Commercializing Regenerative Medicine and the Importance of Collaboration

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Scientia Advisors
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SCIENCE  BUSINESS

WE KNOW SCIENCE
WE UNDERSTAND BUSINESS
WE ARE FOCUSED IN HEALTHCARE

WHO WE ARE ENABLES US TO UNDERSTAND OUR CLIENTS' BUSINESS

WHO WE ARE ENABLES US TO RAPIDLY IDENTIFY AND DEFINE OUR CLIENT’S PROBLEMS AND GENERATE HYPOTHESES

WE LEVERAGE OUR DEEP INTERNAL AND EXTERNAL EXPERTISE TO ANALYZE PROBLEMS AND FORMULATE CREATIVE SOLUTIONS

OUR ROBUST QUANTITATIVE AND QUALITATIVE CAPABILITIES ALLOW US TO GENERATE COMPREHENSIVE STRATEGIC RECOMMENDATIONS

EFFECTIVE STRATEGIC & OPERATIONAL DECISIONS FROM BOARDROOM TO BENCH
Agenda

• Introduction to the Regenerative Medicine Market
• Requirements for Commercialization
  » Opportunities for collaboration
• Examples of Collaboration
  » Examples/Case Studies
• Summary
Regenerative Medicine

**Definition**

Regenerative Medicine (RM) * is the clinical application of biologic approaches to repair, replace, and restore functional living tissue. The regenerative approaches cover cellular, genetic, or inducer technologies that stimulate a biologic response.

*Passive scaffolds and wound care products are not included. Also excluded from this study are cosmetic regenerative products.

Source: Scientia analysis; Lysaught, 2008; Daar, 2007.
Segmentation of Regenerative Medicine

Regenerative medicine is segmented into three technology classes

- **Cellular**: The administration of cells (stem cells and non stem cells) that have been selected, multiplied, and treated or altered outside the body.
- **Inducers**: The use of local in situ pharmacological or other agents to induce endogenous re-growth or repair of functional tissue.
- **Gene Therapy**: The introduction of genes through vectors that, when expressed, provide sustained levels of biologically active molecules that induce tissue regeneration in vivo.

*The use of scaffolds are considered under cellular, inducer, or gene therapy approaches
Forecasted Regenerative Medicine (RM) Market

*Regenerative medicine is expected to support a new, growing therapeutic market*

Future growth is predicted based on:
1. Pipeline position of therapies for different indications
2. Total addressable population
3. Estimated price points for RM therapy

**PROJECTED GLOBAL REGEN MEDICINE MARKET**

- **Cardiovascular** candidates are in Phase 1 / 2 – 7 to 10 year time frame
- **Next Gen. Cartilage**, multiple candidates in Phase 2/3 – 1 to 5 year time frame
- Neurologic clinical trials are primarily preclinical – 10 to 15 year time frame

**Collaboration between industry participants will be critical to success (or failure) for the industry**

Source: Scientia analysis, Company presentations and 10Ks; Smith Frankel Group, World Stem Cell report 2008
Regenerative Product Development Requirements

Each regenerative product requires a variety of capabilities for successful commercialization; rarely can this be done without collaborations.

The product development process requires many capabilities, at different stages.

Typically, successful commercialization of a product is the result of a series of partnerships between participants who can bring their core strengths to bear on select portions of the product development process.

However, incentives and capabilities are misaligned.
Opportunities for Collaboration

There are ideal interfaces for fruitful collaboration between academia, startups, and industry along each organization’s workflow.
Clinical Workflow Unmet Needs

Workflow bottlenecks can often become a hurdle in adoption of novel products; Addressing these needs can create opportunities (e.g. BMP)

BMP FUSION PROCEDURE

- Anterior incision
- Remove intervertebral disc
- Prepare BNP + Collagen Matrix
- Fill cage and area around cage with BNP-Matrix
- Decompress nerves and put instrumentation to hold cages in place
- Posterior incision

AUTOLOGOUS ILIAC BONE GRAFT PROCEDURE*

- Anterior incision
- Remove intervertebral disc
- Remove wedge of bone from iliac crest
- Set bone graft in place
- Pack with cancellous bone
- No 2ndary Operation
- Posterior incision

*BMP removes the need for this invasive step

Regenerative product development should start by identifying and targeting clinical unmet needs, either better outcomes, lower costs or simpler work flows


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The Infuse Story – Eventual Success Preceded with Significant Delays
While Infuse generated clinical and economic value, we believe partners could have collaborated closely for faster time to marker for

Future Trends:
• Dr. Urist discovered and researched BMP-2 (and other BMP’s)
• Pfizer (then the Genetics Institute) took it to POC and scaled up manufacturing
• Medtronic (then Sofamor Danek) took it through clinic and marketed
• Improvements needed in this model

