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## NEWS RELEASE

April / May 2009



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

Dear Colleague

In April we focused primarily at refining the VALVEXCHANGE™ tool set and acquiring additional exchange data in the chronic sheep model. We performed our second exchange experiment and presented the data at the Dallas-Leipzig conference in Dallas, Texas later in the month, at the invitation of Dr. Michael Mack of Baylor, co-organizer of the meeting. At that conference, we held another dinner meeting with key surgeons and cardiologists to solicit feedback about our technology and our clinical approach.

We also presented our exchange experience at the ACTS2009 conference in New York City, under the invitation of Dr. Subramanian of Lenox Hill Hospital, the organizer of the meeting. At that conference, we participated as a sponsor and exhibitor, and also demonstrated our transapical exchange tools set for the first time.

We are most excited to announce that ValveXchange has signed an option agreement to license a key technology from Dr. Gerard Guiraudon, that will enable the exchange procedures to be done entirely off-pump, through the apex of the heart. A brief introduction to that technology is presented below.

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 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.

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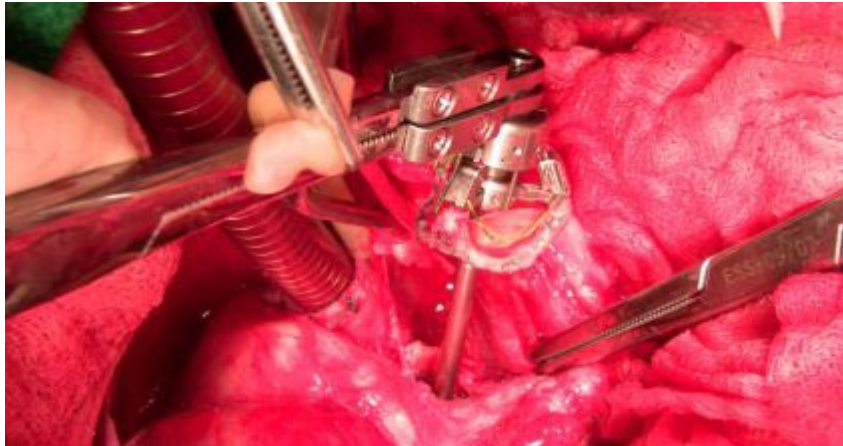
## Press Release

### ValveXchange Presents its Chronic Animal Data at the Dallas-Leipzig Meeting

**April 23, 2009. Dallas, TX.** - Dr. Vesely, Founder and Chief Scientific Officer of ValveXchange Inc. presented the company's latest data on the exchange of a fully healed-in valves in the chronic implant sheep model. The presentation took place during a "New Technology" forum that was well attended. After delivering his overview of the strategic objectives of the ValveXchange technology and the recent progress in the animal model, Dr. Vesely was asked by the moderator "*How does this technology relate to the new wave of transcatheter-implantable valves*". Dr. Vesely responded, "*We are not competing with transcatheter valves at all. Those valves are great for the end-stage, inoperable patient. Our valve is suitable for the active, healthy individual who does not wish to be on Coumadin. Our first objective is to obsolete all mechanical valves.*"

By having an exchangeable valve, a younger, otherwise healthy patient can have the choice of standard therapy, which is a mechanical valve and life-long Coumadin therapy, or the ValveXchange device. By opting for the VXi valve, the patient receives a tissue valve which does not require Coumadin, and when replacement of the leaflets is required, it is done through a relatively benign, minimally invasive procedure in which the heart does not need to be arrested. Such off-pump techniques involve none of the complications and pain of open-chest surgery that typically involves cardiopulmonary bypass. "*We believe that a younger patient would rather opt for one or two off-pump exchanges later in life, rather than suffer through anticoagulation and a mechanical valve*", says Vesely.

As a lifetime solution, however, the VXi Vitality™ Heart Valve System will appeal to patients of all ages. Physicians and industry professional have said that the VXi System will become the preferred product for the mainstream heart valve marketplace due to its unique ability to deliver long-term performance without the drawbacks of current valve technology. Having seen photos of the exchange procedure at the Dallas-Leipzig and ACTS2009 conference, they view the ValveXchange pipeline of increasingly minimally invasive tools and techniques as further support for market preference.



