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**NEWS RELEASE**

July / August 2010



**From the Desk of Ivan Vesely, Ph.D.**

Dear Colleagues

The ValveXchange product portfolio will soon contain a validated, transapically-implantable version of our exchangeable valve - The Vanguard™. Prototypes are finished, testing is underway and results will be available in September. I will report on their progress in the next newsletter.

Also scheduled for September is the publication of a review article on transcatheter valves that I was invited to submit to the Journal of Heart Valve Disease. Please look for it on-line or in print, if you have a subscription to the Journal, or feel free to contact me for the PDF. The title of this manuscript is "*Transcatheter Valves: A Brave New World*".

The summer is also ending on a very positive note from the financial point of view - ValveXchange has been awarded yet another NIH grant. This time it is an SBIR Fast Track entitled "*Beating Heart Surgery for Heart Valve Replacement*". This award will fund the portfolio of technologies related to accessing the aortic root through the apex and performing valve implant and valve leaflet exchange.

For those new to this Newsletter, ValveXchange is an emerging technology 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, we believe that the ValveXchange system will offer the best combination of least-invasive techniques and greatest valve longevity and durability.

## Press Release

### ValveXchange Receives its Fifth NIH SBIR Grant

**August 19, 2010. Denver** - ValveXchange Inc. is pleased to announce the receipt of a \$1.3 million Small Business Innovation Research (SBIR) grant from the National Institutes of Health (NIH) under the Fast Track program. The Fast Track program is reserved for highly innovative and competitive projects with a short time-line to commercialization. Unlike the conventional Phase I / Phase II program in which a small Phase I award is made and progress from that completed research project can be used to support an application for a Phase II award, the Fast Track program combines the two components into a single application. Once the single application is approved by the NIH, money is set aside and the Phase II component is no-longer a competitive application. The Phase I monies are released first and the project completed over a 9 to 12 month period. The company then writes a progress report and, if the objectives are met, the Phase II monies are immediately released. This shortens the timeline for receipt of the Phase II project by nearly a year, and essentially guarantees the much larger Phase II component, provided that the Phase I project is successful.

This newly awarded grant from the NIH is entitled "*Beating Heart Surgery for Heart Valve Replacement*." This project will fund the continued development of the Vanguard™ transapically-implantable, transapically-exchangeable bioprosthetic heart valve. Implantation and exchange of heart valves through the apex is facilitated by the use of the *Guiraudon Universal Cardiac Introducer™*, which we refer to as "*The GUCI™*". This technology was licensed from its inventor - [Dr. Gerard Guiraudon](#) - a distinguished cardiac surgeon, and its development is also being funded by this Fast Track SBIR grant.

ValveXchange, Inc. is dedicated to improving the lives of patients requiring heart valve replacements. VXi is developing a two-piece bioprosthetic tissue valve system that resolves the long standing compromises between conventional mechanical and tissue-based prosthetic valves. Unlike today's transcatheter valves, the VXi technology is **Without Compromise**. The VXi exchangeable valve system is being designed to offer leaflet exchange, as well as the original implant, without open-heart surgery and without the safety and longevity compromises of current-generation transcatheter approaches.

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## Technology Report

### The Transapically Implantable Vanguard™ Docking Station

At the risk of sounding overly enthusiastic about our own technology, I really need to share some recent progress on our transapically implantable docking station. The two-piece concept for a bioprosthetic valve not only makes minimally invasive, off-pump leaflet exchange possible in the embodiment of the surgically-implantable Vitality™, but it also enables the transapically implantable Vanguard™ to address the deficiencies inherent in current generation transcatheter valves. A comparison of the design

features of transcatheter valves was presented in the [January 2010 edition of the Newsletter](#). In that issue, there is a [table that summarizes](#) all the relevant design features of 17 current and future contenders for the heart valve market. Some key features are expanded upon below.

