NIST
Visiting Committee on Advanced Technology

Bioscience Panel
Robert Deans, Athersys
Gaithersburg 6.9.15

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Product Development Portfolio

MultiStem®

adherent adult stem Cell isolated from bone marrow

Immunological

- **Inflammatory Bowel Disease w/ PFIZER: phase 2**
- **HSC Transplant / GVHD → phase 2/3**
- **Solid organ transplant: phase 1**

Neurological

- **Ischemic Stroke: phase 2**
- Traumatic brain injury & related
- Spinal cord injury
- Multiple sclerosis

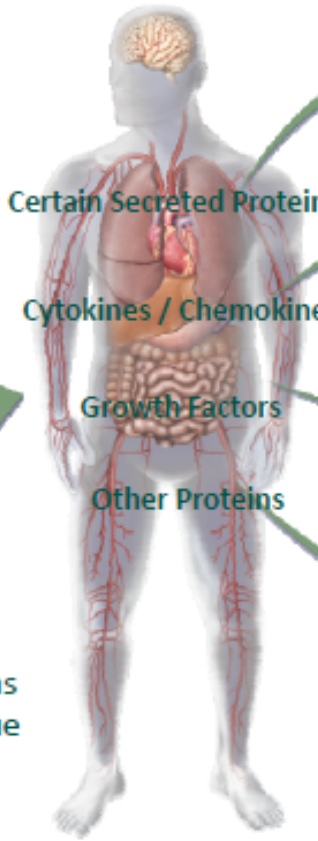
Cardiovascular

- **Acute Myocardial Infarction → phase 2**
- Peripheral vascular disease
- CHF
- **Acute Respiratory Distress Syndrome**

Other

- **Orthopedic (e.g., allograft combo) → RTI Surgical**
- Tissue repair (e.g., wound, muscle)

