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NEWS RELEASE

January 2009



[From the Desk of Ivan Vesely, Ph.D.](#)

Dear Colleague

The VXi team hit the ground running as the New Year began and by the end of January, a number of important activities have come to fruition. (i) We completed our initial acute animal studies and performed 2 chronic sheep implants. (ii) We expanded our prototype valve line from the initial 19 mm valves for animal implants to now add 23 mm clinical grade valves for demonstration purposes, and (iii) we strengthened our visibility within the surgical community by way of a dinner presentation at the recent STS (Society for Thoracic Surgery) meeting in San Francisco hosted by [Dr. Joe Sabik](#), Chair of Thoracic and Cardiovascular Surgery at The Cleveland Clinic Foundation.

The "Reality Check" column continues from last month's review of valvular Tissue Engineering and discusses some interesting new developments in this field.

For those new to this Newsletter, ValveXchange is a start-up company based in Colorado. We call ourselves "*The Lifetime Tissue Valve Company*" and are developing the first-of-its-kind "serviceable" bioprosthetic valve. By offering the possibility of periodic, minimally invasive exchange of the worn-out leaflet set, young and physically active patients can avoid the use of a mechanical valve and the associated Coumadin anticoagulation therapy. By adhering to the time-proven design tenets of conventional bovine pericardial valves, the ValveXchange system offers the best combination of least-invasive reoperation and greatest longevity and durability.

I look forward to sharing news with you about this exciting technology in the coming months.

Press Release

ValveXchange announces start of chronic animal studies

January 30, 2009. Denver - ValveXchange Inc. announced that it has begun animal testing of its proprietary exchangeable valve technology. CEO, Larry Blankenship, stated *"This is a major milestone for VXi and the development of our technology. Working with two expert teams, we have confirmed our implantation technique and are moving to chronic animal studies. We are particularly pleased that we have been able to achieve this milestone on time and under budget!"* The two centers working in partnership with ValveXchange are the laboratories of Dr. Eric Monnet at the College of Veterinary Medicine at the Colorado State University, Fort Collins, CO, and Professor Richard Bianco, Director of Experimental Surgical Services, University of Minnesota, Minneapolis, MN. Both Institutions are well-recognized for their expertise in animal surgery.

The [Veterinary Hospital](#) at Colorado State University has been ranked as one of the top veterinary center in the U.S. [Dr. Monnet](#) and his colleagues have interests in ventricular and valvular function in various animal models and have [published](#) extensively in this field. [Dr. Chris Orton](#), one of the team members at Colorado State, is known for his early work in developing a tissue-engineered valve and is listed as the inventor on perhaps the first major patent ([5,192,312](#)) on the decellularization of animal tissue valve, a technology that ultimately led to the first therapeutic use of decellularized valves.

[Prof. Richard Bianco](#) of the University of Minnesota is known world-wide for his high volume of prosthetic and bioprosthetic valve implants into the juvenile sheep model, and his many [publications](#) on this topic. Many of his key publications relate to developing pre-clinical animal models for testing heart valves, and he has implanted virtually every valve that is currently on the market. During the first implant of the VXi valve, Prof. Bianco commented that our first generation sewing cuff *"felt just like that of the Edwards valve"*, and that *"not having the leaflets in the way avoided worry about damage during implantation"*.

The acute animal studies were particularly important to VXi as they enabled us to *"identify the need for new accessory tools for insertion and exchange early in our animal work, and prepare for the exchange experiments in the coming months"*, said Ivan Vesely, Ph.D., Founder and Chief Scientific Officer of VXi.

Other News

Technology Update

Six months after our NIH funding became active, we have essentially completed the development of our animal-grade, 19 mm exchangeable valve. Our objectives have been to mimic, as closely as possible, the off-patent design features of the highly regarded Edwards Pericardial valve. By basing our design on the well-proven functional features of the Edwards valve we can be sure that our long-term performance is comparable. For example, the VXi valve leaflet shape, free-edge angle and stent post compliance matches that of the Edwards valve. These are features that affect leaflet stress, and hence valve longevity the most. Pictured here is the 19 mm valve. Note the presence of the central gap in the leaflets. As in the Edwards valve, this central gap has been tailored to close completely when the valve is loaded as the pericardial leaflets stretch and the stent posts deflect inward. Without this central gap, the leaflets would experience "pinwheeling" and buckling and would thus be subjected to undue compressive stress - a known mechanism of valve leaflet failure. Besides the engineering considerations related to valve longevity, there is also the surgical "feel" of the sewing cuff when a needle is passed through it. This is achieved by way of material selection and thickness of the sewing cuff insert. As noted by our animal surgeons above, we have succeeded in that characteristic also.