**Durability** is a design attribute of our valve portfolio that is currently unmatched by other transcatheter or minimally invasive valve technologies. Durability is a property that emerges from the embodiment of specific design features in a particular valve concept. Durability has been shown historically to be a result of adherence to the time-proven "*Three Tenets of Good Valve Design*" - the incorporation of (i) flexible stent posts, (ii) precise central leaflet gap, and (iii) absolute 120 degree leaflet symmetry. None of the transcatheter valves on our [summary table](#) has all three of these features, although some may have one of them.

**Repositionability** is a feature of some, but not all transcatheter valves. As physicians become better at TAVI, it might be argued that a repositionable valve is not important. However, Dr. Thomas Walther, a surgeon extremely experienced with transapical valve implants, asked at the EuroPCR meeting in Paris "*Would you buy a car without seat belts?*" This, being a reference to the safety factor, or lack thereof, if a transcatheter valve is not repositionable. The balloon-expandable [Edwards Sapien valve cannot be repositioned once inflated](#), the CoreValve can be, as long as it is still partially contained in its sheath, and the Sadra and [DirectFlow are inherently repositionable](#) since they can be actively collapsed. The ValveXchange Vanguard™ is also repositionable.



**Retrievability** after deployment is a completely new issue that no current transcatheter valve embodies. What do you do if you deploy a valve and it slips out of position? This can happen with the [Sapien](#) and with the [CoreValve](#). Once deployed, these valves [cannot be retrieved](#). What do you do when you fully deploy and release the valves and you find out that a coronary artery is occluded or the valve is malpositioned and impinges on the mitral valve? What if there is [severe periprostheses leak](#)? None of these situations can be sustained long-term - the valve has to be retrieved and repositioned. No valve currently on the market has the ability to be retrieved, re-collapsed and repositioned after all control lines have been severed. The Vanguard™ does.

**Resizability** has not even been thought of. Sizing of transcatheter valves is a huge challenge with today's technologies. Unlike the implant of a surgical valve, where the surgeon cuts out the calcified native leaflets and inserts a series of sizers (see image right) into the aortic annulus to determine which size prosthesis will fit the best, [sizing of transcatheter valves is done through imaging](#). Even then, the most that can be imaged is the diameter of aortic root. There is no ability to gauge in advance how far the calcified native leaflets can be pushed aside, and thus exactly how



large a valve can be implanted. If the valve is undersized, there is the danger of the valve embolizing since it is not secure enough once fully dilated. This can occur with the [Edwards Sapien design](#), although the larger [CoreValve has also embolized](#). In many cases, the valves are oversized during implant so that the risk of embolization is minimized. This leads to the problem of underdeployment. [Underdeployment is a particular feature of self-expanding, Nitinol-based valves, like the CoreValve](#), or valves that [cannot generate sufficient radial force to expand highly calcified native calcified leaflets, like the soft DirectFlow valve](#). Underdeployment is remarkably common with the CoreValve. For example, [Schultz from Rotterdam analyzed 30 patients implanted with the CoreValve system](#) using multi-slice computed tomography. In that manuscript, they report that "*none of the frames reached the nominal dimensions*", with the mean cross sectional area of the valve being 24% lower than that of the patients' annulus. In most cases, the CoreValve cage expanded to an elliptical shape with a major-axis/minor-axis diameter difference of 2.3 mm. For the two valves sizes that were designed to have a 22 and a 24 mm diameter at the critical leaflet coaptation region, the mean minor axis diameters were 20.0 and 20.8 mm indicating significant underdeployment in both valve sizes. As noted in previous newsletters, underdeployment produces wrinkled leaflets, [as shown by Zegdi previously](#) (see images below).