Adherent Stem Cells Promote Healing Through Multiple Mechanisms



Shifting Balance in Repair Processes

Immunomodulation

Inflammation Reduction

Neuroprotection, Cytoprotection

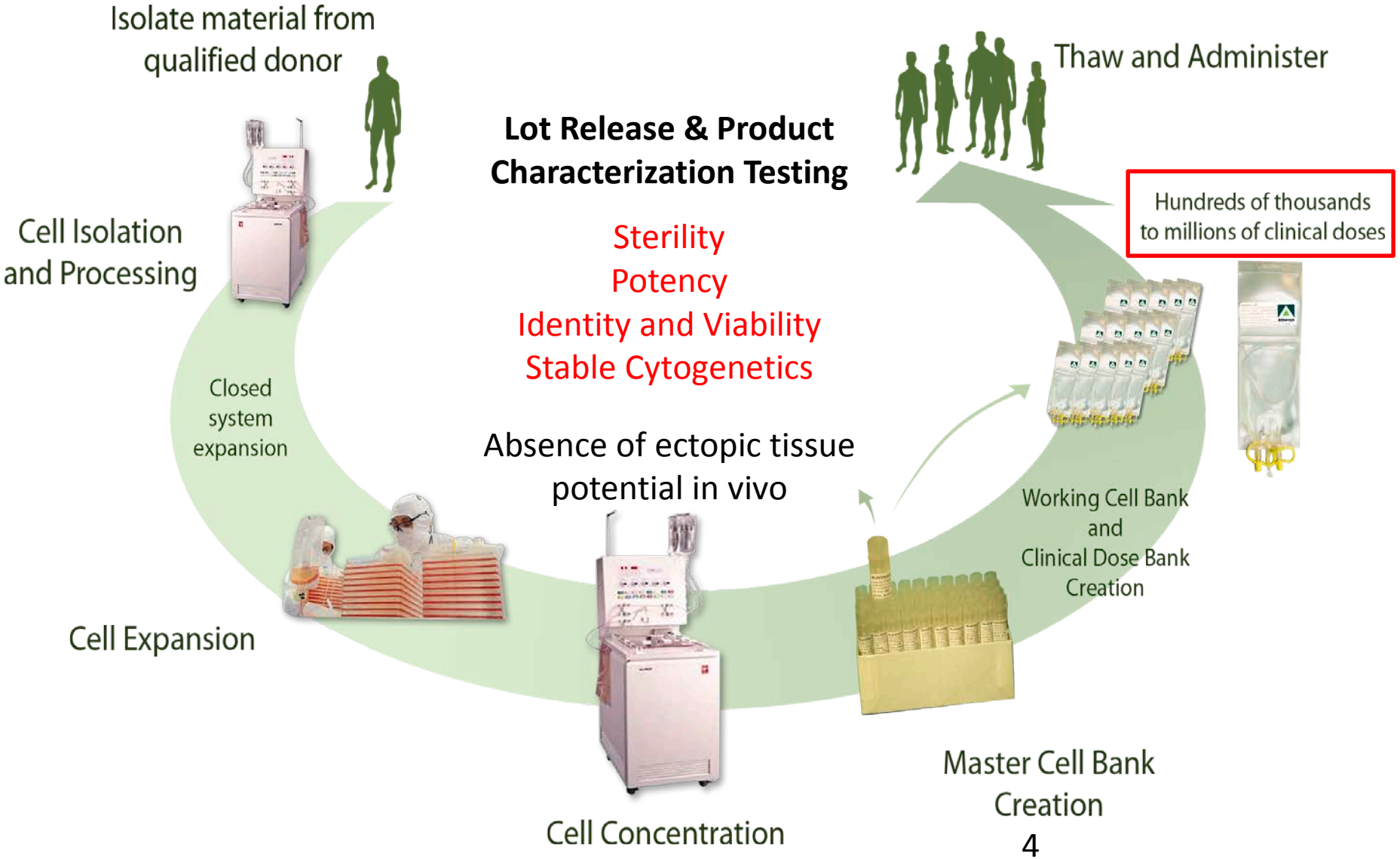