The image above is an extract of one of the conference presentations. It shows the leaflet set being pulled out of the aorta, in an open exchange procedure, in the sheep model. Note that the shaft of the valve stabilizer tool remains attached to the docking station, This enables the new leaflet set to quickly inserted, as it is delivered already pre-aligned to the stent posts. A copy of the entire presentation delivered at the Dallas-Leipzig meeting in PDF format (without any of the movie loops) is available for [download](#) at the VXi web site.

### **ValveXchange signs option agreement for Dr. Gerard Guiraudon's Universal Cardiac Introducer (GUCI)**

**May 15, 2009. Denver** - ValveXchange Inc. is pleased to announce that it has signed an option agreement with Dr. Gerard Guiraudon to license his Universal Cardiac Introducer technology. Unlike rigid trocars, the Guiraudon Universal Cardiac Introducer (GUCI) is a flexible, collapsible system that allows multiple tools to work side-by-side inside the ventricular cavity under 3-D ultrasound guidance. This creates the potential of MIS intracardiac beating heart surgery for the repair, implantation and replacement of cardiac valves, and for a host of other cardiac conditions. Early animal tests working with Dr. Guiraudon suggest that this technique is practical and may be adaptable for routine use for intracardiac surgery.



Dr. Gerard Guiraudon had a long and successful career in cardiac surgery because of a rare combination of [pioneer](#) spirit, creative thinking to problems, [dedication](#) to science and a true passion for the field. At the beginning of his career, Dr. Guiraudon contributed to the understanding of arrhythmia mechanisms, documented the concept of arrhythmogenic substrate and described new surgical approaches for every cardiac arrhythmia. Dr. Guiraudon was the first to perform a wide range of

procedures: (i) First guided surgery for the mapping of ventricular tachycardia after myocardial infarction in 1975 or associated with cardiomyopathy in 1973. (ii) Description of the right ventricular disconnection for arrhythmogenic right ventricular dysplasia in 1981, a disease that he was the first to identify in the operating room in 1973. (iii) First operation for atrial flutter in 1985 and atrial fibrillation (Corridor operation) in 1986 paved the way to the current development of surgery for atrial fibrillation. (iv) With the description of the epicardial approach to the Wolf Parkinson White syndrome in 1983, he was the first surgeon to replace an open heart technique by a routine beating-heart off-pump technique with remarkable success, setting the gold standard for arrhythmia surgery and describing along the way new techniques for exposure and dislocation of the beating heart that are routinely used today for off pump coronary artery bypass surgery. Besides his contributions to arrhythmias, Dr. Guiraudon performed the first heart transplantation in Europe in 1968 and described an original approach to the mitral valve in 1990.

His guiding principles in science were observation and experimentation. Astute observation in the operating room allowed him to identify unrecognized pathology, such as the arrhythmogenic right ventricular dysplasia, the coronary sinus diverticulum, and many other pathological entities. He strived to make surgical technique both an experiment and optimal therapy - surgery being an experiment to evaluate the mechanisms of success, and failure the necessary condition for progress in understanding pathophysiology and improving surgical technique in the best interest of patient.

The career of Doctor Guiraudon spans over three decades and two continents: in Paris France, London Canada, Buffalo New York, Ottawa Canada and now back home in London to meet his latest challenge - replacing conventional open cardiac surgery by a more patient friendly surgical technique using off-pump, beating-heart, intra-cardiac surgery. This requires the design and development of entirely new technologies and the use of robotics, haptics and imaging in a dramatic different way. Doctor Guiraudon has already materialized his vision by designing and testing a number of new concepts and devices to make his new project a success. The first of these is the application of the Guiraudon Universal Cardiac Introducer (GUCI) to the ValveXchange technology.

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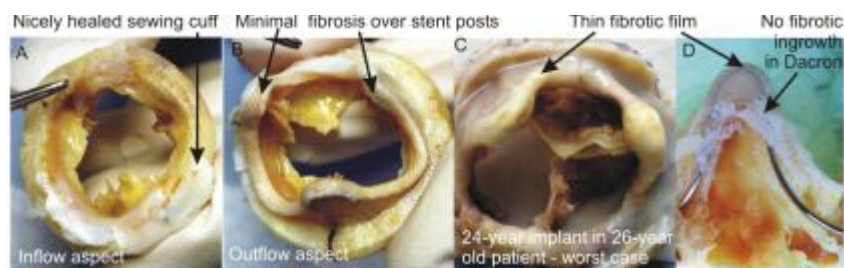
## **Other News**

### **Technology Update**

As reported in our previous newsletter, we have demonstrated that extraction of a fully healed-in leaflet set is possible. In our ongoing studies, we have succeeded in duplicating the exchange procedure in the chest cavity of the sheep, using an open, on-pump technique. In our third planned exchange experiment, we will be using a refined version of our exchange tool set that has been adapted to the relatively narrow chest cavity of the sheep model. When we presented these data to the clinical community at the Dallas-Leipzig and ACTS2009 conferences, the majority of the audience was clearly impressed. A few lingering questions remained. however. regarding the nature of the pannus that

we were tearing through during the valve exchange procedure. Let me then expand a bit more about pannus overgrowth in prosthetic heart valves.