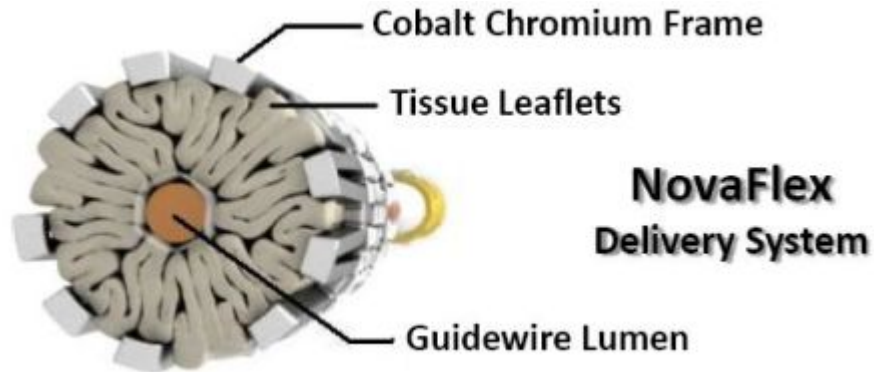


The two-part valve approach that is used throughout the VXi product line not only enables leaflet exchangeability, but also has a number of important advantages over competing concepts.

- (i) Leaflets are not crushed by metal frame

There is data emerging from laboratory studies (not yet published) that crimping the metal frame down to a small diameter by the crimping tool actually crushes and pinches portions of the leaflet tissue - at least to a level where impressions on the leaflets are visible under electron microscopy. [How that affects leaflet durability is unknown, but it does introduce an element of risk](#). An image of the crimping tool is shown at right, and a video of the crimping process can be [viewed at the manufacturers web site](#). Valve manufacturers present illustrations suggesting that the crimping process is actually very well controlled and the leaflets are nicely folded while inside the metal frame. An illustration of the Sapien valve (below) obtained from the Edwards web site is one such example.





But after watching the video of how the crimping is done, one can imagine that the unsupported leaflets will simply fold up any way that they can, and likely seldom have the nicely arranged system of pleats shown on the Edwards engineering drawing. With that in mind, it is highly likely that some portions of the leaflets will be crimped and pinched more than others. Again, how that affects leaflet durability is unknown, but it does introduce questions of risk.

A better approach is to avoid crimping the leaflets within the collapsed metal frame. This is done with the Vanguard™. Being a two-part valve, the leaflets and the frame are collapsed separately, deployed to their open shape and then snapped together. This not only makes collapsing the two parts of the valve less complex and offers a tighter package, but also ensures that folded leaflets never touch the metal frame.

(ii) Vanguard is fully retrievable

Having a tool set that can identify the position of the valve stent posts inside the aortic root and engage with the valve components for leaflet exchange also provides the ability to retrieve the valve any time during the implant procedure. The design feature that enables the Vanguard to be re-collapsible for full retrieval is the use of the wound-up metal band (see image right). That metal band is mechanically dilated until it reaches its expanded state. An animation of the [unwinding of the metal band is available by clicking here](#). A similar process is used to re-collapse the metal band. The combination of tools that can identify the position of the stent posts and engage with the Vanguard, and the ability to actively expand and re-collapse the metal band, make the Vanguard™ a fully retrievable valve; even after all connections to the valve have been severed during initial deployment - the valve can be re-grabbed and re-collapsed.



(iii) Vanguard is resizable

Resizability is perhaps the most exciting new feature of our evolving Vanguard™ technology. When fully expanded, the end of the metal band clicks into a latch that fixes its final diameter. One may stop at the 19 mm

setting, for example, and then elect to try 20 or 21 mm, simply by expanding the band open further. The implications of this are profound. This resizability feature, combined with a transapical implant, means that the physician no longer needs to rely on imaging and guesswork to size the valve. During the transapical implant procedure, the Vanguard™ is at the end of the implant tool which is held by the physician. Once deployed, the physician can test the security of placement by gently tugging on the tool handle and watching the imaging display. If the valve appears to not be secure enough, the Vanguard™ can be dilated to the next larger size, and its purchase against the native valve leaflets retested. Once the final size is established, a properly sized leaflet set is delivered through the lumen of the introducer and snapped onto the Vanguard™ stent posts. This ensures that regardless of the final size of the Vanguard™ docking station, it is always fitted with the perfectly sized leaflet set. Moreover, the final size is selectable in increments of 1 mm, and is of a precise diameter and circular shape to ensure durability of the tissue leaflets, just like in our surgical valve - the Vitality™. During the implant and sizing procedure, cardiac output is maintained by a temporary sub-valvular valve that is part of the Vanguard™ tool set (patent pending). Delivery of the valve therefore does not have to be a rushed, breath-holding experience for the physician.