Angio- / Vasculogenesis

Cellular regeneration / replacement by host progenitors

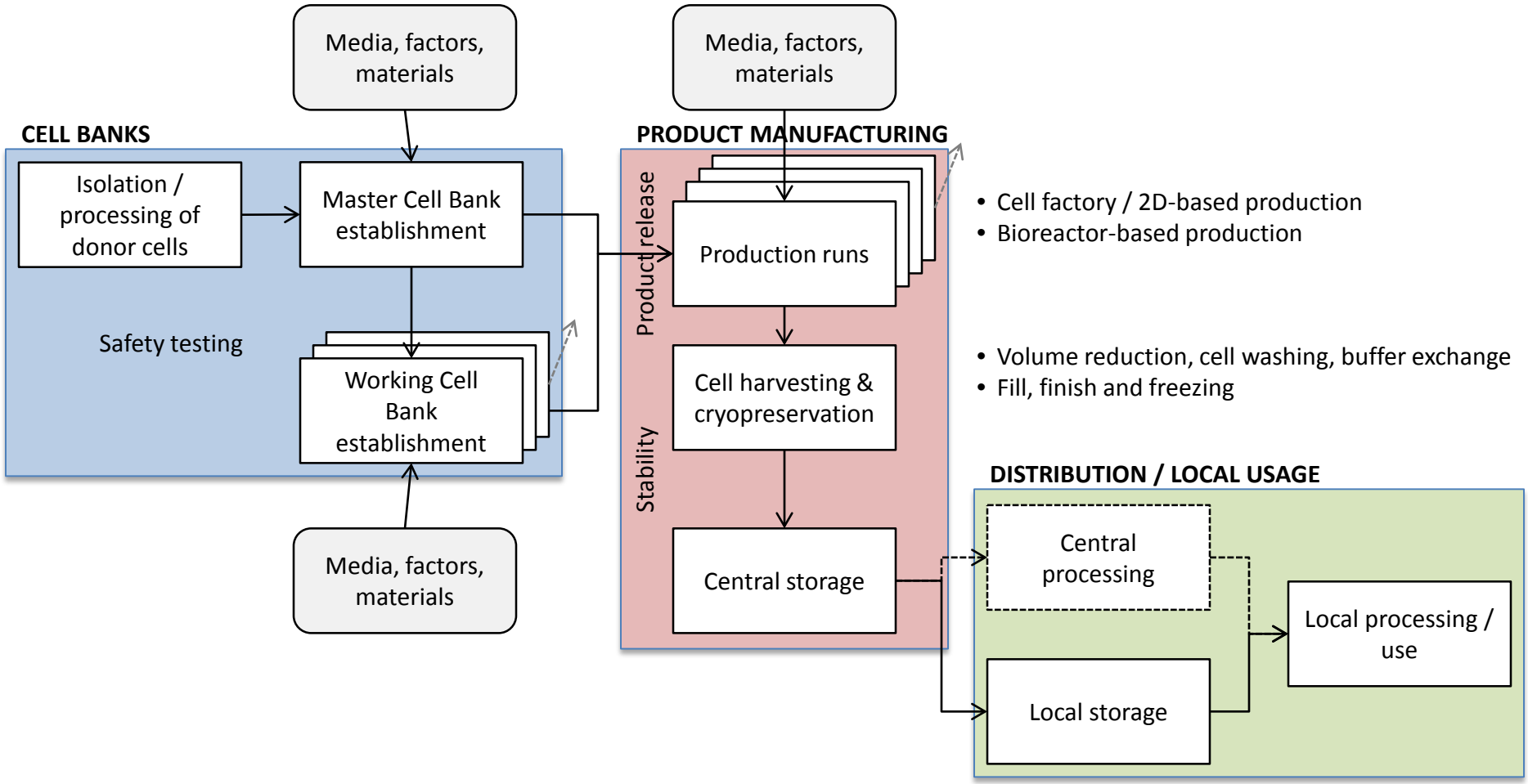
MultiStem® cells express multiple therapeutic proteins to enhance healing and tissue repair in multiple ways

