Interview: Jason Beith on manufacturing and commercializing polymer valves

Jason Beith PhD, is Vice President of R&D at Foldax®, Inc., a leader in the development of polymeric heart valves with the goal of creating the next generation of heart valves that are more durable than current tissue valves with no need for lifetime anticoagulation of mechanical valves. He is the inventor of the Tria™ aortic and mitral surgical valve platforms and led the development of the novel robotic manufacturing and production system. He has worked previously as a Senior Principal Engineer in R&D with Medtronic where he was the technical lead and inventor of the Avalus pericardial tissue valve. Dr. Beith recently spoke with Rob Fraser, ViVitro Labs applications manager, about polymeric valves and advice to others trying to commercialize a radical idea.

Rob Fraser You are making a flexible polymer surgical valve that also has transcatheter options. Please tell us how that work is progressing?

Jason Beith We are making great progress. Our goal is to bring a suite of polymeric heart valves to the market that significantly improve upon current options. We've looked at different disease states and, in the west, the aortic is the biggest disease to address. We made the strategic decision to start with the aortic valve, prove the concept, and then move through to mitral and ultimately transcatheter aortic valve replacement (TAVR). I'm happy to say that we are the first polymer heart valve to be approved by the FDA for clinical investigation. We are currently conducting an Early Feasibility Study (EFS) that started out as fifteen patients, but we have actually extended that to 40 patients based on FDA review of the initial results. We currently have in excess of thirty patients walking around with an aortic valve and everybody is doing remarkably well. We have patients out over one year with no

anticoagulation. The one year follow up and paper should be published relatively soon. On the heels of that, we've also been approved for an EFS for a mitral valve. We just recently had our first two implants in this study, so that is pretty exciting.

Polymeric Heart Valve

Rob Fraser That's amazing. Are there patients past the twelve months' follow-up? Is twelve months the limit where the devices are at today?

Jason Beith Our longest patient is about twenty-two months and he's doing exceptionally well. We can't quite believe how much of an impact it's had on him. He is a runner and recently reported that he is running roughly six miles. One advantage that the polymer gives is there is no deposition or thrombosis or anything forming on the leaflets. The normal wound response for a tissue valve is pannus forming on top of the tissue. That pannus will grow out over the leaflets and over time it will calcify and stiffen. As that happens, the pressure gradient starts to increase, and the patient starts feeling tired and fatigued just like before the first replacement. Then the surgeon or cardiologist decides it's time to get you back in for a reoperation. What we've seen in this technology through preclinical testing was that we didn't see the typical wound response. We could see head to head against tissue controls that our valves performed better.

Rob Fraser The whole phenomenon of subacute thrombosis caught a lot of people by surprise. They were looking, but maybe not looking with the right tools. Are you using 4-D MRI to really get in the leaflets and see what's happening?

Jason Beith We've had pilot studies where we've used 4-D CT to try and better understand what's going on. There are several schools of thought about its utility, it's a new tool. It seemed to come along at the same time as TAVR. So when they were initially looking at the images, everybody was saying "ok we have this and we see it on TAVI, so it must be a TAVR phenomenon". Then cooler heads started looking at it saying, "let's look back at surgical valves". As it turned out, it was always there. I think there's an ever-growing database of information, and everything has to be taken with a grain of salt. You can't jump to any conclusion by saying this is a new technology or by using a new telescope to look at what we see, this incredible image. Yes, that's true, but let's qualify it by looking at something that we think we understand. I think that database is increasing, but it's still not complete enough. Certain articles are published that appear quite dramatic, but when you look at them across a broader spectrum, it's almost expected.

Rob Fraser It's very promising that your device isn't seeing any thrombus, that's amazing news. Your manufacturing process is quite unlike other valves. Being a polymer, it's an automated process. Can you tell us more?

Jason Beith The conventional method is rooms full of operators with sutures and needles and pieces of pericardial and fabric. We are completely robotic. The use of a polymeric material actually facilitated the use of robots, unlike tissue which is much a much more manual and craft process. The valve itself is not touched by human hands in the process of being made. What that does is give us incredible repeatability. It also gives us very predictable outcomes. We have the system dialed into where it has to be now, size by size and even valve type by valve type. We can basically predict the outcome of the valves from the parameters on the way in. It gives us a huge advantage

when it comes to the throughput of the product. When you get to the tertiary step, we don't have to do any kind of functional testing. Because of the amount of measurement we actually do on the valve as it's processing through the production process, gives us great confidence in what its final hydrodynamics will actually be. We're pleased to say that we're getting down to the level where the standard deviation across the three leaflets on a valve is single-digit micron. We have levels of repeatability for kinetics that you can't really get with tissue.

Jason Beith holding a polymeric heart valve

Rob Fraser One of the advantages of both the material and the automation is cost goes down quite a bit. Does that change how you are trying to go after markets? You mentioned the West has a big impact on aortic disease. Elsewhere in the world, there's a lot of mitral and their health care systems aren't as rich as ours. Is that a strategy?

