Venture Funding for Regenerative Medicine Companies

Gregory A. Bonfiglio
Proteus Venture Partners

CIRM ICOC Loan Task Force – January 16, 2008
Agenda

- Proteus Venture Partners: Overview
  - Who Are We?
- Funding Environment for RM Companies
  - Where Are We And How Did We Get Here?
  - Current Market Dynamics: Technology Push & Market Pull
- Access To Venture Capital
  - Funding & Value Creation: The Valley of Death
  - Venture Capital Metrics: What Do VCs Want?
  - Typical Venture Terms: What Do VCs Get?
Proteus Fund: Summary

- **Regenerative Medicine Fund**
  - Stage Agnostic
  - Geographically Diverse
  - Top Tier Venture Returns
  - 1st Mover Advantage

- **Technology Focus**
  - Cell Therapies
  - Tissue Engineering
  - Tools & Enabling Devices
  - Aesthetic Medicine

- **Addressing Large Markets**
  - Aging Population
  - Large Unmet Medical Needs
  - Increasing Healthcare Spend

- **World Class Team**
  - Core Team with Complementary Skills
  - Deep Domain Expertise
  - Outstanding SAB & Strategic Partners
  - Industry Visibility & Leadership

- **Disciplined Investment Approach**
  - Proprietary Deal Flow
  - Rigorous Due Diligence
  - Build Value Thru Active Management
  - Timely Exits

- **Target Investments**
  - Outstanding Technology & Team
  - Defensible IP
  - Viable Business Model
  - Near Term Path to Clinic or Revenues
Funding Environment for RM Companies

- Where Are We And How Did We Get Here?
- Current Market Dynamics: Technology Push & Market Pull
Gartner’s Hype Cycle of Emerging Technologies

- Technology Trigger
- Peak of Inflated Expectations
- Trough of Disillusionment
- Slope of Enlightenment
- Plateau of Productivity

Visibility

Time
Funding Environment: 1st Cycle 1985-2002

- Cell Therapies & Tissue Engineering Were Hot In The Early 1990s
  - VCs Funded The Sector Aggressively
  - Research Projects
  - Grand Business Visions

- Many New Companies Created
  - ATS, Curis, Systemix, Bresagen, Organogenesis

- Products Launched
  - Carticel; Apligraf; Dermagraf

- Market Peaked in 2000
  - 3000 jobs; 73 companies; total market cap of $2.6B
  - Time Magazine: “TE Number 1 Job in USA”
Funding Environment: 1st Cycle 1985-2002

- Market Collapsed in 2001
  - ATS, Organogenesis filed Bk in 2002

- Political Controversy Over hESCs

- Many High Profile Failures or Retrenchments
  - ATS, Curis, PPL, Bresagen, BioTransplant, Organogenesis

- VCs Withdrew Support For the Sector
  - Overall Healthcare Funding Remained Strong
  - But RM Companies Got Under 2%
  - Many Big VCs had Nuclear Bombs in Portfolio
Funding Environment: A New Cycle

- **Gov’t Funding Increasing**
  - California Prop 71 & Wisc, NJ, NY, MD, etc
  - UK; Singapore; Australia; Canada

- **Political Risk Declining**

- **RM Market Maturing**
  - Technology Advancing
  - Products Entering the Market

Stem Cell Poll 2006

*Next, I’m going to read you a list of issues. Regardless of whether or not you think it should be legal, for each one, please tell me whether you personally believe that in general it is morally acceptable or morally wrong. How about -- medical research using stem cells obtained from human embryos?*
Technology Push: Beginning the 2nd Half of the Gartner Curve