In vitro cross-talk ⟷ In vivo microarray

Overview of MultiStem® Production Process



Production Overview



Next Generation Xeno-free formulation, bioreactors in development

Current Development Needs Outstrip Technology and Capacity

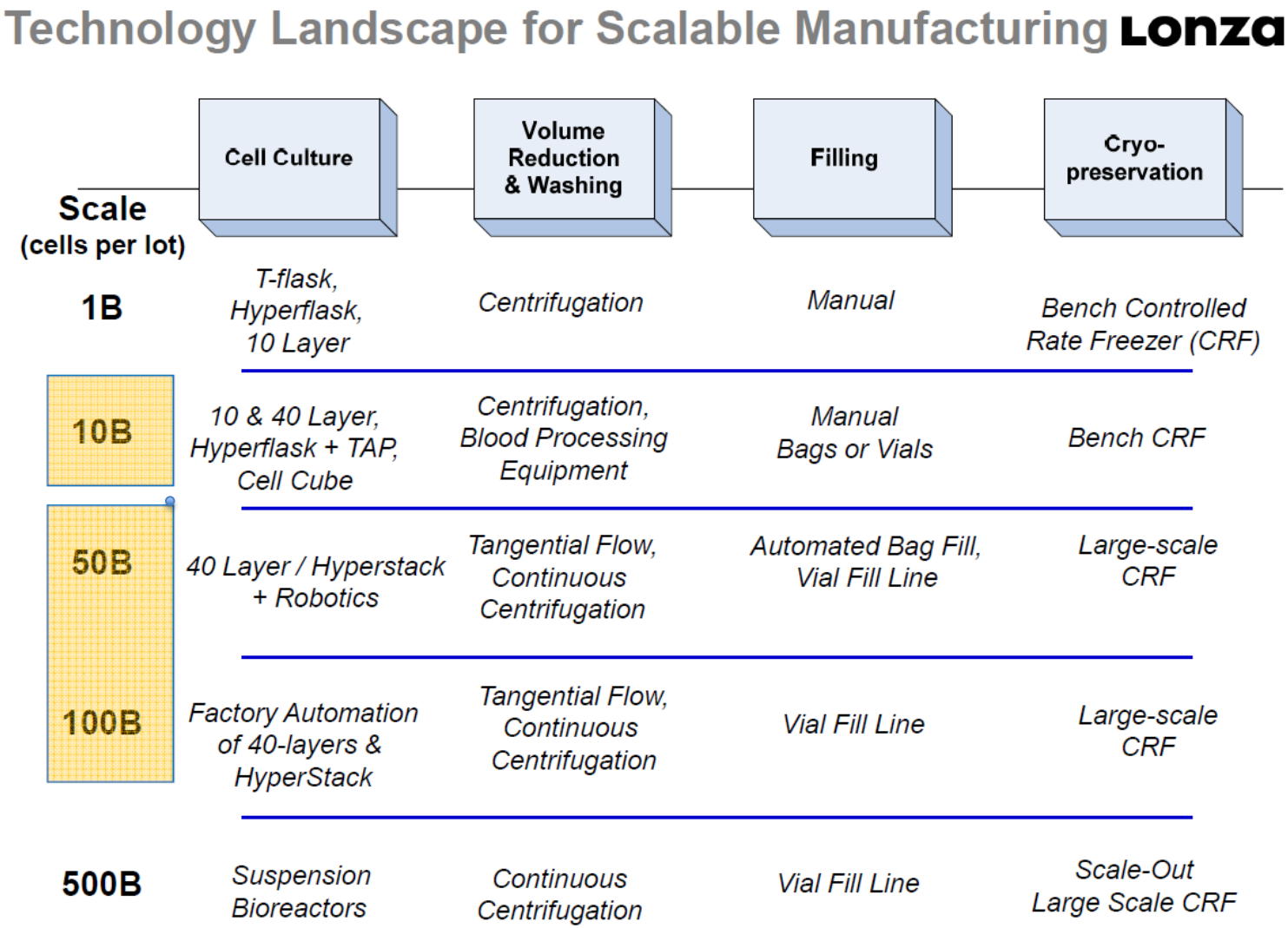
- Technology: current MFG platforms (eg., Mab) were not developed to harvest viable cell product
  - Downstream processing tools do not exist for efficient viable cell recovery (50% of COGS) or uniform cryoformulation and fill
  - Analytical methods insufficient for many determinations particularly those linked to in vivo function (biodistribution, potency)
- Capacity: current 2D technologies cannot meet commercial need
  - international contract mfg capacity is rate limiting
- Regulatory: standards are dynamic in this field
  - Raw material control is already and will become increasingly utilized as a trade barrier
    - Fetal calf serum, donor ethnicity
  - Accelerated Regulatory approval has become strong component of development decisions