Sources: Scientia Analysis; WSJ online; Aboutlawsuits.com, www.clinicaltrials.gov
Making Market

*Academia and industry alliances will be critical in helping RM “Cross the Chasm”*

**Key Takeaways**

- **First wave Regen indications, Skin and Cartilage**, succeeded at bringing a technology to market, but did not see the desired commercial success for ‘market’ reasons
  - Example: Cartilage. Making autologous chondrocytes commercially available involved overcoming novel technological, regulatory, and reimbursement challenges
  - However, certain clinical challenges remained. Namely, difficulty for the average orthopedic surgeon to perform the surgery properly
    - Difficulty with the periosteal flap
    - Difficulty securing the cell mass in the defect
    - Two surgeries; one for harvest, one for implant
- **Second wave Regen markets, e.g. Spine Fusion, succeeded both technologically and commercially**
  - Making and selling Infuse (BMP + Fusion cage) had novel development challenges
  - Infuse addressed specific, high-need clinical challenges, actually simplifying spine fusion
    - Eliminated secondary bone harvest used to pack the fusion cage; eclipsed previous gold standard

**Technology Adoption Life Cycle Model**

- **Skin**
- **Cartilage**
- **Mainstream Market**
- **Chasm**
- **Early Majority**
- **Conservatives**
- **Skeptics**

**Future success will be founded on overcoming both technological and market challenges**

**High unmet need in lumbar fusion made an excellent Early Majority beach head market**
Regenerative Product Development Requirements

Collaborations can be of two types; to develop a regenerative therapy or to develop tools in support of each function along the development process.

1. ‘Therapeutic’ Collaborations:
   - Pre-Clinical Testing – Securing IP
   - Developing Proof of Concept
   - Running Clinical Trials
   - Clinical
   - Regulatory
   - Manufacturing
   - Distribution & Marketing and Awareness Building
   - Life Science Tools (e.g., new cell lines, techniques)
   - Clinical Tools
   - Manufacturing tools
   - Regulatory Guidance
   - Selection and pursuit of clinical indications

2. ‘Infrastructure’ Collaborations:
   - Opportunities for collaboration exist for ‘therapeutic’ projects that are advancing a regen therapy to the market, and for ‘infrastructure’ projects that develop the tools, processes, and guidelines used in developing new regenerative therapeutics.
Focal Points of Collaboration

Participants can collaborate to bring a regenerative therapy to market or to develop required infrastructure such as new manufacturing technologies.

**COLLABORATION REGARDING “THERAPEUTICS”**

- Collaborators can cooperate to generate the foundation of a clinical therapy. For example, developing:
  - Therapeutic processes that result in autologous therapies (e.g. Cytori)
  - Allogeneic products themselves (e.g. Organogenesis)
  - ‘Drug Delivery’ systems

**COLLABORATION REGARDING “INFRASTRUCTURE”**

- Collaborators can work together to develop the infrastructure of a space, for example developing:
  - Cell culture tools
  - Cell & animal lines for R&D
  - Manufacturing methods
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Organogenesis’ Apligraf

The Apligraf tissue graft was developed by MIT and then transferred to Organogenesis, who later partnered with Novartis for marketing & distribution.

Dr. Eugene Bell’s MIT cellular biology laboratory focused on using human cells and collagen to graft “skin equivalents” to reduce scaring for patients with burns.

Organogenesis was formed in 1985 and was initially research-centric, but gradually moved into development and manufacturing.

In 1996, a marketing partnership was formed with Novartis. FDA approval was received in 2000 their Apligraf product -- a living, allogeneic, cell based product designed to promote healing of venous and diabetic foot ulcers, the first product of its kind on the market.

Source: Scientia analysis, www.technologyreview.com, Organogenesis press releases, other news websites
Osiris’s Prochymal and Chondrogen

Case Western Reserve research served as the basis for Osiris, which then partnered with larger companies to help bring products to market

Dr. Arnold Caplan’s research at Case Western Reserve was aimed at using stem cell to treat life-threatening diseases using mesenchymal cells.

His research lead to the formation of Osiris Therapeutics in 1992. Pre-clinical research continued until 1997 when manufacturing began for the first human trial for bone marrow transplantation.

Osiris and Japan-based JCR Pharmaceuticals developed a partnership in 2003 to develop a treatment for Graft-vs.-Host disease (GVHD), Prochymal, which received FDA fast-track designation in 2005 and approved in 2008. JCR now has an exclusive licenses in Japan.

In 2008, Osiris and Genzyme entered into an agreement of up to $1.25B (milestones) payments for the rights and license to commercialize Prochymal and Chondrogen.