The two-step valve implantation and the exchange, in particular, are facilitated by tools that stabilize the docking station and align the leaflet set for insertion or removal. We have developed and tested preliminary functional versions of these tools in a laboratory setting, and look forward to testing them further during upcoming chronic animal implants. These early prototype tools were shown to selected surgeons at the recent STS meeting in San Francisco and received positive comments along with a variety of helpful suggestions.

STS Meeting - San Francisco

During the course of the STS Conference, ValveXchange set up a dinner meeting hosted by [Dr. Joe Sabik](#), Chief of Thoracic and Cardiovascular Surgery, The Cleveland Clinic Foundation. At that meeting, VXi showed its 19 and 23 mm valves to a few select surgeons and Medical Device Industry professionals from the U.S. and Europe. At the dinner meeting VXi presented its progress and upcoming milestones, its portfolio of surgical tools, and expanded on the technological features of the exchangeable valve that are critical to its long-term durability. Feedback from the audience confirmed the desirability of completely removing of calcified native aortic valve cusps during the first surgery to implant the VXi valve. Enthusiasm was also evident for the two-step implantation approach, in which the empty docking station is implanted first, and after

all sutures have been tied, cut and security of the sewing cuff verified, the leaflet set may be snapped into position. Absence of the leaflet set during the initial implant procedures facilitates quick, "rough handling" of the docking station, prevents inadvertent damage to the leaflet set during suturing and pushing of the knots against the sewing cuff, and also enables checking for paravalvular leak by way of a probe inserted through the annular space of the docking station. Regarding leaflet exchangeability, the audience was clearly enthusiastic for it. [Dr. Michael Banbury](#) (Chief of Cardiac Surgery, Christiana Care Health System, Newark, Delaware) commented that his "... 45-year-old patients are already opting for bioprosthetic valves with the knowledge of future re-do's, rather than having a mechanical valve and being on Coumadin". An exchangeable valve that makes these inevitable redo's safer and easier is thus likely to gain quick market acceptance, regardless of the invasiveness of the surgical approach taken. Indeed, [Dr. Richard Cochran](#) (Chief of Cardiothoracic Surgery, Maui Memorial Medical Center, Hawaii) noted that "Once this valve is on the market, it will clearly be the gold standard against which percutaneous valves must be compared."

Reality Check

Tissue Engineering - Part II.

Last month in this column I commented on the relatively slow progress of the field of tissue engineering in developing a clinical-grade product. Perhaps I spoke too soon..... A few weeks ago, a remarkable new development in tissue engineering was revealed through the popular press. A series of web articles ([article1](#), [article2](#), [article3](#)) spoke of a female patient from Spain as the recipient of a tissue-engineered trachea. To my knowledge, this is the first example of success in the clinical use of allogeneic tissue seeded with autologous stem cells. According to the articles, the donor trachea was first subjected to a detergent-enzymatic extraction process to remove cell-based antigens, and then cultured in vitro for about one week in a bioreactor with the patient's own bone marrow stem cells. This approach is not new and is similar to the many attempts to develop tissue-engineered heart valve implants. What is different, however is that (i) this appears to be the first clinical use of cell-cultured allogeneic tissue, and (ii) the approach appears to work. Admittedly, implementing tissue engineering principles to the trachea is less demanding than it is for heart valve applications. First of all, the substrate was of allogeneic, rather than xenogeneic origin, and thus less antigenic. Unlike human aortic valve allografts that are in high demand for transplantation, there is little use for cadaveric trachea. The investigators could thus hone their skills and technique on plenty of available tissue. Secondly, human allograft valves have good long-term performance after transplantation already, and there is thus little benefit to attempting to devitalize and re-seed them with cells in culture and risk potential remodeling complications after transplantation. Finally, unlike the highly dynamic aortic valve, the trachea is a simpler, static load-bearing structure. It experiences none of the large strains and deflections of the aortic valve, and is thus likely more forgiving to

mismatch of mechanical properties. Nevertheless, the clinical use of autologous stem cells in a load-bearing structure is very exciting. If successful in the long term, much can be learned about the way an autologous matrix responds to decellularization, repopulation in vitro, and subsequent implantation into a location where it experiences mechanical stress.