Scale-Up vs Scale-Out Manufacturing Options

- 40 Layer Cell Factory, Hyperstack
  - direct path to scale up with existing technologies in 2-D format

- Suspension bioreactor using microcarriers
  - 3-D footprint targeting large scale stirred tank bioreactors mimicking MAb technology
- Disposable patient designated options
  - Quantum Hollow Fiber Bioreactor (Terumo)
  - Xpansion Bioreactor (ATMI)

Heavy Lifting Scale Up Comes with Costs



Courtesy of Jon Rowley, Lonza

What Are We Facing in MFG Challenges?

	Stroke	AMI	GvHD
Annual treated patients	100,000-500,000+	100,000-500,000+	10,000
Dose / treatment	500MM-1B cells	50 MM cells	400-800 MM cells
Cells required	50-500 trillion	5-25 trillion	4-8 trillion

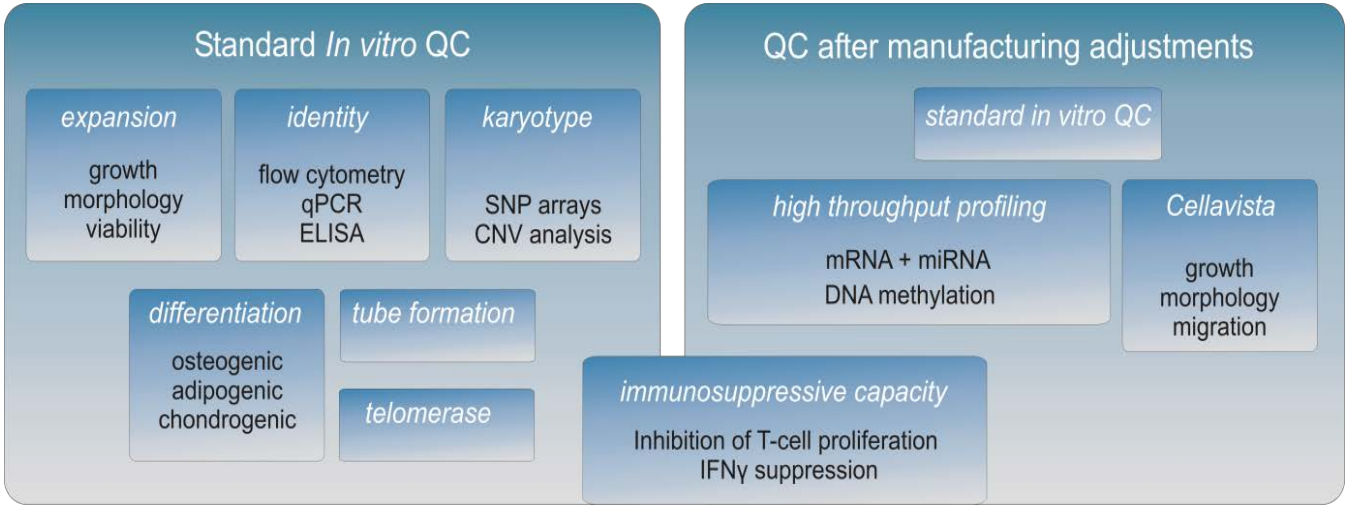
With a clinical campaign producing 50 billion cells, a 5 trillion annual production requirement would entail 100 campaigns per year in robotic 2D

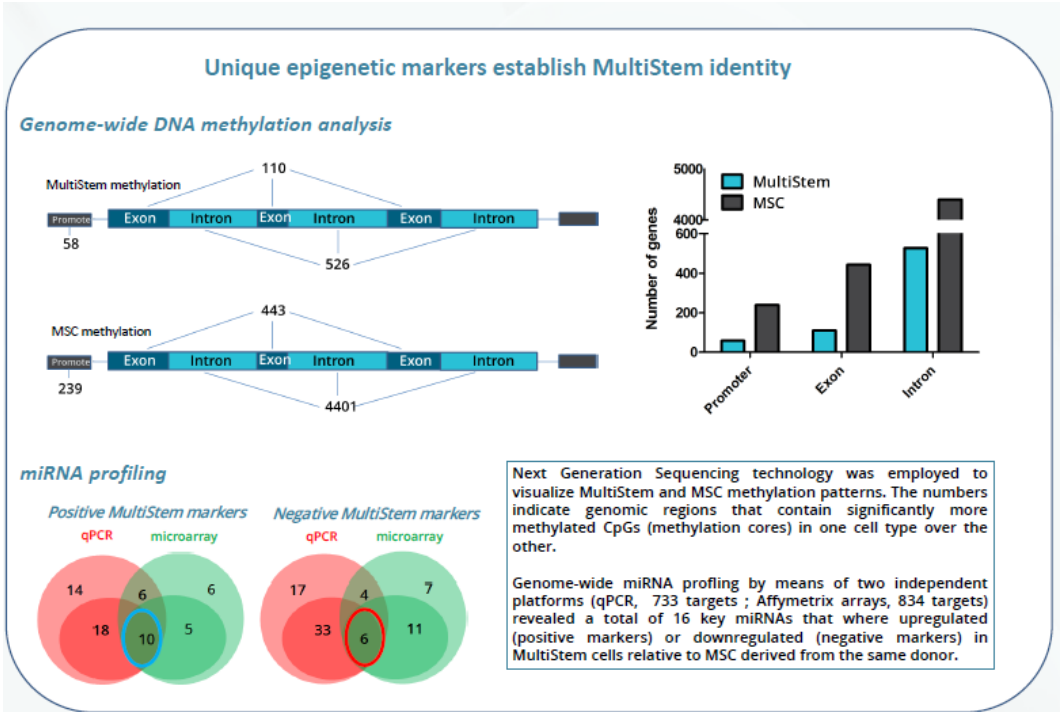
5 trillion cells equates to 5 2000L bioreactor runs yielding 10e12 cells: industry average $10 / million cells = $2 MM per run

