Medical Device Development in a Large Multinational Company

Stanton Rowe
Corporate Vice President
Chief Scientific Officer
An Amazing Job

What is it like to develop a life-saving device and meet some of patients whom have benefitted?
What is it like…?

- It takes talent and time and a medical problem to solve that you really understand.
- It takes resources; money, capabilities, testing, quality & regulatory talent.
- It is highly regulated and the processes and requirements are understood.
- Innovation (not iteration) in a large or small company means about a 25-40% success rate.
What does success look like?

- You develop something proprietary - patents matter!
- You develop something that has sustainable competitive advantage
- You develop something that proves clinical benefit in clinical trials
- You develop something that payors, CMS or patients value and will pay for
- You develop something that is sold into the market and helps patients live better lives
Current Therapy- Open Heart Surgery
Cardiac Cath Procedure
Percutaneous Valve Technologies, Inc. (PVT)

- 1999 Incorporated - Founding Partners
  - Dr. Alain Cribier
  - Dr. Martin Leon
  - Stanley Rabinovich
  - Stanton Rowe

- May-2000
  - Angels, founders and Aran funded 9 months $740k at $2M valuation
Engineering questions

- What compressive forces must the frame (stent) resist?
- How strong must we make the frame to form a circular valve?
- How can we 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?
What surgeons said about THVs... (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
Eugène à cœur vaillant.

Première mondiale au CHU de Rouen : le professeur Alain Cribier et son équipe ont posé une valve cardiaque artificielle sans chirurgie. Inopérable hier, Eugène, 57 ans, récupère.

Une première mondiale, aboutissement de quinze années de recherches, ça se raconte et ça se fête. Hier au CHU de Rouen, le professeur Alain Cribier, chef du service de cardiologie, s’est retrouvé au centre de toutes les sollicitations.

Alors il a expliqué, détaillé, partagé sa réussite en racontant l’aventure scientifique et humaine qui a permis d’obtenir un tel résultat. Car la technique d’implantation sans chirurgie d’une valve aortique, inventée sous son impulsion, a permis mardi dernier de sauver la vie d’un homme de 57 ans, inopérable et condamné à très brève échéance.
PARTNER Manuscripts in NEJM
(October, 2010 – May, 2012)

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael J. Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Block, M.D., Robert A. Guyton, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Pamela S. Douglas, M.D., John L. Petersen, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duvloao Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators

Transcatheter and Surgical Aortic-Valve Replacement in High-Risk Patients

Craig R. Smith, M.D., Martin B. Leon, M.D., Michael J. Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., Matthew Williams, M.D., Todd Dewey, M.D., Samir Kapadia, M.D., Vasilis Babaliaros, M.D., Vinod H. Thourani, M.D., Paul Corso, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duvloao Wang, Ph.D., and Stuart J. Pocock, Ph.D., for the PARTNER Trial Investigators

Transcatheter Aortic-Valve Replacement for Inoperable Severe Aortic Stenosis


Two-Year Outcomes after Transcatheter or Surgical Aortic-Valve Replacement

All Cause Mortality

Δ at 1 yr = 20.0%
NNT = 5.0 pts

![Graph showing all-cause mortality over time with Standard Rx and TAVI lines. The graph indicates a difference of 20.0% at 1 year with an NNT of 5.0 pts.]

<table>
<thead>
<tr>
<th>Numbers at Risk</th>
<th>TAVI</th>
<th>179</th>
<th>138</th>
<th>122</th>
<th>67</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Rx</td>
<td>179</td>
<td>121</td>
<td>83</td>
<td>41</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>
No structural valve deterioration that required re-intervention.

Mack M et al. Lancet 2015;6736(15)60308-7
### SAPIEN Platforms in PARTNER

**Device Evolution**

<table>
<thead>
<tr>
<th>Valve Technology</th>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
<th>SAPIEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Valve Technology" /></td>
<td><img src="image" alt="SAPIEN Valve" /></td>
<td><img src="image" alt="SAPIEN XT Valve" /></td>
<td><img src="image" alt="SAPIEN 3 Valve" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sheath Compatibility</th>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
<th>SAPIEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Sheath Compatibility" /></td>
<td>22-24F</td>
<td>16-20F</td>
<td>14-16F</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Available Valve Sizes</th>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
<th>SAPIEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Available Valve Sizes" /></td>
<td>23 mm</td>
<td>26 mm</td>
<td>23 mm</td>
</tr>
</tbody>
</table>
Unadjusted Time-to-Event Analysis
All-Cause Mortality and All Stroke (AT)

Number at risk:
P2A Surgery 944
S3 TAVR 1077

Months from Procedure

0 3 6 9 12

P2A Surgery
SAPIEN 3 TAVR

All-Cause Mortality / Stroke Rate (%)

0 10 20 30 40

3.7% 9.7% 10.8% 18.8%
TAVR Experience Has Changed Our Understanding of Aortic Stenosis

2015 Severe Symptomatic AS Patients in the U.S.¹

Observations
For Severe, Symptomatic AS Patients

- Advanced age is a barrier not only to treatment but diagnosis
  - A safe interventional procedure has the potential to reduce these barriers

- Historically, patient treatment rates decreased with age
  - Opportunity for TAVR to lift treatment rates in older age groups

Total 1-Year Costs

Δ = -15,511 (p<0.001)

- S3-TAVR:
  - Follow-up: $26,861
  - Index Hospitalization: $54,117
  - Total: $80,977*

- SAVR:
  - Follow-up: $38,238
  - Index Hospitalization: $58,250
  - Total: $96,489*

* Trimmed means
Conclusions

- For patients with severe AS and intermediate surgical risk similar to those enrolled in the PARTNER 2A and S3i trials, TAVR should be the preferred strategy based on both clinical and economic considerations.
It’s About Patients!
Total US VC Investment to CA

US Venture Capital Investments
$82.7B $55.9B

CA Venture Capital Investments
$34.5B $33.6B

2017 California Digital Health VC Investment by Category

Digital Diagnostics, Devices & Therapies $772M
Consumer Health and Wellness $356M
Care Management and Administration $339M
Life Sciences Tools $242M
Analytics / big data $238M
Wearables / biosensing $173M
Other $380M
Telemedicine $75M
Genomics and sequencing $44M
Remote patient monitoring $12M

2017 California Life Sciences Wages by Sector

Average Wage Total Wages

Academic Research $73,007 $3.1B
Biopharmaceuticals $152,703 $7.7B
Biorenewables $72,696 $2.78M
Medical Devices, Instruments and Diagnostics $94,528 $7.3B
Research & Development and Testing Laboratories $140,574 $10.5B
Wholesale Trade $101,261 $5.1B

Total $113,674 $34.0B


Total Life Sciences Employees by Sector

in California, 2016

77,278

50,747

50,496

41,950

3,822

Medical Devices, Instruments & Diagnostics
Research & Development & Testing Laboratories
Wholesale Trade
Biopharmaceuticals
Academic Research
Biorenewables

Edwards

Helping Patients is Our Life’s Work, and life is now