Challenges in the Translation and Commercialization of Regenerative Medicine

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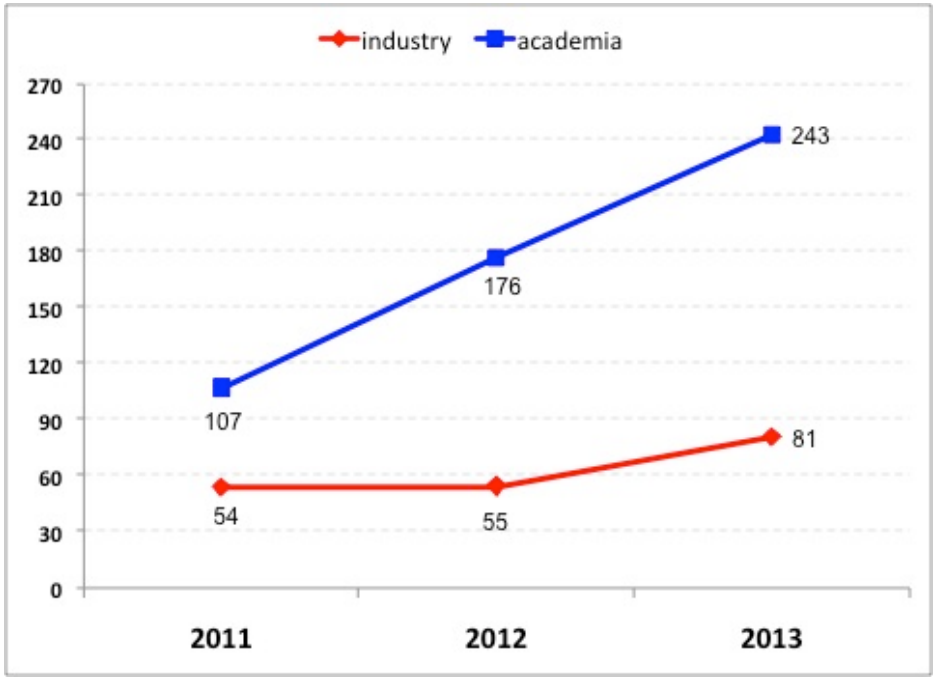
Motivation: Facilitating the development of cell therapies

- Potential of cell therapies to address unmet medical needs
- Growing clinical "pipeline"
- Narrative of unmet expectations



Source: Alexey Bersenev, StemCellAssays.com

1. Develop more systematic understanding of cell therapies
2. Inform future translation / commercialization efforts

Two-pronged methodological approach

1. Retrospective evaluation of existing cell therapies
   - Systematic document collection & review

2. Interviews with experts in cell therapy
   - Academics, industry (CEO, CMO, SVP, etc) consultants, journalists, others
   - Eleven interviews thus far (work ongoing)

Retrospective analysis focused on seven products

Product	Company	Type	Indication
Epicel	Sanofi / Aastrom	Autologous	Severe burns
Carticel	Sanofi / Aastrom	Autologous	Cartilage defects
Provenge	Dendreon	Autologous	Advanced prostate cancer
Apligraf	Organogenesis	Allogeneic	Venous leg / diabetic foot ulcers
Dermagraft	Organogenesis	Allogeneic	Diabetic foot ulcers
Osteocel	NuVasive	Allogeneic	Bone grafts
Prochymal	Mesoblast	Allogeneic	GvHD, others?

Several common challenges were identified

Pre-market	Post-market
• Persevering through lengthy developmental timeframes • Navigating variable (& uncertain) regulatory environment • Acquiring necessary intellectual property	• Securing reasonable & consistent reimbursement • Encouraging physician/ patient adoption • Setting & meeting growth expectations

- Maintaining product consistency
- Addressing distribution logistics
- Producing at necessary scale
- Managing cost of goods sold

Manufacturing

Lengthy developmental timelines raise funding concerns

- Initial company formation → commercial product ranged from 11 to 18 years for the seven products studied

- Potential funding strategies
  - Angel / VC investing
  - IPOs
  - Partnering with larger firms
  - Selling research tools or other products

Highly variable regulatory processes complicate translation

- Evolving and improving regulatory regime in US
  - Early products addressed in ad hoc manner
- Greater regulatory clarity today
  - Pre-market approval required for most products (Section 351)
  - Some (controversial) use of alternative pathways (Section 361)
- But regulatory classification still problematic for some firms

International variability also poses translational challenges

- Substantial differences between policies in major markets (e.g. US, EU and Japan)

- Most firms pursuing one of two key regulatory strategies
  1. Highest bar / biggest market
  2. First to market

Manufacturing challenges exist across the full product development timeline

- Autologous vs. allogeneic decision
  - Driven by efficacy considerations but has major manufacturing, distribution implications
- Maintaining consistency & potency
  - Lack of standardization / tools / accepted assays
  - Manufacturing flexibility / scale-up
- Distribution logistics

Reimbursement is a crucial step for successful commercialization

- Complicated reimbursement processes due primarily to novelty of cell therapies
  - Reimbursement levels hard to predict
  - Reimbursement levels may be insufficient to recoup investment
  - Reimbursement levels may change substantially over time

Convincing physicians to change their behavior is difficult

- Cell therapies are often more complex than existing therapeutic options
  - May require clinician processing prior to administration
  - May create high efficacy bar for adoption
  - May necessitate substantial sales and training effort

Preliminary best practices

- Prepare for commercialization early
  - Develop manufacturing and distribution strategies
  - Clarify regulatory status
  - Engage relevant physician community
- Use capital efficiently
  - Collaborate and outsource non-core work
  - Expand deliberately
- Develop multiple revenue streams

Some governance considerations

- The novelty and complexity of cell therapies complicates oversight for key federal agencies (i.e. NIH, FDA, CMS)
- Regulators must balance flexibility with consistency and predictability
- Regulators should consider range of challenges and interactions among various challenges when promulgating rules