Visibility

Technology Trigger

Plateau of Productivity

Peak of Inflated Expectations

Trough of Disillusionment

Slope of Enlightenment

Stage of Development

- 1980 Early TE research (MIT)
- 1985 Term “TE” coined
- 1986 ATS & Organogenesis founded
- 1988 SyStemix founded
- 1992 Geron founded
- 1996 Launch of Intercytex
- 1999 TE bladders in clinic
- 1999 First TE product FDA approved (Apligraf)
- 1998 Plan to build human heart in 10 years
- 1998 Human ESCs first derived
- 1997 Dolly the sheep
- 1997 Ortec FDA approved
- 1999 TE blood vessel enters clinic
- 1999 TE bladders in clinic
- 1999 Intercytex founded
- 2000 Apligraf FDA approved
- 2001 Ortec FDA approved
- 2001 TE blood vessel enters clinic
- 2001 Dermagraft FDA approved
- 2001 Bush “partial ban” on HESCs
- 2002 ISSCR founded
- 2002 ATS + Organogenesis file Chapter 11
- 2003 UK Stem Cell Bank set up
- 2005 CIRM founded
- 2006 Carticel - 10,000 patients
- 2006 hESCs derived without harming embryo
- 2006 Batten’s Disease trial
- 2006 Remeuron file IND for stroke trial
- 2007 Apligraf - 200,000 patient therapies
- 2007 Mouse fibroblast to mESCs
- 2007 Intercytex start Phase 3 ICX-PRO
- 2007 Osiris Named Biotech Co. of the Year
- 2008 Geron expected to file IND - spinal cord

2001: 3000 jobs, 73 firms, mkt cap > $3B

1980 Early TE research (MIT)

1985 Term “TE” coined

1986 ATS & Organogenesis founded

1988 SyStemix founded

1992 Geron founded

1996 Launch of Intercytex

1999 TE bladders in clinic

1999 First TE product FDA approved (Apligraf)

1998 Plan to build human heart in 10 years

1998 Human ESCs first derived

1997 Dolly the sheep

1997 Ortec FDA approved

1999 TE blood vessel enters clinic

1999 TE bladders in clinic

1999 Intercytex founded

2000 Apligraf FDA approved

2001 Ortec FDA approved

2001 TE blood vessel enters clinic

2001 Dermagraft FDA approved

2001 Bush “partial ban” on HESCs

2002 ISSCR founded

2002 ATS + Organogenesis file Chapter 11

2003 UK Stem Cell Bank set up

2005 CIRM founded

2006 Carticel - 10,000 patients

2006 hESCs derived without harming embryo

2006 Batten’s Disease trial

2006 Remeuron file IND for stroke trial

2007 Apligraf - 200,000 patient therapies

2007 Mouse fibroblast to mESCs

2007 Intercytex start Phase 3 ICX-PRO

2007 Osiris Named Biotech Co. of the Year

2008 Geron expected to file IND - spinal cord
Funding Environment: Market Dynamics

- Technology Push
  - Research programs proliferating: 65+
  - Technology maturing
  - Clinical activity accelerating (800+ FDA trials)
  - Increased Government Funding

- Market Pull
  - Healthcare Spend is 17% of US GDP Heading Towards 23%
  - Demographics: aging populations
  - Large unmet medical needs
  - Pharma pipeline diminishing
  - Public markets receptive

RM is Maturing after 40 Years of Development

Companies Emerging to Fill the Gap

300+ Companies

The Market is at a Crucial Inflection Point
Technology Push: RM Programs Proliferating

Over 65+ Regenerative Medicine Programs Nationwide

Source: TFG Analysis
Technology Push: Increased Gov’t Funding

Worldwide Funding for RM Expected to Reach $14B Worldwide in 10 years

US Total - ~$1B/year
- US (Federal) - $600M/year
- California - $300M/year
- Wisconsin - $375M for research institute, $5M/year
- New Jersey - $250M for stem cell research centers, $5M/year
- Connecticut - $20M/year
- Maryland - $15M/year
- Illinois - $10M/year

Canada - $30M

UK - $54M

Germany - $10M

Switzerland - $4M

Israel - $15M

China & South Korea focused funds in regenerative medicine

Singapore - $20M
$4B on Biotech through 2006 with $8B more committed through 2010

Australia - $50M

Source: Media Articles, Navigant, TFG Analysis
Technology Push: Products Entering the Market

