From Dream to Reality

The PVT Story

the Israeli connection

Stan Rabinovich
Vice President, Discovery
Advanced Technology
Aortic Stenosis
Aortic Stenosis

- Severe Aortic Stenosis
  - Balloon Aortic Valvuloplasty
  - Aortic Valve Replacement Surgery
  - Non-Surgical Refusals
  - Medical Therapy
  - Asymptomatic
Balloon Aortic Valvuloplasty

- The First Percutaneous Approach
  - Balloon dilatation of the aortic valve
  - Popularized in the mid-1980’s and performed in many cath labs
  - Good acute results with low complications
  - 0.6 cm² valve area to 1.0 cm²
  - Poor patency: 75% restenosis at one year
Catheter-based Systems to treat AI/AS

Davis valve (1965)

Moulopoulos valve (1971)

Andersen valve (1992)
Andersen – Balloon-Expandable Valve

- First implantation in pig: 1989
- Porcine aortic valve sutured inside SS
- Stented valve compressed over triple balloon catheter: 41F
- First publication EHJ: 1992
- First patent issued: 1995
- IP acquired by Heartport
- No further development
Patents and Development Efforts

- Andersen, 1995 5,441,552
- Stevens, 1996 5,545,214
- Andersen, 1998 5,840,081
- Cribier filed PCT, 1996 PCT/EP97/07337
  - Issued on May 4, 2011 (EP 2000115 B1)
- Andersen, 2001 6,168,614

- Heartport attempted this project in 1993-1994 and filed patents on **REMOVING** the old valve with a catheter designed to cut out the valve
Rouen: first sketches

After balloon predilatation of the native valve
• 1985: BAV for calcific AS (>1,500 cases performed)

• 1990: First attempts of intra-aortic valve stent delivery in dogs

• 1995: Stent (Palmaz) implantations in the stenotic calcific aortic valve of human cadavers

• 1995-1996: Search for a company interested in development of percutaneous heart valve
Comments from medical device companies:

- “Interesting idea but not a priority”
- “Totally unrealistic, major technical issues”
- “Definitely impossible to stent a calcific aortic valve”
- “Occlusion of coronary arteries in 100% of cases”
- “Would never be approved by FDA”
- “Surgery covers 100% of the need. No indication”
- “Most stupid project ever heard…”
• 1996
  – JJIS negotiations with Cribier and Letac
  – Agreement was signed in August
  – Applied for European patent, assigned to Cordis
  – Program developed and transferred from BD to R&D
  – R&D never happened at Cordis

• 1998
  – Cordis terminated contract
Original Associates

- **Alain Cribier**
  - Pioneered Balloon Aortic Valvuloplasty (BAV) in 1985
  - Invented and pioneered Mitral Commissurotomy Valvuloplasty in 1995
  - Over 1,500 communications and publications

- **Stan Rowe & Stan Rabinovich**
  - Johnson & Johnson Interventional Systems (JJIS)
  - Marketing/Strategy/Clinical/Technical/BD/KOLs
  - Mktg Mgr/BENESTENT/Stent Mfg/IVUS/New Technology
Partnership

• 1998
  – Brainstorming session with Alain in Rouen
  – Meeting with Marty in Washington
  – Decision to develop Percutaneous Heart Valve
  – Created a partnership between physicians (Alain & Marty) and industry (Stan & Stan)
Pre-PVT Meetings in Israel June 1999

• 1999
  – Cribier had to make a payment to maintain the European patent application by June 30
  – Decided to raise $$ to fund development
  – Stan & Stan attended Interventional Cardiology meeting in Jerusalem
  – Presented to several VCs
  – Met with engineering company: ARAN R&D, Ltd.
    • Just decided to enter into medical device development
    • Interested in investing and developing
Percutaneous Valve Technologies, Inc. (PVT), a Delaware Corporation was incorporated on July 21, 1999

Founding Partners:
- Dr. Alain Cribier
- Dr. Martin Leon
- Stanley Rabinovich
- Stanton Rowe
PVT – Initial Developments with ARAN

• December 1999
  – Signed development agreement with ARAN R&D
    • Investment AND Development
    • Development up to feasibility proof defined as: PHV implantation in animal with two weeks follow up
    • Five Milestones
    • Warrants

• January 2000
  – Start development of polymeric Percutaneous Heart Valve (PHV)

• May 2000
  – Raised $500k from angel investors and founders
Itai Pelled, Assaf Bash, Netanel Benichou, Abi Zakai, Benjamin Spenser
Microsoft

Would you have invested?

Microsoft Corporation, 1978
2000 PVT Goals

- Develop aortic heart valves for the treatment of aortic stenosis delivered via a percutaneous route.