In Process and Lot Release Quality Metrics

- Lot Release Template
  - Sterility
  - Cytogenetics (sampling size; relevance of high sensitivity testing)
  - Identity and viability (FACS based with options for long term cell cell viability)
  - Potency (generally in vitro surrogates for presumed clinical mode of action)
  - *GAPS: testing for recovery post thaw for in vivo surrogates of function (attachment, biodistrubtion) and correlating in vitro function to in vivo hypotheses*
- In process testing
  - Marked gap in real time analytical tools to determine cell health and surrogates of in vivo function (emphasizing biophysical measurements of cytoskeletal integrity)
  - Particulates and residual testing are complicated (microcarriers and fragments are particulates inseparable from cells
- Next generation cell manufacturing platforms and cell processing instruments are emphasizing automated sampling but need to be informed

Cell Characterization Approach (Do We Like Big Data?)





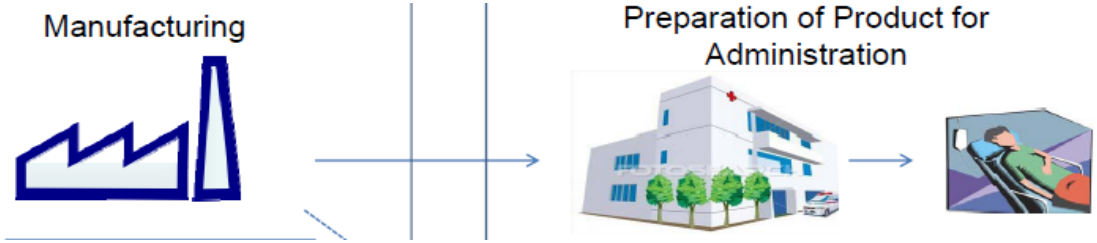
Roobrouck 2011
Vaes 2013

Quality Approaches in Clinical Delivery

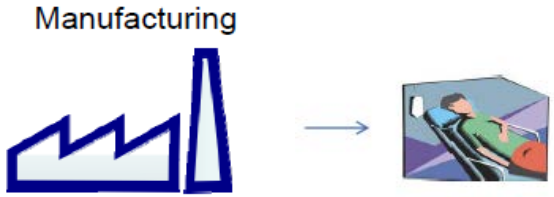
Clinical product flow – Clinical centers on study did not have stem cell processing lab capacity

Cryoformulation for direct infusion, optimal temperature storage became key development challenges

Past



Future



Reformulation of product at MFG facility with drop shipment for infusion w/o further testing

Formulation enables shipment at 4 degrees with 36 hour stability window

Clinical Measurements and Standards

- Biodistribution tools and sensitivity
- Analytical markers for donor cell persistence
- Biomarkers of disease response for treatment decisions
- Companion diagnostics to determine response to treatment

Current emphasis is on emerging epigenetic tools as surrogates for clinical effect and brings computational standards into mix

  - Transcriptional profiling
  - Gene methylation
  - miRNA fingerprints

Going Forward

- Visibility and authority
  - Center of Excellence for Cell Standards can provide guidance and nucleate resolution between engaged parties – currently lacking
  - NIST has very effectively led industry engagement in ISO cell standards activity

- Leading by science -- driving consensus
  - Anticipating gaps and building tools with necessary sensitivity, durability
  - Promoting non-competitive co-development options
    - Gains industry segment endorsement and validation
    - Promotes international harmonization

Working Group 4: Analytical Technology:

NIST / Alliance for Regenerative Medicine Initiative

Tasks	Tactics	Deliverables	Time-Line (Months)
Define environments for deployment of technologies	• Brainstorm categories with team and align with WG3 • Cell Type: allogeneic vs. autologous cells • Formulation: single cell vs. multi-cell (tissue engineered product) • Point of Care versus centralised	•List of environments with required attributes for deployment in selected workflows	3-5
Defining available technologies	•Review and categorize existing platforms using relevant criteria	•Register of technologies with objective mapping to relevant criteria	4-6
Pair relevant bioassays with technology	•Align technologies with bioassays	•Mapping of technologies to WG3 assays •Identification of gaps required	5-8
Define validation pathway	•Validate identified assays on suitable platforms	•R&D investment to validate use of platforms on identified assays	8-12

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