90+ Programs In Development – 30+ Clinical Trials – 25+ Products Launched

Products in Development By Stage

<table>
<thead>
<tr>
<th>Company</th>
<th># Products</th>
<th>Company</th>
<th># Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geron</td>
<td>6</td>
<td>Osiris</td>
<td>2</td>
</tr>
<tr>
<td>Living Cell</td>
<td>4</td>
<td>ReNeuron</td>
<td>2</td>
</tr>
<tr>
<td>Isolagen</td>
<td>3</td>
<td>Saneron</td>
<td>2</td>
</tr>
<tr>
<td>Bioheart</td>
<td>2</td>
<td>Sangamo</td>
<td>2</td>
</tr>
<tr>
<td>Cellerant</td>
<td>2</td>
<td>StemCells</td>
<td>2</td>
</tr>
<tr>
<td>CellMed</td>
<td>2</td>
<td>TiGenix</td>
<td>2</td>
</tr>
<tr>
<td>Freserius</td>
<td>2</td>
<td>Other</td>
<td>47</td>
</tr>
<tr>
<td>Gamida</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 94

Products in Devel. by Therapeutic Area

- Skin disorder cell therapy
- Chondrocytes
- ICX PRO (varicose ulcer)

Source: ADIS R&D Insight
RM Revenues Are Ramping: $130M in 2001 to $1.15B in 2006

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Market</th>
<th>2001 ($USM)</th>
<th>2005 ($USM)</th>
<th>2006 ($USM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic</td>
<td>INFUSE</td>
<td>BMP (US)</td>
<td>0</td>
<td>500.0*</td>
<td>570</td>
</tr>
<tr>
<td>LifeCell</td>
<td>AlloDerm, Cymetra, Repliform, GraftJacket, AllocraftDBM</td>
<td>Skin, Urology, Bone (US)</td>
<td>26.6</td>
<td>88.9</td>
<td>136.8</td>
</tr>
<tr>
<td>Genzyme</td>
<td>Carticel</td>
<td>Cartilage (US)</td>
<td>18.4</td>
<td>66</td>
<td>67.5</td>
</tr>
<tr>
<td>Tutogen</td>
<td>Tutoplast</td>
<td>Bone</td>
<td>12.8</td>
<td>31.9</td>
<td>37.9</td>
</tr>
<tr>
<td>Organogenesis</td>
<td>Apligraf</td>
<td>Skin (US)</td>
<td>20.0*</td>
<td>40.0*</td>
<td>45.0*</td>
</tr>
<tr>
<td>Interpore (Biomet)</td>
<td>AGF, Pro Osteon, Bone Plast</td>
<td>Orthobiologics</td>
<td>20.1</td>
<td>21.0*</td>
<td>22.0*</td>
</tr>
<tr>
<td>Integra Life Sciences</td>
<td>Neuragen, Integra, Newdeal, Duragen, Collagen Sponge</td>
<td>Skin, Orthopedics (US)</td>
<td>8.7</td>
<td>135</td>
<td>166</td>
</tr>
<tr>
<td>Biotissue technologies</td>
<td>BioSeed-S, BioSeed-C, BioSeed Oral Bone</td>
<td>Skin, Cartilage, Bone (GER)</td>
<td>1.3</td>
<td>2.0*</td>
<td>2.0*</td>
</tr>
<tr>
<td>Co.don</td>
<td>Chondrotransplant</td>
<td>Cartilage</td>
<td>1.6</td>
<td>0.4</td>
<td>0.6*</td>
</tr>
<tr>
<td>Stryker</td>
<td>OP-1</td>
<td>BMP (US)</td>
<td>0.5*</td>
<td>23.0*</td>
<td>25.0*</td>
</tr>
<tr>
<td>Orquest (DePuy)</td>
<td>Healos</td>
<td>Bone, Cartilage, Soft Tissue (US)</td>
<td>1.1*</td>
<td>2.0*</td>
<td>2.0*</td>
</tr>
<tr>
<td>ReGen</td>
<td>Collagen Meniscus Implant</td>
<td>Cartilage (US Trials)</td>
<td>0.5</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Isolagen</td>
<td>Autologous Fibroblasts</td>
<td>Skin</td>
<td>0</td>
<td>8.8</td>
<td>6.1</td>
</tr>
<tr>
<td>Others</td>
<td>Various</td>
<td>Various</td>
<td>10</td>
<td>40.0*</td>
<td>60*</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>~$130M</td>
<td>~$900M</td>
<td>~$1,150M</td>
</tr>
</tbody>
</table>

Source: PJB Publications 2003; Equity Research; Company websites; SEC; *=Estimated
## New RM Companies Forming