First of all, we recognize that most surgeons have seen a variety of fibrotic tissue overgrowth during heart valve redo procedures and are concerned about such overgrowth preventing the removal of the leaflet set. The sewing cuff is certainly very well integrated into the patient annulus with robust pannus overgrowth. Indeed, one of the reasons for having an exchangeable valve with a permanent docking station is to avoid disruption of the healed-in sewing cuff. Closer to the actual leaflet tissue, and up the stent posts where the line of separation between the leaflet set and the docking station would exist, fibrosis is much less severe. Nevertheless, it is known in the heart valve field that fibrosis is highly variable between patients, between valves and between regions on the valve itself. In mechanical valves, fibrosis can be severe enough to impinge and immobilize the valve leaflets, requiring replacement surgery. It begins on the Dacron-covered sewing cuff and extends into the outflow orifice, almost as a nozzle, suggestive of a response to the turbulent flow through the valve.



In conventional bioprosthetic valves, fibrosis is far less severe. While the sewing cuff is nicely covered with pannus (image A), the stent posts are often bare or covered with a very thin endothelial cell layer (image B). Fibrosis, however, can be severe in stentless bioprosthetic valves; apparently related to the inflammatory response that stentless valves induce. Stentless valves are implanted with the aortic wall component directly in contact with the host tissue. The residual glutaraldehyde, or the porcine valve tissue itself, appear to generate a foreign body response as evidenced by inflammation and fibrotic overgrowth. Indeed, the fibrotic overgrowth obtained from explanted, heavily fibrosed [mechanical](#) and [bioprosthetic](#) valves is rich in inflammatory cells, suggesting that is related to inflammation, whether induced by a foreign body response or by mechanical trauma, such as turbulence. Over the 9 years that Dr. Vesely spent at The Cleveland Clinic, he has examined thousands of specimens of explanted prosthetic valves and native aortic and mitral valve tissues, (typically 2 explanted bioprostheses per day) and has published on the [largest collection of explanted valves at that time](#). (Dr. Butany of Toronto, has recently reported on a much [larger collection of explanted Hancock and Edwards valves](#)).

Indeed, it was this experience in examining so many valves that the theoretical possibility of exchanging valves came about. The anecdotal evidence that pericardial valves have less fibrotic overgrowth than porcine valves suggests that there is a link to hemodynamics.

Pericardial valves are known to have better hemodynamics than porcine valves and this may contribute to their lower fibrotic potential. Even in possibly the worst case scenario of fibrotic overgrowth (image C) - a porcine valve was implanted into a 26 year-old woman and explanted 24 years later - the fibrosis is still thin and translucent. Fibrosis such as this can be readily separated with the appropriate tools. We have demonstrated this in our chronic implant study. Moreover, pannus overgrowth is exactly that - a surface phenomenon. As seen in image D above, when the pannus is peeled off the cloth and the interior of the valve is revealed, it is completely empty of any fibrotic ingrowth. Apparently, once the Dacron grows over the fibrotic tissue does not penetrate into the internal cavities of the valve.

As a final testament to the exchangeability of our valve after 10 to 15 years in a patient, we measured the mechanical strength of the pannus peeled off explanted valves. Note that this had to be done on archived, formalin-fixed tissue which is considerably stronger than the fresh, raw tissue that we will be dealing with. Integrating the worst-case mechanical strength of our formalin-fixed specimens over the perimeter of the contact surface of the valve gave a pull-off strength of 2 kg (20 Newtons). With the appropriate tools, this relatively low pull-off force can be readily managed. Indeed, it was quite easy to pull the leaflet set off the docking station by hand, using our first generation tool set. In summary, experiments have confirmed what 10 years of research have indicated - that fibrotic overgrowth is easily manageable with a properly designed exchangeable valve. The exchangeable valve will thus provide an exciting and practical lifetime tissue valve solution for patients of all ages.

