is a regenerative medicine manufacturing plant that is focused on making a different organ for each person who orders one and is designed both from facility and process standpoints to deliver reliable, high-quality neo-organs. It’s a facility that’s been designed to minimize the risks associated with scaled manufacturing of personalized medicine products. It represents, we think, a generation advance versus currently approved facilities in that regard.

And through the integration of additional advances - the use of information technology and things of that nature - we think there is an opportunity for us to fundamentally advance our lead through the core competency of manufacturing that we think is so important in this field.

TGS: Do you have an estimate of the type of capacity you will need and will be able to handle for Phase III and launch?

Nichtberger: There have been weeks where we have sent upwards of 15 neo-organs out the door in one week, and successfully so, for implantation. We are already experiencing a certain amount of scale-up.

For our launch manufacturing facility, we have built our facilities in a way that we can incrementally tack on additional capacity with additional clean rooms using existing HVAC systems in a way to minimize the incremental disruption and cost associated with expansion. So our facility in Pennsylvania would, with some modest incremental investment, be capable of handling many thousands of neo-organs on an annual basis.

TGS: Is the device/scaffold component made individually for each patient or will those be mass-produced?

Nichtberger: There are a couple of different sizes we offer for the pediatric patients and a couple of different sizes for the adult patients. The scaffold size would be chosen by the physician with guidance as to how one goes about choosing, whether it is simply based on body nomograms or other dimensions or criteria that would tell us what size neo-bladder to create for the patients.

TGS: What are your plans for physician training and education?

Nichtberger: In the bladder, today's surgery is frequently nearly a full day in the operating room, where the bowel is carefully resected or removed from the patient's normal physiology and formed into the shape of a bladder and then sutured to the appropriate connection points. That is a technically challenging, tedious procedure.

In contrast, in the case of our neo-bladders, it is required that the surgeon takes a biopsy and sends the biopsy to our facilities. We then return the neo-bladder to the physician, who really has a pretty straightforward implant procedure, where they suture the appropriate points of the neo-bladder to the appropriate connection points in the patient. In our experience, it is a much shorter procedure, many hours less than the standard procedure.

It is our expectation that we will be able to train physicians in a single session, where the technical know-how is transferred to the physician, so that we can be sure that the quality of the neo-organ implantation that we study in our clinical study is repeated by surgeons in general.

TGS: How many surgeons will you be targeting from the start?

Nichtberger: We think there are hundreds of physicians. They fall into a number of buckets, but they are usually, in one form or another, trained urologists.

TGS: The two current trials are focusing on bladder problems tied to spina bifida and spinal injury. Are there other indications you will pursue?

Nichtberger: We are exploring whether we pursue a trial in severe urge incontinence and we expect to be able to enter a Phase II clinical trial in patients with bladder cancer.

TGS: What are the sizes of these markets?

Nichtberger: Precious little data is published on the number of augmentations, cystoplasties and bladder replacements that are performed. What we do know is that there are about 10,000-15,000 augmentations or replacements of a bladder each year in the U.S.

In some of those cases, the patient is left with a plastic bag which they connect to their abdomen and urinate in each day. In other cases, they have a procedure done where a piece of the bowel is turned into a bladder for a patient to urinate into. It is this group of patients who are willing to have these sub-optimal outcomes - I mean, you are peeing into a plastic bag or into a piece of bowel that is formed like a bladder - who we are most focused on.

We do not know how many more patients might move into the mix, if indeed there were a safer, better tolerated procedure with better outcomes in the long run. If you implant a neo-bladder, you do not absorb things that you shouldn't absorb. You do not secrete mucus into your urine. You just have a bladder that does what it is supposed to do. That difference of offering probably mobilizes other patients into the mix.

The 10,000 to 15,000 that currently have the procedure annually, that is U.S. only. We expect and believe Europe is comparable in the numbers of patients.

TGS: How much will neo-organs cost and what reimbursement challenges do you expect?

Nichtberger: We do not know the pricing and reimbursement of the neo-organs yet, but we do know the price when a [real] organ is procured for implantation into a patient. To procure an organ to show up in the operating room where it is about to be implanted - not the care of the patient who is about to get it or the after-surgical care - but just to get the organ to show up in the operating room is on the order of \$50,000 to \$150,000 per patient.

I do not know where we will price and reimburse our product, but what I just relayed to you identifies that society appreciates the importance of being able to implant and replace organs that have failed. I am hopeful that if we deliver the safest and most effective product that we can deliver, we will have appropriate reimbursement.

TGS: You were in senior management at Merck before you started Tengion. Can you talk a little bit about the difference between a traditional drug and device firm and a company focusing on bioengineered organs like yours?

Nichtberger: Interestingly, the similarities are probably greater than the differences. Where I think we are quite different is that to succeed, we require a highly integrated view of health care discovery development, manufacturing and ultimately marketing and sales.

By that I mean we cannot limit ourselves. We are not about one pill, once a day. We are not about biologics only, or proteins only, and we are not about devices only. Our expertise lies within the notion that we can integrate the biologic insights, the device know-how and the combination of those two in a scaleable manufacturing capability with emerging regulatory understanding and expertise.

TGS: How does that translate into a business plan?

Nichtberger: We can put all that together and be integrators. It is similar to the early personal computer industry. Early on, Apple and IBM were the companies that knew how to integrate very well, better than others. Therefore, they were the leading companies in the early days of the PC industry. And then ultimately, the value chain flows to components or to selected expertise within the integration process.

We are trying to set ourselves up at the start as a leader through our capabilities of integration and scaling up and working through the regulatory process with FDA. Ultimately we will succeed, driven by the expertise of our people, by identifying the key leverage points of value creation in the industry.

This is an industry that is transformational and it is not going to stand still. What it takes to succeed at the start is going to be different than what it takes to succeed five to ten years from now.

TGS: Okay, so ten years down the line, what will your company and the regenerative organ space look like?

Nichtberger: One of the important emerging platforms over the next decade is going to be regenerative medicine. I think that is true because the biological insight from the past decade has set the table for the industry to emerge over the next decade.

That is the fundamental insight that our company and our investors have: By using technology that is ready to be brought into patients safely and properly, we can advance the field and build a successful commercial organization around regenerative medicine. Our neo-organ approach is certainly not a replacement for any of the other efforts in the field. But it is a highly valuable next platform.

It really is driven by the fact that the science is ready. Some people who I talk to about Tengion say, “Gee, that is pretty straightforward. That is not stem cells. That is not embryonic stem cell technology.” I sort of enjoy the idea that people see our technology as not being controversial, as not being today’s latest fad, but instead being something that is accepted as proven.

I think by building a company that delivers a strong growth opportunity and revenue and profitability, we put ourselves in the position to then capture the subsequent successes of tomorrow with core competencies in regulatory expertise and running clinical trials.

All of this, with the financial wherewithal, puts us in the position to be able to capture future breakthroughs in regenerative medicine.

When we think about where we see the company over the next ten years, first and foremost it is driving toward profitability as soon as we can. Second, it is to be in a position where our core competencies put us in a position to be the partner of choice for future breakthroughs in the field.

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