(iv) High expansion force

[Underdeployment of transcatheter valves](#) occurs largely because the relatively soft Nitinol frame (or balloon, in the case of DirectFlow) cannot generate sufficient radial expansion force to fully expand the prosthetic valve inside the stenotic calcified native leaflets. By mechanically expanding the metal frame of the Vanguard™, we have no such problem. Indeed, the Vanguard™ frame can be expanded to its fully deployed size even when held in a clenched fist!

The Vanguard™ transapically implantable/exchangeable valve is thus a platform that improves significantly on the pioneering efforts of transcatheter valve predecessors, like the CoreValve and the Sapien, and offers important advantages over other emerging technologies, such as Sadra and DirectFlow. It is truly the **Next Generation** transcatheter valve.

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## Reality Check

### Childhood's End:

Let me first apologize for overusing references to dystopian science fiction novels - Yes, two in one month! We have the publication of my review article: "*Transcatheter Valves: A Brave New World*" coming out in the September issue of the Journal of Heart Valve Disease, and the same month the Reality Check is entitled "*Childhood's End*".

The reference to "*Childhood's End*" came by way of recent NIH grant application I wrote for a pediatric valve. The technology capitalizes on our

recently awarded patent for a "*Cardiovascular Valve Assembly with Resizable Docking Station*". This patent was granted in Canada and Europe, and will soon issue in the US also. The patent claims the concept and the design for a tissue valve that can be used in children. Children born with congenital heart defects are left with few options. Just a few decades ago, children born with congenital heart defects, like aortic stenosis, pulmonary valve atresia, tetralogy of Fallot, and truncus arteriosus, used to die immediately after birth. Today, they can be saved with a surgical reconstruction of the outflow tract and the use of prosthetic valves. The most commonly used valves are allografts, either in isolation to replace a stenotic aortic valve, or as a right ventricle to pulmonary artery conduit. Some physicians also use flaps of bovine pericardium to fabricate uni-leaflet valves for the aortic position. Mechanical valves are seldom used because of the [risks associated with chronic anticoagulation in the growing child](#). Although a [number of factors affect the longevity of these valves](#), such as patient age, size, and rate of growth, patients born with such cardiac malformations can expect to [undergo multiple surgical procedures over the course of their lives](#) to replace failed aortic and pulmonary prosthetic valves.

One approach is to reconstruct the right ventricular outflow tract by obliterating the stenotic pulmonary valve, producing a [wide open connection from the right ventricle to the pulmonary artery](#). The second involves bypassing the obstructed valve with a tube graft from the right ventricle to the pulmonary artery, also called the [Rastelli procedure](#). Both strategies, however, induce long-term problems. Absence of a pulmonary valve causes severe regurgitation back into the right ventricle. Though this can be tolerated for one or two decades, the severe volume overload eventually leads to failure of the right heart and [increases the risk for sudden cardiac death](#). Treatment of this situation involves a subsequent cardiac surgery to replace the absent pulmonary valve. The typical valves used for this operation include porcine bioprostheses and allograft valved conduits. Mechanical valves are rarely used in children because mechanical valves smaller than 17 millimeters are generally not available and children do not tolerate chronic anticoagulation well. In the case where the obstructed pulmonary valve is bypassed with a tube graft or a pulmonary allograft, the size of the graft can be only as large as the vascular structures to which it is attached. Since most of these surgeries are performed before the patient is six months of age, the graft is quite small, and no candidate graft material has the potential for growth. As the child grows, the graft becomes obstructive and requires eventual replacement. Furthermore, the longevity of valve allografts is limited and [a high percentage fail within one year](#). Thus with either approach, children born with cardiac malformations can expect to [undergo multiple major cardiac surgeries during the course of their lives](#). Indeed, a fascinating account of how one patient (Ms. Candy Murray) with a congenital heart valve defect suffered through 8 cardiac valve surgeries from age 5 to 27, before being a candidate for an adult-size Allograft valve, can be [viewed on the CryoLife web site](#).