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## **Reality Check**

### **How Long Will PIVs Last?**

In my last Reality Check article, I commented that Percutaneously Implantable Valves (PIVs) will have a limited lifespan because of a whole host of engineering compromises. I would like to revisit one of these and elaborate a little bit more on the importance of valve design.

The Edwards Perimount valve has arguably demonstrated the best longevity of all tissue valves. This has been a huge point of contention with other valve manufacturers whose marketing teams struggle to come up with some distinguishing factors in their own valves that could be used as an advantage over the Edwards valve. In the early days of the bioprosthetic valve field, porcine bioprosthetic valves had the rationale that they were "real valves" and had the physiological, microstructural, and biomechanical advantage over a simple flat piece of pericardium that tried to only "mimic" a real aortic valve. Back in those days, many scientists (myself included) studied the structural and functional basis through which aortic valves are endowed with remarkable durability, even though they are essentially dead tissue ([ref1](#), [ref2](#), [ref3](#)). The clinical basis for the preoccupation with heart valve microstructure was the remarkable longevity of aortic allografts (homografts). Even today, the homograft valve is considered to be the best solution for patients.

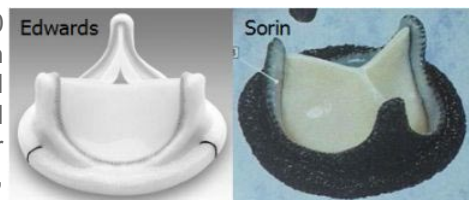
particularly the younger ones in which even the Edwards valve has less than satisfactory durability. Clearly, there is something about the native aortic valve structure that is inherently durable. Even when completely [dead and devitalized](#), the native aortic valve allograft can still last 20 years or more.

Stentless valves at one time were expected to have an "edge" over conventional bioprosthetic valves in that they offered greater effective orifice area and enabled surgeons to apply their unique approach to implantation. The absence of a supporting stent enabled the surgeon to sculpt the valve somewhat during implantation. Unfortunately, over time it became clear that the freedom to modify the valve prior to implant and the absence of the supporting stent were actually detrimental to their longevity. The lack of a frame to maintain coaptation geometry ultimately lead to early failure of the stentless valves. Recent reports demonstrate an [average durability of only eight years](#) - a very disappointing outcome for a very promising technology.

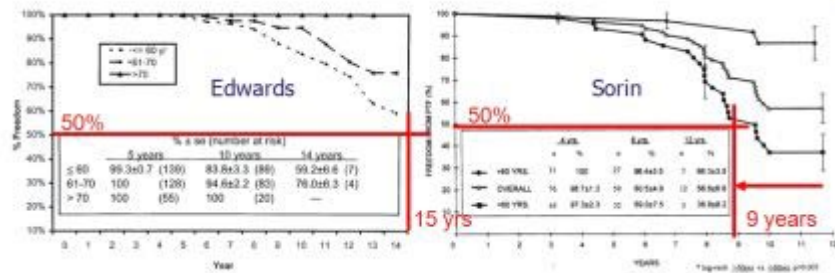
Clearly, time and clinical experience have been the major factors that have established the Edwards pericardial valve as the "gold standard." In patients over 70 years of age, one study has shown the Edwards valve to have [100% freedom from structural valve deterioration at 14 years](#). This is quite remarkable for a valve made of essentially dead, leather-like material whose microstructure was never intended to withstand hundreds of millions of cycles of flexural fatigue. One interesting feature of glutaraldehyde-fixed pericardium, however, is that it appears to [buckle less](#) when bent, than do leaflets of fixed porcine valves. Since [compressive buckling](#) was established to be a primary mechanism of bioprosthetic valve failure, an apparently greater resistance to buckling when bent is potentially the only measurable reason why bovine pericardial valves may have a slightly greater durability than valves made from glutaraldehyde-fixed porcine aortic valves.

Quality of design and manufacture, however, are the hallmark of a long-lasting, durable heart valve. Ernie Lane clearly got the [design](#) right from the outset and the Edwards LifeSciences team has done a great job at maintaining the high standards of valve manufacture.