<table>
<thead>
<tr>
<th>Cell Therapy</th>
<th>Cell Therapy (Cont.)</th>
<th>Genomics/Tools</th>
<th>Tissue Engineering</th>
<th>Aesthetic Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Cell Technology</td>
<td>CytoMatrix</td>
<td>Aclara Biosciences</td>
<td>Aastrom Biosciences</td>
<td>Allergan</td>
</tr>
<tr>
<td>Alexion Pharmaceuticals</td>
<td>Cytori Therapeutics</td>
<td>Affymetrix</td>
<td>Befutur Biotechnologies</td>
<td>Artefill</td>
</tr>
<tr>
<td>Allicells, LLC</td>
<td>Dendreon</td>
<td>Agilent Technologies</td>
<td>BioHeart Inc.</td>
<td>Artes Medical, Inc.</td>
</tr>
<tr>
<td>Amcell, Inc.</td>
<td>Desmos, Inc.</td>
<td>BioAnalyte</td>
<td>BioMimetic Pharmaceuticals</td>
<td>Candela Corporation</td>
</tr>
<tr>
<td>Anergan</td>
<td>Educell d.o.o</td>
<td>Celera Genomics</td>
<td>Collect Bio</td>
<td>Galderma</td>
</tr>
<tr>
<td>Argos Therapeutics</td>
<td>ES Cell International</td>
<td>CuraGen Corporation</td>
<td>Chrysalis BioTechnology</td>
<td>Genaera</td>
</tr>
<tr>
<td>Athersys</td>
<td>Gamida Cell</td>
<td>Diversa Corporation</td>
<td>Co.Don</td>
<td>Inamed</td>
</tr>
<tr>
<td>BioE</td>
<td>GenOWay</td>
<td>Geneos</td>
<td>CryoLife</td>
<td>Intercytx</td>
</tr>
<tr>
<td>Biohybrid Technologies</td>
<td>Geron</td>
<td>GeneLogic</td>
<td>Cytograft Tissue Engineering</td>
<td>Karo Bio</td>
</tr>
<tr>
<td>BioMark International</td>
<td>Histostem</td>
<td>HGSI</td>
<td>Dentigenix</td>
<td>Ligand</td>
</tr>
<tr>
<td>Cell Transplant</td>
<td>Interpore International</td>
<td>Illumina, Inc.</td>
<td>Encelle</td>
<td>MediCor</td>
</tr>
<tr>
<td>Celltris AB</td>
<td>Islet Technology, Inc.</td>
<td>Lab Key</td>
<td>ExacTech</td>
<td>Mentor</td>
</tr>
<tr>
<td>Cellerix</td>
<td>Ixion Biotech</td>
<td>Lexicon</td>
<td>Kourion Therapeutics</td>
<td>Milbar Labs</td>
</tr>
<tr>
<td>Cellex Biosciences</td>
<td>Medra, Inc.</td>
<td>Luminex Corporation</td>
<td>MG Biotherapeutics</td>
<td>Nastech</td>
</tr>
<tr>
<td>Cellpro, Inc.</td>
<td>Nephros Therapeutics</td>
<td>Myriad Genetics</td>
<td>Neuronyx Inc.</td>
<td>Neurogen</td>
</tr>
<tr>
<td>CepTor</td>
<td>Orion Biosolutions</td>
<td>Nanogen, Inc.</td>
<td>Orthovita</td>
<td>OrthoNeutrogena</td>
</tr>
<tr>
<td>Chromos</td>
<td>Progenitor Cell Therapy</td>
<td>Orchid Biosciences</td>
<td>Osiris Therapeutics</td>
<td>Pherin Pharmaceuticals</td>
</tr>
<tr>
<td>Circe Biomedical, Inc.</td>
<td>ReNeuron</td>
<td>Perkin Elmer, Inc.</td>
<td>Osteotech</td>
<td>Predix Pharma</td>
</tr>
<tr>
<td>Collagen Corporation</td>
<td>Stem Cell Technologies</td>
<td>Proteome Software</td>
<td>Regeneration Technologies</td>
<td>Phytopharm</td>
</tr>
<tr>
<td>Creative Biomolecules</td>
<td>StemCells, Inc.</td>
<td>Sage-N Research</td>
<td>Selective Genetics</td>
<td>Q-med</td>
</tr>
<tr>
<td>Cryolife, Inc.</td>
<td>Theravita Inc.</td>
<td>Sequenom</td>
<td>Thermogenesis</td>
<td>Sapphire Therapeutics</td>
</tr>
</tbody>
</table>

Public Markets Increasingly Receptive to RM Companies

15+ RM Companies are Already Public in the US

7 Public Companies
Average: $124M each
- Aastrom
- Cell Genesys
- Cell Therapeutics
- Geron
- Lifecell
- Stem Cell Innovation
- Stem Cells Inc.