For this patient, "*Childhood's End*" came as a relief from the suffering of repeated open-chest surgeries.

The most serious of [complications during redo surgery can result from repeat sternotomies](#) that risk tearing of critical tissues, vessels and even the heart itself, due to adhesions. The main barrier to the effective treatment of patients in this field is the permanent, non-serviceable nature of cardiac valves - a problem that can be solved with the ValveXchange technology. Although the arrival of the [Melody valve offers relief from one of the surgeries](#), the prospect of an exchangeable, resizable bioprosthetic valve promises to essentially eliminate all but perhaps the first surgery. Children with congenital valve defects could thus potentially enjoy the same complication-free lifestyle after valve surgery as their adult counterparts.



### "Childhood's End" for TAVI

If you have not read Arthur C. Clarke's book "*Childhood's End*", it describes a transformation of humanity from physical frailty to nearly limitless mental powers. Along the way, however, a lot bad things happen. After nearly a decade of innovation and clinical usage and well over 10,000 transcatheter valve implants and many failures, TAVI's naïve childhood is coming to an end.

Current generation transcatheter valves are remarkably crude devices with design attributes associated with severely limited durability. In our [previous newsletter](#), I wrote about how the importance of transcatheter valve durability has finally made it into the collective consciousness of the proponents of TAVI, as evident by the sober discussions at [EuroPCR](#), highlighted by the panel discussions available for viewing on the web at (<http://www.theheart.org/article/1086029.do>).

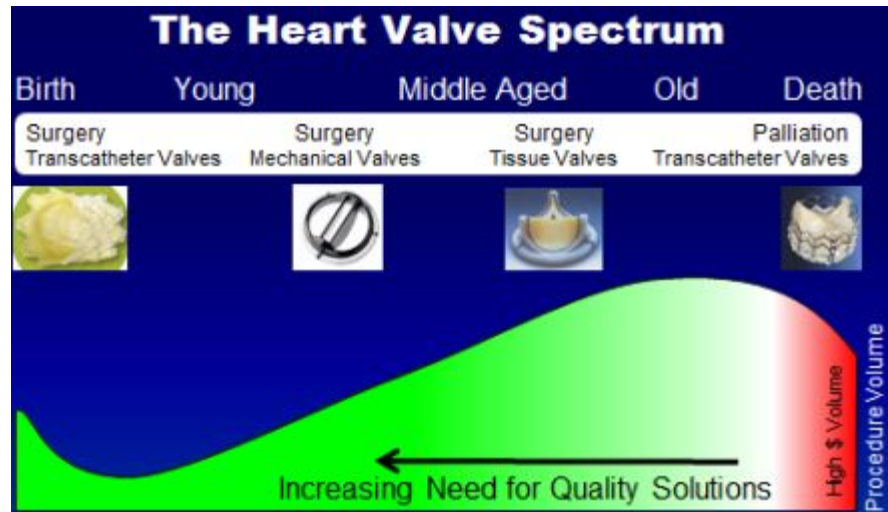
The efficacy of TAVI will come to full public light when the PARTNER trial data on the Edwards Sapien valve will be released at this year's [TCT meeting in mid-September](#). How well the Sapien valve met the primary endpoints of the Cohort B component of the trial will apparently be revealed on Thursday, September 23. In that particular study, the primary end-points are a composite of (i) time to all cause mortality, and (ii) time to first recurrent hospitalization. The assumptions of that trial are that control patients will have more cardiac related complications than test patients, and superiority of the treatment over Control must be demonstrated. In this trial, the Control arm is Medical Management, which really means doing little but managing the fluid balance of a patient with a dying heart, or possibly doing a [balloon valvuloplasty](#). The [one-year mortality for such patients is over 30%](#) and cited as 37% in Edwards company literature. By comparison, TAVI patients have less than 20% mortality. Given the low bar for success, everyone predicts a resounding victory for transcatheter valves.