As we look back at the past 20 years of clinical experience with different designs of pericardial valves, much can be learned from comparative analyses. For example, to the untrained eye, the Edwards Perimount and the

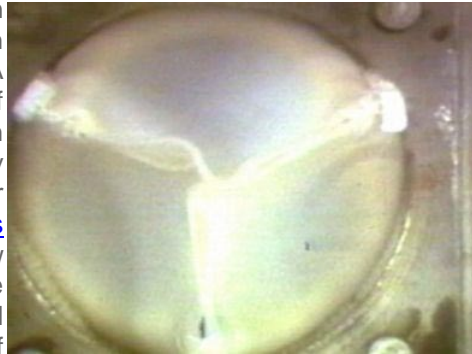


Sorin Pericarbon valve look almost identical. However, the two valves have remarkably different long term durability history. In the graphs below are two sets of published actuarial plots of freedom from structural valve failure for the [Edwards Perimount](#) valve and for the [Sorin Pericarbon](#).



I have highlighted data for patient groups that were younger than 60 years of age at the time of implantation. We see that for the Edwards valve, this patient group had a 50% freedom from structural valve failure at 15 years. For the Sorin valve, the same 50% freedom from valve failure came much sooner - at only 9 years. Similar reductions in durability were observed with older patient groups, as the other actuarial curves above show.

So what could be the reason for the diminished durability of the Sorin valve relative to the Edwards valve? The only obvious feature is the absence of the central gap between the closed leaflets. That feature alone could do it. The purpose of the central gap is to accommodate the distended leaflets at the point of valve closure. The central gap has been tailored to match both the leaflet compliance and the deflection of the stent posts at maximal transvalvular pressure. Without the gap, the leaflets will bunch up on themselves and pinwheel when the valve is fully closed. A classic example of this type of pinwheeling is found in an image of the Ionescu-Shiley valve which had very poor durability, [75% of the valves failing at seven years](#). Note how the leaflets are wrinkled in the central coaptation point and twisted clockwise. A video of this valve can be downloaded from [here](#).



An important feature of the Edwards pericardial valve therefore is the ability to maintain absolute precision in the coaptation geometry of the closed leaflets. Even a 0.5 mm mismatch in leaflet coaptation can lead to single leaflet prolapse, elevated stresses and early valve failure. Such precision in leaflet geometry is facilitated by the supporting valve stent which defines the shape of the leaflets of pericardial valves. The stent posts also deflect slightly during each cardiac cycle. This precise deflection allows the central gap to close, prevents leaflet pinwheeling (see above), and creates a shock-absorbing effect that cushions the leaflets to maximize the durability of the pericardial valve.

PIV's have none of these features in their supporting stent. First of all, PIVs are mounted on a metal frame that is designed to keep the calcified native aortic valve leaflets pushed back against the aortic root. They certainly cannot flex inward with each cardiac cycle to cushion the

leaflets of the PIV. Secondly, there is no guarantee that when fully deployed, the stent will attain a fixed, circular geometry. When deployed, the final shape and diameter of the PIV is a balance between the elastic expansion of the valve stent and the elastic recoil of the distended, calcified native valve. This is particularly the case with self-expanding valves made of Nitinol, though it is also true of balloon explanted valves which experience some recoil. Secondly, the valve is seldom perfectly circular when fully deployed because the three calcified native leaflets are seldom symmetrically calcified and hence do not push back with symmetrical force.

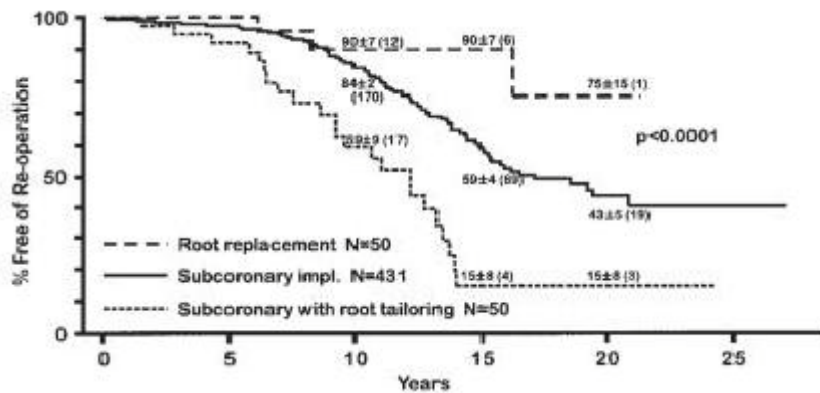
Moreover, it is still unclear what design features transcatheter valve developers consider important. A brief comparison of current generation PIVs to the long-lasting stented, surgically implantable valves suggest that the valve designers have either not learned from the historical success of the surgical valves, or have purposely deviated from their tried and true design features. As an example, we have an image of the Edwards SAPIEN valve obtained from the <http://www.jumpintotomorrow.com/> web. Two departures from the traditional design are readily apparent:



- (i) *This PIV appears to be missing its central gap.*
- (ii) *There appears to be some pinwheeling and wrinkling at the central coaptation point.*

Presumably the photo is shown at the optimal dilation diameter for the valve. Note the slight pinwheeling of the leaflets and the wrinkle in one of the leaflets. While these features may seem trivial to the untrained eye, they are not. These are serious departures from the proven design features of the Edwards surgically implantable pericardial valves. If the above valve is underdilated the pinwheeling and wrinkling will worsen. If the valve is overdilated, a gap will be created in the central area because there is no compliance in the supporting stent post to allow the central point to gently close. The durability of the PIV is thus reduced by (i) the lack of key design attributes such as the compliance of the stent, (ii) the skill of the physician who dilates the valve during implant, and (iii) the variables associated with the calcified native leaflets.

This brings us full circle back to stentless valves and the expectations placed on the physician installing it. In the case of allograft valves, an excellent study by Sir Magdi Yacoub's group tracked the [freedom from failure of allografts as a function of the surgical approach.](#)



As can be seen from a summary plot of freedom from reoperation (above) the best longevity can be obtained by doing a full root replacement - where the leaflets are held in apposition by the original aortic root of the implanted valve - their most natural configuration. Conversely, the worst performance comes about when the original root is scalloped and the least amount of tissue is implanted into the subcoronary position. This is where the surgeon can most alter the natural geometry of the valve leaflets. Leaving the final leaflet geometry up to the implanting physician is thus a huge gamble. Over twenty years of history have established that, on average, valves with uncontrolled leaflet geometry will do worse than those where geometry is well-controlled - even in the hands of a highly skilled and internationally renowned surgeon. Combine that now with a non-circular, calcified landing ground for the leaflets of PIVs and we have the ideal conditions for reduced durability that can potentially be just as bad as the original Ionescu-Shiley valves - 7 years.

Sincerely,

Ivan Vesely, Ph.D.  
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 ValveXchange Inc.  
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## Recent News Releases

**March 18, 2009. San Francisco, CA** - Frost and Sullivan held their annual "Excellence in Medical Technologies & Life Sciences Awards" banquet on this date, honoring companies in the bioscience and medical device fields. ValveXchange Chairman and CEO, Larry Blankenship, was there to accept the award. [Read More.](#)

**March, 2009. Denver** - ValveXchange Inc. announced that Dr. Tirone E. David has joined the VXi Medical Advisory Board. Dr. David is recognized world-wide for his pioneering work in valve sparing surgery, his remarkable surgical skills and his commitment to teaching. [Read More.](#)

**March 30, 2009. Denver** - ValveXchange licensed its exchangeable valve technology patents from the Cleveland Clinic. The Clinic and ValveXchange have now entered into an arrangement whereby the Cleveland Clinic will in the future receive an equity position in ValveXchange, Inc. [Read More.](#)

**February, 2009. Denver** - ValveXchange Inc. announced that it is the recipient of the 2009 North American Frost & Sullivan Technology Innovation of the Year Award. According to Frost & Sullivan Research Analyst S.R. Priya, "The ValveXchange Heart Valve System represents a safe and less invasive alternative to conventional therapies.... Overall, the ValveXchange system provides the innate hemodynamic and non-thrombogenic benefits of tissue valves to patients of all ages, thus obviating the need for expensive and potentially problematic anti-coagulation therapies and major lifestyle modifications." concludes Priya.

**February, 2009. Denver** - ValveXchange Inc. announced that of Dr. Joseph Sabik, Chair of Cardiothoracic Surgery, The Cleveland Clinic Foundation, will serve as the Chair of the VXi Medical Advisory Board. [Read More.](#)

**January 30, 2009. Denver** - ValveXchange Inc. announced that it has begun animal testing of its proprietary exchangeable valve technology, working with the College of Veterinary Medicine at the Colorado State University, Fort Collins, CO, and with Experimental Surgical Services, University of Minnesota, Minneapolis, MN. Both Institutions are well-recognized for their expertise in animal surgery. [Read More.](#)



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