Plus 2
Average: $111M each
- Curis
- Isolagen

Plus 6
Average: $234M each
- ACT
- Intercytex
- Stem Cell Sciences
- Stem Cell Therapy International
- Viacell
- Osiris

Source: Yahoo Finance; Company Websites; SEC
## Public Markets Are Rewarding Clinical Progress

<table>
<thead>
<tr>
<th>Company</th>
<th>Product / Stage</th>
<th>Market</th>
<th>Revenue</th>
<th>Mkt Cap Range / M&amp;A</th>
</tr>
</thead>
<tbody>
<tr>
<td>AnorMED</td>
<td>Mozobil, Phase III</td>
<td>Hematopoietic stem cell transplantation</td>
<td>&lt;$1M</td>
<td>Acquisition by Genzyme: $580M (10/2006)</td>
</tr>
<tr>
<td>Aastrom Biosciences</td>
<td>Tissue Repair Cell (TRC) technology: Ph III; Ph IIb Ph II</td>
<td>bone regen-osteonecrosis of the femoral head critical limb ischemia non-union fracture</td>
<td>&lt;$1M</td>
<td>$140M ($128 - $202M)</td>
</tr>
<tr>
<td>Dendreon</td>
<td>Provenge,:FDA review (prostrate cancer) Neuvenge: Ph I (breast, ovarian, colon cancer)</td>
<td>Cellular immunotherapy, monoclonal antibody, and small molecule product candidates to treat various cancers</td>
<td>&lt;$1M</td>
<td>$640M ($301M - $2.1B)</td>
</tr>
<tr>
<td>Geron</td>
<td>Filing IND for spinal cord early 2008</td>
<td>treatment of cancer, spinal cord injury, heart failure, diabetes, and HIV/AIDS</td>
<td>&lt;$4M</td>
<td>$551M ($425M - $753M)</td>
</tr>
<tr>
<td>Intercytex</td>
<td>ICX-PRO, Ph III – in Ph III for VLUs &amp; Ph II for DFUsVAVELTA®, Ph II ICX-TRC, Ph II</td>
<td>Stimulate active repair in chronic wounds Facial rejuvenation Hair regeneration</td>
<td>&lt;$1M</td>
<td>$90M (LSE-AIM mkt)</td>
</tr>
<tr>
<td>LifeCell</td>
<td>AlloDerm; GraftJacket; AlloCraft</td>
<td>Tissue-based prods for reconstructive, orthopedic, and urogynecologic surgical procedures</td>
<td>$166M</td>
<td>$1.3B ($650M - $1.3B)</td>
</tr>
<tr>
<td>Osiris</td>
<td>Prochymal, Ph III &amp; II Provaceel, a phase I</td>
<td>GVHD &amp; Crohn’s Disease Acute MI</td>
<td>$10M</td>
<td>$377M ($290M - $847M)</td>
</tr>
<tr>
<td>ViaCell</td>
<td>UC storage Pre-clinical work in cancer, cardiac &amp; diabetes</td>
<td>Collecting and preserving stem cells from umbilical cord blood</td>
<td>$59M</td>
<td>$300 (purchased by PerkinElmer 10/02/07 – 52% premium)</td>
</tr>
</tbody>
</table>
Venture Capitalists Getting Back in the Game

FORGET BLOOD-GET INTO STEM CELLS.
RM Companies - Access To Venture Capital

- Funding & Value Creation: The Valley of Death
- Venture Capital Metrics: What Do VCs Want?
- Typical Venture Terms: What Do VCs Get?
RM Product Development Timeline

### Probability of success

- **Basic & Discovery Research**
  - Proof of Concept: 66%
- **Preclinical Research**
  - Therapeutic Candidate: 70%
- **Preclinical Development**
  - 1-3 years: 40%