- Other therapeutic opportunities
  - mitral stenosis
  - aortic regurgitation
  - venous insufficiency
PVT – First Polymer Valves

The PVT Story at ICI 2015
PVT - Mounted Crimped PHV
PVT - Ongoing Animal Experiments

• Started in August 2000
• Valve implantations in sheep
• Use of a 22 Fr sheath introducer
• Implantations in thoracic aorta, native aortic valve, and native pulmonary valve
• Presentation at TCT 2000
Animal Experiments at CERA, Paris

A. Cribier

TCT Meeting, Washington, USA
What surgeons said about PHV to VC’s

• Don’t touch the pericardial tissue, it’s fragile and cannot withstand crimping to a smaller profile
• The native calcified aortic valve cannot be stented open
• If you tried to stent open the calcified native valve, you will cause strokes by embolizing the calcium and debris
• The THV cannot/will not be retained and will embolize itself
• THVs will have smaller valve areas and therefore be inferior to surgical valves in performance
• The THV cannot be made durable
• The THV will have perivalvular leaks which will cause endocarditis
• Cardiologists know nothing about Aortic Stenosis and should not treat these patients
PVT Financials

• October - December 2000
  – Andersen Patent Portfolio License Agreement negotiations (12 revisions)
  – Closed on December 27, 2000

• December 2000: Series A Financing
  – Raised $5.5M from:
    • Oxford Bioscience Partners       Jeff Barnes
    • Medica Venture Partners          Yuval Binur
PVT - Engineering Questions

- What compressive forces must the frame (stent) resist?
- How strong must we make the frame to form a circular valve?
- How can new manufacture a frame that large; no tubing that large?
- What material is preferred for the frame?
- How do we attach a fixed diameter valve to an expandable and collapsible frame?
- How do you make the attachment durable?
- How can we seal around the valve and prevent PVL? Without increasing profile?
- What is the optimal valve design for hemodynamics/profile/tissue damage? Unicuspid, bicuspid, tricuspid or quadracuspid?
- What is the optimal valve material? Polymers, co-polymers, tissue?
PVT - Valve Materials

- 316L Stainless Steel Stent
- Traditional Dacron/Suture
- Valve Material?
  - Started with polymers
    - Looked for polymeric partners
    - Attachment issues, sought alternatives
  - Sourced bovine pericardium
  - Sourced equine pericardium
    - Sourcing, processing, chemical treatment, qualification, expertise

December 14, 2015
Early PVT prototypes
PVT - Percutaneous Heart Valve

- Equine pericardium
- Highly resistant balloon expandable stent
- Optimal hemodynamics with durability > 5 years on bench testing
PVT - Cadaver Heart Study at AFIP
PVT – FIM on April 16, 2002
PVT, Ltd in June 2002
PVT Financials

- December 2002: Series B Financing
  - Strategic Investors:
    - Medtronic: $5M  Steve Oesterle
    - Boston Scientific: $5M  Paul LaViolette
  - Original VC’s:
    - Oxford Bioscience Partners: $2M  Jeff Barnes
    - Medica Venture Partners: $2M  Yuval Binur
PVT after ACC 2003

• Alain Cribier’s presentation on Rouen’s initial experience from clinical cases
  – Standing room only
  – Incredible interest
• O’Neill’s BRAVEHEART IDE submission
• Meeting at FDA
• First I-REVIVE case
• First case in Detroit
PVT History in a Nutshell (prior to EW)

- June 1999: Introduction to ARAN R&D
- July 1999: Founded PVT, Inc.
- January 2000: Official polymeric project initiation
- August 2000: First animal implantation
- March 2001: Opened PVT office in Fort Lee, NJ
- May 2001: Changed to tissue material
- April 2002: FIM case in Rouen
- May 2002: Formed PVT, Ltd.
- June 2002: Signed agreement with 3f Therapeutics
- December 2002: PHV1-23 design freeze
- March 2003: O’Neill’s IDE Submission (BRAVEHEART)
- July 2003: GLP animal study
- August 2003: Meeting at FDA
- August 2003: First I-REVIVE Case
• September 16
  – Meeting with Mike at TCT, Washington
• November 14
  – Meeting at the O’Hare airport, Chicago
• December 12
  – Signing of the Merger Agreement, Fort Lee
Edwards’ Acquisition of PVT

- **December 12, 2003**
  - Edwards and PVT signed a merger agreement to acquire PVT
  - PVT as a business unit will report to CEO

- **January 27, 2004**
  - Official closing and registration in Delaware
  - All PVT employees are retained
Edwards’ Acquisition of PVT