What may or may not come to light is how Cohort A is doing. In that component of the PARTNER trial, operable patients were randomized between TAVI and surgical aortic valve implantation and the objectives are non-inferiority to the surgical valve cohort in terms of one-year survival. That data is scheduled to come out next year, but perhaps some indications will be revealed at this year's TCT. Regardless, the

honeymoon period for TAVI is over as hard data are finally coming out. It is only through these well-controlled clinical trials, the extended experience with the patients, and the ensuing scrutiny of the data by the FDA and the medical community, that we can finally determine if TAVI is right for anyone but the truly inoperable patient. TAVI's "Childhood's End" is coming. The technology has finally grown up and the age of responsibility during adulthood is upon it.

This age of responsibility means that TAVI and the current generation valves - the Sapien at first and the CoreValve second - will finally be measured against established clinical practice. TAVI clearly makes sense for the frail, inoperable patient as it improves survival by about 1/3 over conventional therapy. It does not prevent death, however. It only postpones it for a few more years. That is an expensive proposition. How payers will respond to a [\\$25K bill for the device alone](#) if it prolongs life by a few more years is uncertain. The cost of the entire TAVI procedure is presently on par with conventional surgical AVR. Approval is thus only one of the many hurdles that these juvenile technologies will need to cross on their way to adulthood. As their childhood ends, the hard road ahead is just beginning.

Valved metal cages; these "packsaddle sons" of intravascular stents, however, may be culled-off along the way as the second-generation devices come on line in the next few years. As shown in the graph below,



the patient group near death is the most tolerant of immature technologies because of lower life expectancies. For them, palliation can be readily replaced by a transcatheter valve. On the opposite end is the child who faces multiple open-chest heart valve redo's before reaching adulthood. These young patients are helped by transcatheter valves, no matter how little time they may actually serve the patient, by simply avoiding one of the surgeries during their childhood and moving them closer to their own Childhood's End wherein they can receive an adult size valve. Immature technologies also have some role in this patient group. However, the key point of the above graph is that through the adult population and into the

pediatric patient, there is an increasing need for high-quality solutions as the age of the patient goes down. This is why we have long-lived surgical valves, like the Edwards Perimount, for old patients and why the exchangeable valve makes sense for younger patients - there is the need to avoid the long-term, [cumulative side effects of Coumadin](#). The exchangeable valve, particularly if it is resizable, would be a tremendous solution for both the pediatric and the adult patient.

As current generation transcatheter valves move into the sober reality of their own adulthood, competitive pressures from 2nd generation technologies will mount. The durable, resizable, exchangeable Vanguard™ technology is their most significant future competitor. It is the only foreseeable technology that can challenge current generation transcatheter valves for the younger patients that demand much higher quality solutions than the primitive transcatheter valves of today can offer.

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### **Closing:**

Over the past 5 to 10 years, enormous resources have been poured into developing transcatheter valve therapies for the inoperable, extremely aged, high-risk patient population. While this has been an underserved market segment, let's look at this in context. Recent market reports project that the US aortic valve market will consist of about 118,000 procedures in 2015. Surgical procedures will hold reasonably steady, increasing from about 85,000 procedures in 2009 to around 87,000 procedures in 2015. Research by the same organizations assume that TAVI will be introduced for sale in the US in 2011, growing to about 31,000 TAVI procedures in 2015. Presumably, these 31,000 TAVI patients will not be candidates for surgery, and therefore were not adequately served prior to TAVI. The revenue projections for valve sales for the 87,000 US surgical procedures in 2015 is \$644 Million, while the revenue projections for the 31,000 US TAVI procedures is a whopping \$734 Million that same year! Yes, TAVI means fewer valves but for more money! Converting the rest of the patients to TAVI will thus need more than just durable heart valves. It will need major adjustments in the reimbursement for these devices. And that will not happen unless clear evidentiary data supporting this technology become available - welcome to adulthood!