### Steps

- **Preclinical Development**
  - 1-3 years
- **Clinical Phase I**
  - 1.4-1.8 year: PII
- **Clinical Phase II**
  - 2.5-3.8 years: PII
- **Clinical Phase III**
  - 1.4-1.8 year: PIII
- **Market**
  - Product Release

### Outcome

- **PI** $10-15MM
- **PII** $20-25MM
- **PIII** $50-75MM
- **Product Release** $75-100MM

### Investment Amount

- **Universities, Research Institutes, Hospitals** $5-10MM
- **Big Pharma / Bio** $75-100MM

### Key Metrics:

- **Average Time to Market:** 10-15 Years
- **Average Costs:** $1B
- **Failure Rate:** @90%
- **Less than 30% of approved drugs recoup development costs**
Valuation Analysis On Risk Adjusted NPV

FMV = ~5x peak year revenues of $500M discounted by probability of launching

Ind. Period ROI*: 19%
Cumulative ROI**: 19%

Phase of Development

RM Company Funding Vacuum: *The Valley of Death*

Time to *Start of Phase 3 trials* can be up to 7-10 years

Time to *1st Venture Interest* can be up to 5-6 Years

**“Valley of Death”**

- RESEARCH (in vitro/lab)
- DEVELOPMENT (Animal studies)
- CLINICAL TRIALS (Phase 1 and 2)

Grant/Seed Money → Typical VC Investment → Potential Exits
VC Metrics: What Do VCs Want?

- Proprietary Commercial Technology
  - Great Science ≠ Great Business
  - Core Research Completed
  - Proof Of Concept Established

- Strong Management Team
  - Board
  - SAB

- Solid Intellectual Property Position
  - Freedom To Operate
  - Defensible IP (Patents & Trade Secrets)

- Large Market Opportunity
  - Target markets > $1B/year

- Defensible Business Model
  - Allogeneic v. Autologous
  - Product v. Service

- Differentiation
  - How Is Your Approach Different?
  - Why Is It Better?

- Exit Strategy
  - IPO Vs. M&A (Attractive Products For Acquirer)
  - Realistic Timeframe

- Acceptable Risk/Return Profile
  - Multiple Chances To Win
Typical VC Terms: What Do VCs Get?

- **Valuation**
  - % Ownership; Dilution
- **Dividend Rate**: 8%
- **Preferred Return**: 1X-3X
- **Anti-Dilution Protection**
  - Full Ratchet; Weighted average
- **Protective Provisions**
- **BOD Seat**
- **Participation Rights**
  - Right of First Refusal; Follow-on financings
The Final Word

"One embryonic stem cell for you... one for you... one for you..."
Appendices
RM Commercialization Challenges

- Technology Issues
- Business Models
- IP Issues
- Regulatory Hurdles
## Commercialization Challenges: Technology

<table>
<thead>
<tr>
<th>R&amp;D</th>
<th>Manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Creation and Characterization of Optimal Cells for Therapy</td>
<td>- Technologies for Scale-Up</td>
</tr>
<tr>
<td>- Contaminant Free Cell Lines</td>
<td>- Commercial Quantities of</td>
</tr>
<tr>
<td>- Development of Scaffolds &amp; Matrices for Tissue Engineering</td>
<td>- Product</td>
</tr>
<tr>
<td>- Safe &amp; Reliable Expansion</td>
<td>- Pathogen Free</td>
</tr>
<tr>
<td>- Directed Differentiation</td>
<td>- Consistent Lots</td>
</tr>
<tr>
<td>- Imaging Technology and Biological Markers to Track Cell Migration &amp; Engraftment</td>
<td>- Reliable Preservation Methods</td>
</tr>
<tr>
<td></td>
<td>- Control CoGs</td>
</tr>
<tr>
<td></td>
<td>- Standardization in the Field</td>
</tr>
</tbody>
</table>
Commercialization Challenges: Business Models

**Autologous Model**

- Using Pts Own Cells/ Tissue for Therapeutic Effect
  - Personalized Medicine

- Advantages:
  - Easier Regulatory Path (GTP)
  - No Immune Response

- Challenges:
  - Doesn’t Scale
  - COGS

**Allogeneic Model**

- Universal Cells in a Bottle
  - Big Pharma “Drug Model”