Jason Beith The cost is more of a consequence than a goal. We see that we have this phenomenal repeatability and reproducibility going on. Humans are humans and they have good days and bad days. Robots and automated systems just function, they just keep crunching it out. This turns out to be especially important in light of the COVID pandemic – robots don't get COVID, so the impact of this type of event on our manufacturing line was minimal. Aortic for us is our gateway into proving the technology. We considered trying to do an aortic TAVR valve, but it was just a step too far because you have too many things going on. You have nitinol, self-expanding, polymer and you have delivery systems. You have many ways where you could come

undone and not give the valve technology a fair test. The fact that we've done something clean and elegant, that's one piece and can be compared cleanly against other technologies, I think is the way to do it. The promise of this technology, as you say, is mitral. There are 16 to 17 million people suffering from rheumatic heart valve disease all over the world, and they don't have access to any of these technologies. The best tissue technologies that we have right now last only three to five years. The Foldax Mitral valve was specifically designed for the mitral position and is not simply an aortic valve that was flipped over and given a new sewing ring, so if we can bring this mitral valve to the market, that's where I personally feel the technology should begin.

Rob Fraser How has ViVitro helped with your work?

Jason Beith We've had a long history with ViVitro going back now in my career more than 20 years. Going all the way back to David Walker. Most of us used pulse duplicators and your HiCycle testers. The pulse duplicator is something that we rely on, especially when you're in development of the heart valve. The only true feedback of how well a heart valve is working is from a pulse duplicator. You need a solid workhorse that is non-varying and that's definitely what you have with your pulse duplicator.

Rob Fraser Now that you understand all the inputs and outputs, its workhorse days might be numbered.

Jason Beith Believe me, we still use it. From both the regulatory and the company's own interest point of view, we have banks of valves running through hundreds of millions of cycles. We want to understand how stable the valves are. We take them out and do the full suite of ISO-testing and look at them regularly to see if we have any drift or anything happening to them. I'm happy to say we see nothing; we don't suffer as a technology platform like tissue can from continuous running and we don't suffer from any degradation in performance or stretch of leaflets. Whenever we test the

valve at time zero, the performance is none varying at three, four, five & six hundred million. It just does not move.

Rob Fraser How have the new ISO 5840 standards impacted you?

Jason Beith I think it's the same for everybody across the board. If you were already fairly locked and loaded for submission of your AWT data, you might have to start an extra couple of samples. Currently that's the most impact from a long point of view. The new, more prescriptive real-time testing is obviously going to be an extra burden on proving technologies. Thankfully, we did a lot of that preemptively on our own. The fact that we're working on polymer and we know the history and challenges associated with it. We always knew we had to have a large dossier of information to take to both the market and surgeons to say that polymer is not bad. Polymer is good.

We did a lot of preemptive testing to prove the durability of our polymer where we would test essentially perfect production version valves, and we would start placing suture needles and scalpel cuts in them and continue to test them. You learn more from failure than you do from nothing happening. We had banks of real-time testers where we would monitor these valves day by day, measuring progression of these defects if we saw any, then if we thought we saw a significant change, we would then actually put it back through the pulse duplicator to see if there was detectable change in hydrodynamics. Then we would put it back in the machine and keep going. We have valves that have run for tens of millions of cycles and we see either insignificant growth or no growth. This is a significant step forward for polymer valve technologies, as you may know historically prior polymers were known to have catastrophic failure modes of the leaflet tearing very quickly once a defect happened. Our goal was to eliminate that quick failure mode and we have succeeded

This kind of testing has never been attempted before, but it was something that had something that is possible for us to do because of the polymer and manufacturing process itself. If you were to try to do that to a tissue valve

you already have a natural variability between the three leaflets on a single valve, then trying to test essentially multiple unique samples to determine a response from them would be almost impossible. We had the luxury of having something that was very well defined and repeatable. We could really power up our numbers by looking at specific defects for specific valve sizes and generate some really meaningful data.

Rob Fraser You've been in the medical device industry for a long time. What advice would you give to people trying to commercialize a radical idea like a polymer valve?

Jason Beith I think you have to be very patient. I've been working on polymer valves since 1998 and you can have technologies that we think are good enough, then for whatever reason, be it market forces or even an economic meltdown, you may not make it. You just have to be very patient and be able to do what you're doing with kind of a natural skepticism of how you think other people will perceive it.

It's always interesting talking to surgeons because they see a constant myriad of new devices flying through and there are certain surgeons that will always be very accepting of technology and try it. Then there's a good number of surgeons that will look at something and say, "this is just a variation and I don't want to use it, there's perfectly good products that are there right now that have twenty, twenty-five years of data, so why would I compromise that?" What we are seeing, especially with the polymer valve, it is such a game-changer. Surgeons and patients see it and they go "this is truly novel". The promise is fantastic. So this is something that's worth looking at.

We are finding that we have a great deal of acceptance even from people that we perceived to be skeptical surgeons. So we don't have an issue that way, that's for sure. I think constraining some of the enthusiasm sometimes is a little bit of the issue. But it's great to be working on something that truly should be revolutionary when it's certainly going to work. We're taking small steps here and there, and I know there are several groups that are working on other polymer technologies, and I wish them all success. Because the more that come forward, the more accepted it will be. We can push into essentially what has been a fairly static market. When it comes to innovation for the last 30 or 40 years, it really has been variations on a theme.

Rob Fraser The rising tide lifts all boats is the theme. Their success is your success, it's a double-edged sword too. Their failure could be your failure as well. If polymer valves get a bad name because of someone else, that's a tricky situation.

Jason Beith Exactly. If you take the parallel, 15 to 20 years ago that's what we said about percutaneous valves. There was a great deal of euphoria and everybody jumped on board and everybody was always saying that it basically takes one company to have three or four bad implants and they could kill the industry. That never happened. So I think if everyone is sensible and responsible and moves forward in the best interest, you will succeed. If you build up enough user base that is accepting of the technology, you'll survive. That's always in the back of my mind.

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