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The Cell Therapy Industry: An Industry Perspective

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Definition of Cell Therapy

- *"Cell-based medicine seeks to address organ dysfunction at the cellular level by replacing or supporting dying or dysfunctional cells with healthy **cells as the therapeutic agent**."*

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The Arc of Progress: Legacy Platforms Unmodified Cells

1960s:

- Clonal nature of marrow cells first elucidated(McCulloch & Till)

1980s:

- hHSCs-Hematopoietic Stem Cells(Weisman/SyStemix/Sandoz)

1990s:

- hMSCs-Mesenchymal Stem Cells(Caplan/Osiris)
- hESCs-Embryonic Stem Cells(Thompson/Geron), hRPEs- Retinal Pigment Epithelium Cells from hESCs (Lanza/ACT>Ocata/Astellas)

2000s:

- hNSCs-Neural Stem Cells(Uchida/StemCells;Johe /Neuralstem; Sinden/ ReNeuron)
- hMAPCs-Multipotent Adult Progenitor Cells (Verfaille/Athersys)

Trials &Tribulations: The Legacy Platforms

- HSC/SyStemix technology abandoned by Sandoz; autologous business model; yet more than 1 million patients HSC transplants to date
- Athersys/Pfizer Phase II IBD trial did not meet efficacy endpoints. Now pursuing ischemic stroke in US and in Japan with Healios (after Chugai returned rights)
- Osiris sold culture-expanded MSC assets to Mesoblast for $50mm* in 2013
- Mesoblast in PII HF, RA and back pain in PIII. GvHD appoved. Teva returned HF rights
- ESC technology stymied by safety concerns, complex differentiation protocols, and political and religious objections. Geron licensed drug screening uses to GE Healthcare, then sold assets to Biotime in 2013 for $5mm cash and other considerations. PI/II SCI trial underway(Asterias)
- Ocata(aka ACT) sold to Astellas in 2016
- NSC technology stymied by risk-averse regulations, fetal tissue, immunosuppression; StemCells and Neuralstem exited in 2016. ReNeuron still standing

Legacy Platforms: Observations

- Translation runways too long and too costly; investor fatigue set in
- Small-cap valuations limited size of capital raises
- Resulted in serial punitive financings, significant dilution, shrinking market valuations
- Delisting threats led to serial reverse stock splits
- Encouraging Phase I/II open-label safety/efficacy data not valued by investors
- PII controlled studies slow to come and when they did, didn't excite investors
- Pharma and strategic investors sat on the sidelines
- Funding for additional trials dried up/became overly punitive/dilutive
- New technologies filling the vacuum: iPSCs; Crispr-Cas9 gene-editing; immunotherapy

Legacy Platforms: Learnings

- Cell source matters: embryonic, fetal, placental, BM, PB, adipose, etc.
- U.S ban on Federal funding for ESC research in 2001 and European Parliament ban on the destruction of human embryos cast dark shadow over the **entire** cell therapy field
- Immunosuppression a barrier to widespread adoption of allogeneic therapies
- Robust Phase II data essential to attract Pharma and strategic investors
- Emphasis will then shift to "manufacturability" and COGs !!
- Logistical challenges associated with autologous therapies a barrier to widespread adoption
- Only do trials based on science and the preclinical data in the patient population most likely to benefit
- Conduct early trials outside the U.S., if necessary

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Will The Next Generation Fare Better?

- HLA matched iPSCs: solves cell source issue but requires I/S; long road through the clinic. Japan could be a game changer.
  - Key players: Fujifilm, Sumitomo, JCR Pharma, Astellas, Healios.
- HSCs(+/-HLA matching) to reboot the immune system in leukemia and lymphoma treatment and (potentially) autoimmune disorders. CSFs include: non-toxic conditioning regimens, improved BM harvesting and cell expansion processes.
  - Key Players: Magenta and Nohla
- Immunotherapy for liquid and solid tumor cancers: patient's own activated T cells against cancer: solves I/S issue; adds gene insertion step and chemotherapy conditioning regimens.
  - Key players: Juno, Kite, Bluebird. Developing concern: recent patient deaths in Juno's CAR-T Leukemia trials.
- Autologous cell therapy resolves the I/S issue, but needs significant investment in infrastructure due to complex logistics for each patient to facilitate scale up and adoption.
  - Key players: Quintiles, GE Healthcare/Vitruvian Networks
- "Universal" Cells; goal is to produce non immunogenic, pluripotent, MCBs. **Very** early.

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Most likely, however…

- CURES Act provides more tools to FDA, but not the "BIG FIX"
- Nov. 2013, Japan established expedited pathway to approval for cell therapy products post Yamanaka's 2012 Nobel Prize for IPSCs work
- Bold and disruptive move:
  - Already accelerating cell therapy treatments and cures
  - Creates competitive advantage for Japanese companies
  - Creates incentive for foreign companies to partner with them
  - Japanese Pharma lured into the field

Japan is on the Move

- 2014:
  - Dainippon-Sumitomo JV with Riken and Healios K.K.
- March 2015:
  - CDI acquired by Fujifilm for $307mm
- Nov. 2015:
  - Astellas acquires Ocata(ACT) for $379mm
- Feb. 2016:
  - Mesoblast/JCR Pharma gain full approval for GvHD; now seeking conditional approval for heart disease
- April 2016:
  - Universal Cells/Healios form partnership
- Sept. 2016:
  - Athersys/Healios trial approved for Stroke by PMDA

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China Not Far Behind

- Moratorium on cell therapy trials still in place, yet:
  - Guidance documents slowly emerging
  - Intend to be competitive with Japan
  - Investing in the science; "twinning" of companies and academia
  - Acquiring assets and "know how" e.g. Boyalife/ Cesca/BOCO/StemCells Inc.

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Summary

- More flexible regulatory framework that reflects the unique challenges associated with cell therapy, balancing need for sound science with accelerated development pathways
- New tools given to FDA, step in right direction e.g., Breakthrough Designation and Expedited Programs for life-threatening/serious conditions; Patient Engagement Activities
- 10-15 year runway to clinical POP…"The Valley of Death"
- Financial and human capital will go elsewhere
- Need for more shared responsibility for translation of scientific discoveries between government agencies, academia, pharma/ biotech, cell therapy companies

Thank You