- Advantages:
  - Scalable
  - Low COGS

- Challenges:
  - More Difficult Regulatory Path
  - Immune Response

**Service vs. Product**
RM Business Models: Major Hurdles

Commercialization Challenges: Value Chain Perspective

R&D
- Isolate and Expand Cells or Tissue
- Prove are safe and effective
- Overcome immunology barrier

Regulatory
- Meet std’s for product assessment
- Comply with Applicable Clinical Guidelines

Manufacturing
- Viable Business Model
- Control CoGs
- Manufacture Commercial Quantities of Product

Sales & Marketing
- Simplify into a marketable “product”
- Establish Appropriate Distribution Channels

Autologous Hurdles

Allogeneic Hurdles
## RM Business Models: *Autologous v. Allogeneic*

### Broad Product & Large Patient Base

**Flawed Model?**
- Therapeutic benefit must be extraordinary
- Cost structure is not scalable
- Competing with lower cost therapy
- High risk of substitution & relatively low barriers to competitive entry

**Large Pharma Model**
- Low COGS: Cost structure is scalable
- Lower cost therapy targeted to large patient populations
- Can compete against biologics & possibly small molecules
- Immunogenicity is major issue

### Niche Products & Small Patient Base

**Current Model**
- Small populations with no current efficacious therapy
- “Salvage” therapies
- Can be profitable but is not scalable
- Creates strong relationships with caregivers and patients

**Specialty Biotech Model**
- Efficacious therapy will target populations with high unmet needs
- Moderate COGS
- Cost structure can possibly be spread across multiple diseases

### Autologous vs. Allogeneic

- **Autologous**
  - Low COGS: Cost structure is scalable
  - Lower cost therapy targeted to large patient populations
  - Can compete against biologics & possibly small molecules
  - Immunogenicity is major issue

- **Allogeneic**
  - Efficacious therapy will target populations with high unmet needs
  - Moderate COGS
  - Cost structure can possibly be spread across multiple diseases

---

*Moving From Core Technology to Commercial Product is a Major Challenge*
Autologous Model: Challenges Are Scale and Competition

**Autologous Promise**

<table>
<thead>
<tr>
<th></th>
<th>Promise</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven safe and efficacious cell source</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Overcome immunology barrier</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Standards for product assessment</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cooperate with regulatory authorities</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Achieve scaleable cell expansion</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Simplify into a ‘marketable’ product</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

**Multiple Business Models Emerge**
- Therapeutic Product
  - Novocell
  - Aastrom
  - ACTC
- Device
  - Cytori
- Service
  - Viacell

**Regulatory Risks (FDA Approval) Are Lower, But Costs & Competitive Risks Are High**
### Allogeneic Model: *Promise of Scale & Marketable Product*

#### Allogeneic Promise

<table>
<thead>
<tr>
<th></th>
<th>Promise</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven safe and efficacious cell source</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Overcome immunology barrier</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Standards for product assessment</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Cooperate with regulatory authorities</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Achieve scaleable cell expansion</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Simplify into a ‘marketable’ product</td>
<td>✓</td>
<td>?</td>
</tr>
</tbody>
</table>

### Meet Minimum Hurdles
- Immune Response is a unique allogeneic challenge
- Regulatory hurdles are becoming clarified
- Unique ethical / legislative issues arise with hESCs

### Drive Broader Market Uptake
- Expansion potential enables scalability
- Simplicity will evolve over time
- Reimbursement ultimately drives broad uptake as well

### Regulatory Risks Are Higher, But So Are Barriers To Entry
Commercialization Challenges: Other

Regulatory; IP; and Reimbursement

- **Regulatory Environment Needs Clarity**
  - FDA Standards for Safety & Efficacy
  - Standards & Guidelines Are Evolving
  - Cross Border Inconsistencies

- **IP Landscape Is Treacherous**
  - Large Patent Estates Concentrated in Few Entities
  - Inconsistent & Competing Patents: Invites Litigation
  - Need “Freedom To Operate” Opinions

- **Reimbursement Path Unclear**
Commercialization Best Practices

- **Business Model**
  - Identify drivers of value and focus on these first
  - Manage to Valuation Milestones