Source: Scientia analysis, Osiris press releases, other news websites
Regenerative Product Development Requirements

‘Infrastructure’ collaborations tend to be more limited in scope and focused on solving problems that arise in the product development process.

**Regenerative Product Development Requirements**

**IP**

**Clinical**

**Regulatory**

**Distribution & Marketing**

**Manufacturing**

**VistaGen and Duke University’s Dr. Bursis collaborate to develop new cell systems that can be used in drug development**

**Fate Therapeutics and BD Biosciences formed a 3 year partnership to improve iPSC development**

**EMD Millipore + CCRM collaborate to develop new cell culture systems for Regenerative Medicine Applications**

**Terms of Agreement**

<table>
<thead>
<tr>
<th>Access to Duke’s cardiac electrophysiology and tissue engineering</th>
<th>Funding, research publications</th>
<th>License of Fate’s iPSC patent</th>
<th>Upfront payments, research funding, milestones and royalties</th>
<th>$500,000 funding</th>
<th>Extending the scope of its reactors Diversified portfolio</th>
</tr>
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Collaboration is currently ongoing to develop infrastructure needed to commercialize regen therapeutics:

- VistaGen & Duke hope to generate a new cell line for drug rescue
- Fate & BD Biosciences formed an agreement to increase the efficiency of reprogramming iPSC
- EMD Millipore and CCRM are optimizing stem cell cultivation to decrease production time for clinical therapies

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Collaboration Case Study - Infrastructure

**VistaGen and Duke develop cardiac stem cell technology**

**Background**
- VistaGen is a biotechnology company applying human pluripotent stem cell technology for drug rescue and cell therapy\(^1\). Looking to develop therapeutics for cardiac indications.
- At Duke University, Dr. Bursac is a leader in the field of cardiac tissue engineering and cell-based therapies\(^1\).

**Collaboration**
- Together VistaGen and Duke agreed to explore potential development of novel, engineered, stem cell-derived cardiac tissues to expand the scope of VistaGen’s drug rescue capabilities focused on heart toxicity\(^1\).
- Duke provides cutting-edge cardiac electrophysiology and tissue engineering technology [, and licensed the IP]
- VistaGen provided human stem cell-derived heart cells [and cash infusions, and publication support ]

**Outcome**
- The project is ongoing, but is expected to:
  » Yield a new cardiac cell line for VistaGen
  » Result in [more funding and publications] for Duke/ Dr. Bursac

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Collaboration Case Studies: Infrastructure for scale up drug production
Non-for-profit and Private Company

**Background**

**Canada’s Center for Commercialization of Regenerative Medicine (CCRM)** is a not-for-profit organization with a mission to foster the development of foundational technologies that accelerate the commercialization of stem cell- and biomaterials-based products and therapies.

**EMD Millipore** is one of the top three investors in R&D in the Life Science Tools industry with 2010 revenue of $2.2 billion. Millipore’s focus is to develop cutting-edge technologies and services for bioscience research and biopharmaceutical manufacturing.

**Collaboration**

In February 2012, **CCRM and EMD Millipore** entered into a $500,000 partnership agreement to optimize large-scale stem cell cultivation. The focus of the joint venture is to develop a proprietary monitoring and control methodology using Millipore’s Mobius CellReady Stirred tank bioreactor.

**Outcome**

The immediate goal is to reduce the capital and time expenditure currently required to develop stem cells.

The ultimate hope of the collaboration would be to allow quicker cell-cell production – reducing the time to get therapies into the clinic.

Collaboration will focus on developing a commercially available kit containing reagents and methodologies for optimized stem cell culture on the mini-bioreactor.
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Summary & Conclusions

Regenerative Medicine is witnessing a period of prolific product development, fueling high expectations for commercial therapies.

Collaboration is a key success factor in bringing Regenerative solutions from research into clinical practice.

There are examples one can review to understand how to establish a collaboration of their own:

- The current market for regenerative products is well over $1 Bn and growing:
  - Vascular products soon expected to join existing Bone, Cartilage, and Skin products on the market
  - Frenetic clinical research suggest emergence of cardiovascular, neurological, GI, and endocrine therapies in the future

- There are few organizations that are designed to bring a product from research to the market on their own:
  - Academia is organized to discover rather than commercialize
  - Small companies/startups can advance product development but lack the infrastructure to market products
  - Large industrial firms are averse to the risk of early development but are capable of full scale marketing

- Examples of successful collaborations include:
  - The commercialization of Apligraf by Dr. Bell, Organogenesis, and Novartis
  - The commercialization of Prochymal by Dr. Caplan, Osiris, JCR Pharmaceuticals and Genzyme
  - The development of tools & infrastructure by VistaGen & Duke, Fate Technologies & BD Biosciences, EMD Millipore & CCRM
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