There is a need for caution, nevertheless, regarding the clinical use of biological approaches. At about the same time as the trachea articles came out, it was revealed that Medtronic is being sued over a complication associated with its "Infuse" bone graft. Infuse is [collagen sponge combined with bone morphogenic protein \(BMP\)](#). It has been approved for use in the [lumbar region for spinal fusion](#) and apparently has been used off-label in the cervical spine where it may have led to the death of at least one patient. Although the exact mechanism of failure is unknown, it is thought that the exuberant bone growth that the BMP induces may have impinged on vital nerves and impaired the breathing reflex in one patient (see [link1](#), [link2](#)). There is thus no guarantee, and little evidence for the notion, that stem cells loaded into a matrix will simply settle down and "do the right thing" in their new environment. This is particularly the case with a tissue that has been chemically stripped of its many matrix molecules and thus lacks the normal biological cues that may help in the engraftment of circulating stem cells. Certainly, forced seeding of stem cells is far more efficient than normal engraftment, but the long-term outcomes are clearly unpredictable. In the case of a BMP-loaded matrix, unexpected bone growth occurred when the system was implanted in an untested, new location. What stem cells will do long-term in a chemically modified biological matrix is likely to be similarly unpredictable.

I hope that you have found some of the above information useful and interesting. Please visit our web site for additional information and previous News Releases by way of the links below

Sincerely,

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Previous News Releases

November, 2008. Denver - Dr. Floyd Loop, former CEO of The Cleveland Clinic Foundation, has joined the Board of Directors of ValveXchange Inc., and will also chair the Medical Advisory Board. [Read More.](#)

October 23, 2008. Denver - Aurora-based medical device has recently been featured in an article posted by the RockyRadar, a local medical device industry newsletter. The review of the ValveXchange approach is one in a series of short stories about start-up companies in the Denver-Boulder area, primarily in the areas of Life Sciences, Information Technologies and Clean Energy. [Read More.](#)

October 13, 2008. Denver - Aurora-based medical device company ValveXchange Inc. announced today that it has been awarded a European patent (EP1,671,608) entitled Cardiovascular Valve Assembly, authored by Dr. Ivan Vesely, the company's Founder and Chief Scientific Officer. [Read More.](#)

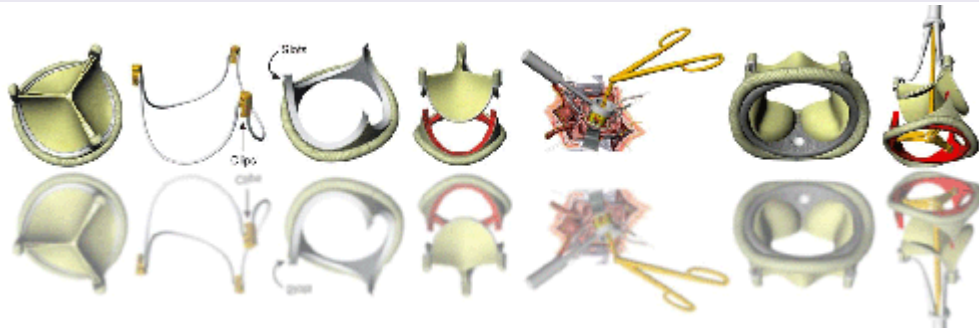
July 29, 2008. Denver -

Aurora-based medical device company ValveXchange Inc. announced today that they have received a \$1.6 million grant from the National Institutes of Health (NIH) for funding under the SBIR Program related to research and development of its proprietary two-piece heart valve technology. [Read More.](#)

January 1, 2008.

ValveXchange Inc. is a featured company in Start-Up magazine. [Read Article.](#)

December 7, 2007. ValveXchange Wins The Third Annual Faegre & Benson Venture Showcase Award, Presented At BioWest 2007. [Read More.](#)



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