- **IP**
  - File Provisional Patents
  - Protect Trade Secrets
  - Identify IP Risks Early

- **Reimbursement**: Address Early in Process (PI or PII, not PIII)
  - Begin conversations with *Centers for Medicare and Medicaid Services (CMS)*

- **Remain sensitive to the external environment / ecosystem**
  - Alternative approaches in the pipeline
  - Complementary approaches in the market or in the pipeline
  - Look for Partners
Total Regenerative Medicine Market

Market Over $11.5B in 2010

CAGR%, 2005-2010

- Cell Therapy: 19.3%
- Tissue Engineering: 36.9%
- Aesthetic Medicine: 21.9%
- Regenerative Medicine Tools: 28.3%
- Total: 25.7%

Source: MedMarket Diligence, MII News, Global Industry Analysts, TFG Analysis
### Recent M&A Transactions in Tissue Regeneration

<table>
<thead>
<tr>
<th>Date</th>
<th>Buyer</th>
<th>Target</th>
<th>Deal</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Q3 ’06  | Smith & Nephew     | Osteobiologics Inc.   | $72M  | • $3M revenues  
• Purchase price 20x revenues                     |
| Q3 ’06  | Orthoflix          | Blackstone Medical Inc.| $333M | • $60M revenues  
• EBIT $2M  
• Purchase price 5x revenues                         |
| Q1 ’06  | Smith & Nephew     | PLUS Orthopedics      | $889M | • $300M revenues  
• EBIT $36M in ’06  
• Purchase price 3x revenues                         |
| Q1 ’06  | Kyphon             | InnoSpine Inc.        | $2.5M upfront & $27M | • Pre-revenue acquisition  
• Followed FDA approval                              |
| Q2 ’04  | Biomet             | Interpore Cross Int’l | $280M | • $68M revenues  
• Purchase price 4x revenues                         |
| Q2 ’04  | Zimmer             | Implex                | $108M |                                                                     |

Mar 07: S&N announced $1.1B available for acquisitions  

Source: RegenTec, Public Market Data
## RM Exit Strategies
### Licensing: Key Metrics 2005-2006

<table>
<thead>
<tr>
<th>Term</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upfront Payments</td>
<td>$19M</td>
<td>$32M</td>
</tr>
<tr>
<td>R&amp;D Funding</td>
<td>$26M</td>
<td>$26M</td>
</tr>
<tr>
<td>Milestones</td>
<td>$187M</td>
<td>$244M</td>
</tr>
<tr>
<td>Equity</td>
<td>$18M</td>
<td>$30M</td>
</tr>
</tbody>
</table>

N = 47 Deals; Source: Recap
Big Pharma May Fuel M&A Exits / Valuations

Deloitte & Touche Survey of Senior Execs of the Pharmaceutical Industry (Dec. 2006)

- “More than 50 percent of large pharmaceutical revenues by 2015 will come from products and services they don't offer today.”
- “Large pharma & biotech need to adopt dramatic changes in their business strategies if they want to maintain their success.”

Case study: Pfizer’s Pharmaceutical Sales (in M’s) WSJ 10/23/07

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment</th>
<th>3Q '07</th>
<th>3Q '06</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipitor</td>
<td>Cholesterol</td>
<td>3,170</td>
<td>3,321</td>
<td>-5%</td>
</tr>
<tr>
<td>Norvasc</td>
<td>Blood pressure</td>
<td>640</td>
<td>1,208</td>
<td>-47%</td>
</tr>
<tr>
<td>Celebrex</td>
<td>Painkiller</td>
<td>577</td>
<td>537</td>
<td>8%</td>
</tr>
<tr>
<td>Lyrica</td>
<td>Nerve pain</td>
<td>465</td>
<td>340</td>
<td>37%</td>
</tr>
<tr>
<td>Viagra</td>
<td>ED</td>
<td>450</td>
<td>423</td>
<td>6%</td>
</tr>
<tr>
<td>Zyrtec</td>
<td>Allergies</td>
<td>428</td>
<td>397</td>
<td>8%</td>
</tr>
<tr>
<td>Zoloft</td>
<td>Antidepressant</td>
<td>124</td>
<td>459</td>
<td>-73%</td>
</tr>
</tbody>
</table>