• A few words about Mike Mussallem (Edwards’ CEO)…
PVT Management at the Board Meeting
The acquisition of PVT gave Edwards access to a valve, a patent portfolio and a talented team of engineers.
THV Technology’s Creation

- New field of medicine
- New relationships, teamwork among physicians
- New medical device industries (accessories):
  - Large Diameter Dilatation Balloons
  - Embolic Protection Devices
  - Large Bore Closure Devices
  - Large Bore Access Devices: TF and TA
  - Introducers, Guidewires
  - Pacers, Inflators
  - Imaging technologies/modalities for diagnostic, guidance, positioning, deployment
History of Edwards’ Transcatheter Heart Valve Technology

- **First successful TAVR procedure in U.S.**
- **Landmark PARTNER clinical trials begin in U.S.**
- **Edwards SAPIEN valve approved in the U.S. for inoperable patients**
- **Edwards SAPIEN valve approved in U.S. for high-risk patients**
- **Edwards SAPIEN XT valve approved in U.S. for high or greater risk patients**
- **Edwards SAPIEN 3 valve approved in U.S. for high or greater risk patients**


- Edwards SAPIEN Valve
- Edwards SAPIEN XT Valve
- Edwards SAPIEN 3 Valve
Clinical Outcomes Improve as Therapy Evolves

Low Mortality and Stroke Rates
Patient selection, procedural techniques, device evolution

- RetroFlex 3 Delivery System
- NovaFlex+ Delivery System
- Edwards Commander Delivery System

Improved Vascular Access
Lower profile devices expands treatment possibilities

- RetroFlex 3 Introducer Sheath
- 22F
- Edwards eSheath Introducer Set
- 16F
- Edwards eSheath Introducer Set*
- 14F

Increased Treatment Range
Larger and smaller valves

- SAPIEN Valve 23 and 26 mm
- SAPIEN XT Valve 23, 26, 29 mm
- SAPIEN 3 Valve 20, 23, 26, 29 mm

*only used with 20, 23, 26 valve sizes
### Edwards SAPIEN 3 Valve Treats a Broad Annulus Size Range

Complete range of valve sizes expands the treatable patient population

<table>
<thead>
<tr>
<th>Valve Size</th>
<th>20 mm</th>
<th>23 mm</th>
<th>26 mm</th>
<th>29 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native Annulus Size By TEE</td>
<td>16-19 mm</td>
<td>18-22 mm</td>
<td>21-25 mm</td>
<td>24-28 mm</td>
</tr>
<tr>
<td>Native Annulus Area (CT)</td>
<td>273-345 mm²</td>
<td>338-430 mm²</td>
<td>430-546 mm²</td>
<td>540-683 mm²</td>
</tr>
<tr>
<td>Area-derived Diameter (CT)</td>
<td>18.6-21 mm</td>
<td>20.7-23.4 mm</td>
<td>23.4-26.4 mm</td>
<td>26.2-29.5 mm</td>
</tr>
</tbody>
</table>
SAPIEN 3 valve builds upon the proven benefits of the SAPIEN platform

Frame Design
- Enhanced frame geometry for ultra-low delivery profile
- High radial strength for circularity and optimal hemodynamics

Bovine Pericardial Tissue
- Optimized leaflet shape
- Carpentier-Edwards ThermaFix* process for anti-calcification

Low Frame Height
- Respects the cardiac anatomy

Outer Skirt
- Designed to reduce paravalvular leak

<table>
<thead>
<tr>
<th>SAPIEN 3 Valve Size</th>
<th>Inner Skirt Height</th>
<th>Outer Skirt Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 mm</td>
<td>11.7 mm</td>
<td>6.6 mm</td>
</tr>
<tr>
<td>26 mm</td>
<td>12.8 mm</td>
<td>7.0 mm</td>
</tr>
<tr>
<td>29 mm</td>
<td>14.4 mm</td>
<td>8.1 mm</td>
</tr>
</tbody>
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SAPIEN 3 Valve
- Nominal Height
  - 23 mm: 18 mm
  - 26 mm: 20 mm
  - 29 mm: 22.5 mm
- Crimped Height
  - 23 mm: 24.5 mm
  - 26 mm: 27 mm
  - 29 mm: 31 mm

December 14, 2015
The PVT Story at ICI 2015
Edwards Commander Delivery System
Designed for reduced vascular complications

Ultra-low Delivery Profile, 14F eSheath Compatible*

Dual Articulation for Coaxiality Even in Challenging Anatomies

Trusted Balloon-expandable Design with Improved Control of Valve Positioning

*14F eSheath compatible for 20, 23, and 26 mm valves. 16F eSheath compatible for 29 mm valve.
It’s about the patients…
Helping Patients is Our Life’s Work, and

Edwards