Sincerely,

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

**June, 2010. Denver** - ValveXchange Inc. is pleased to announce that Lars G. Svensson, MD, PhD, has joined the VXi Medical Advisory Board. [Read More.](#)

**April 13, 2010. Minneapolis** - Dr. Ivan Vesely, the founder of ValveXchange Inc., presented a review paper entitled "The Three Tenets of Good Valve Design: Where transcatheter Valves Fail", at the 2010 [Design of Medical Devices conference](#) in Minneapolis, Minnesota. Other noted invited speakers were Manny Villafona, the founder of St.Jude Medical, and Dr. Robert Levy, a pioneer in understanding prosthetic valve calcification. Dr. Vesely's presentation can be viewed [here](#).

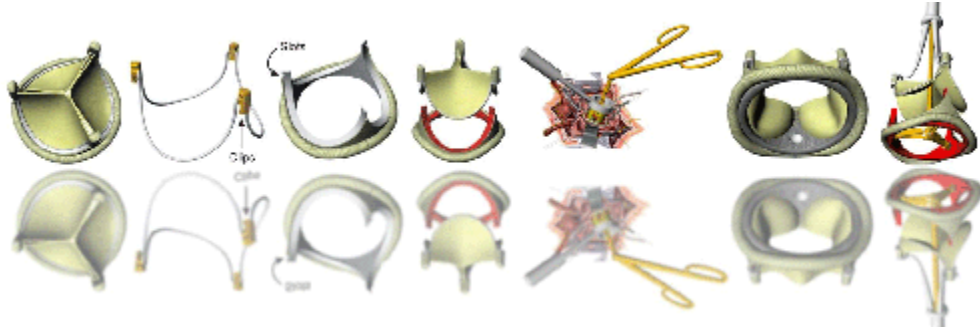
**January, 2010. Denver** - ValveXchange Inc. is pleased to announce that it has received a \$250,000 grant from the State of Colorado under the Bioscience Discovery Evaluation Grant Program (BDEGP). [Read More.](#)

**November 19, 2009. Aurora, CO** - ValveXchange Inc. recently executed a license agreement with the University of Colorado for a process to transform cardiac imaging data into high-quality three-dimensional models used for heart valve product development, clinician training, and pre-procedure planning. [Read More.](#)

**October, 2009. Denver** - ValveXchange Inc. is pleased to announce that Dr. Antonio Calafiore has joined the VXi Medical Advisory Board. Dr. Calafiore is recognized internationally for pioneering off-pump coronary artery bypass grafting and the "Calafiore technique" of myocardial preservation. Dr. Calafiore has recently moved from Italy to Riyadh, Saudi Arabia as the director of the Prince Sultan Cardiac Center. [Read More.](#)

**September, 2009. Denver** - ValveXchange Inc. is pleased to announce that Michael J. Mack, M.D., has joined the VXi Medical Advisory Board. Dr. Mack is Director of Cardiovascular Research and Cardiovascular Medicine of the Heart Hospital Baylor Plano and Director of Cardiovascular Surgery for the Baylor Healthcare System. He is considered to be the most noted authority on the emerging field of transcatheter valves. [Read More.](#)

**June, 2009. Denver** - ValveXchange Inc. announces that Walter Randolph "Randy" Chitwood, Jr., M.D., FACS, FRCS has joined the VXi Medical Advisory Board. Dr. Chitwood was the principal investigator of the FDA robotic mitral valve trials that led to approval for this use in the United States. Today, he is the world's leader in robotic mitral valve surgery. [Read More.](#)



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