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Strategies to Improve Characterization of Stem-Cell Based Cellular Products

National Academies of Sciences, Engineering, and Medicine's

Forum on Regenerative Medicine

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Product Testing

Chemistry, Manufacturing, and Controls (CMC)

- Should ensure product safety
- Should ensure consistency of process and product
- Should (ideally) predict *in vivo* activity
- Is guided by detailed understanding of the manufacturing process and the product

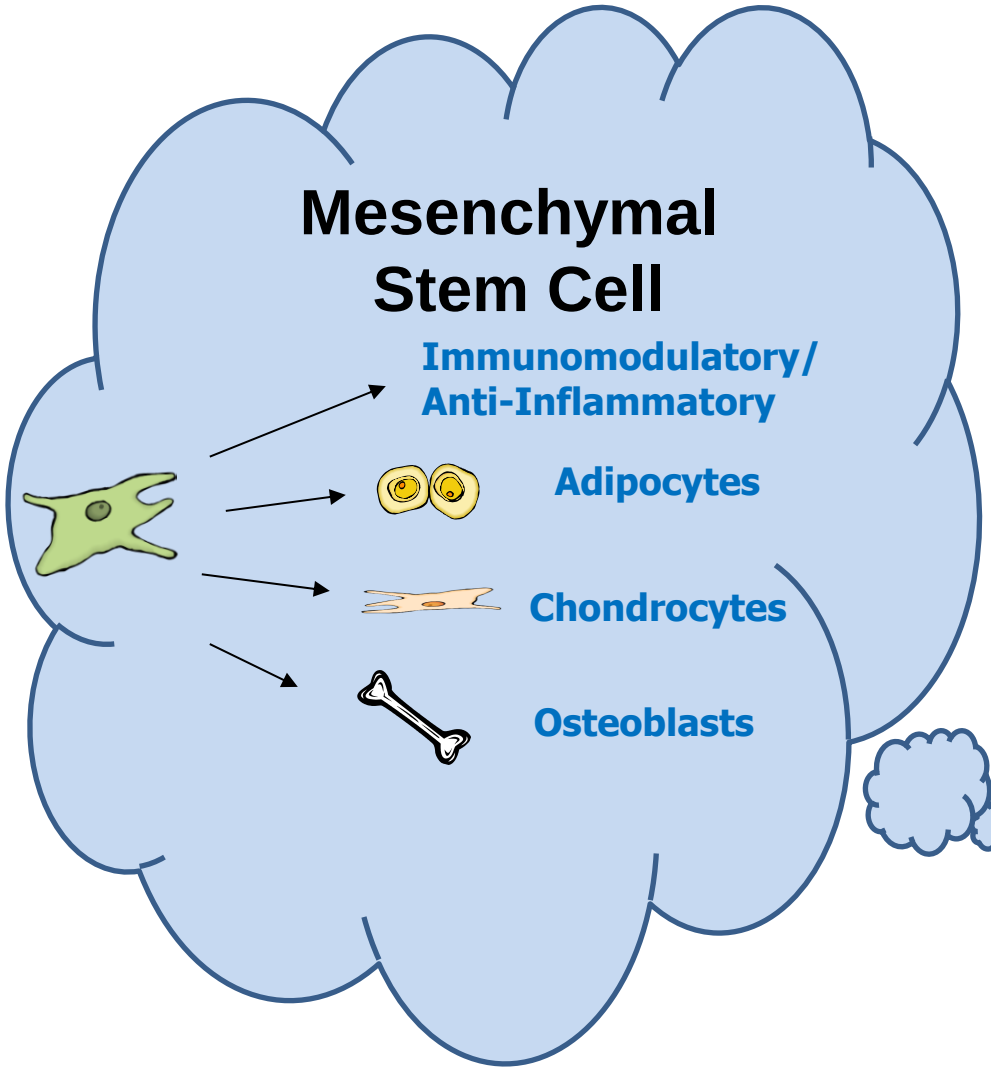
Characterization

Multipotent Stromal Cells (MSCs) in Clinical Research

- **MSCs are diverse**
  - **Characterization**
  - **Manufacturing**
  - **Source**
- **Quality attributes?**
- **Relation to performance in clinical trials?**

MSC-Based Product Characterization for Clinical Trials: An FDA Perspective. *Cell Stem Cell:14, 2014 pg 141-145*

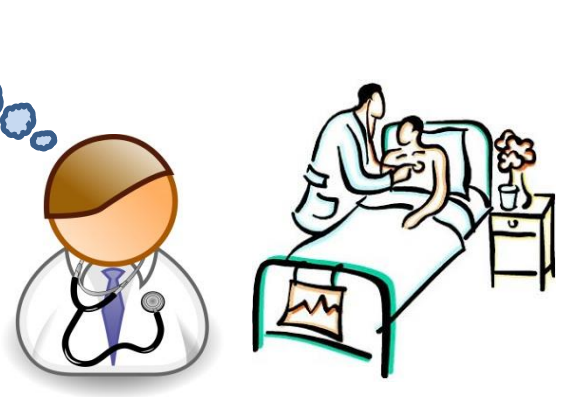
MSCs and Product Characterization



?

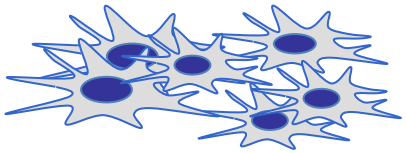
Manufactured MSC

Adherent in culture
CD73+, 90+, 105+
Lymphoid lineage negative

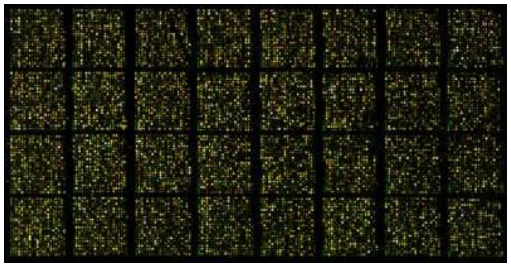


CBER/FDA MSC Consortium: Identification and correlation of MSC attributes with *in vivo* and *in vitro* assays of safety and efficacy

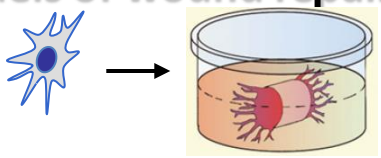
MSC Characterization



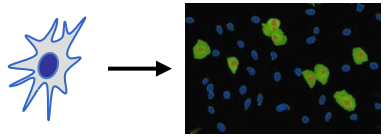
Puri Lab: genomics



McCright Lab: *in vivo, in vitro* models of wound repair



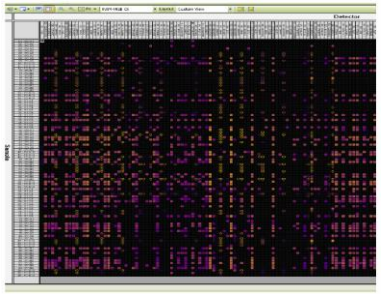
Bauer Lab: *in vitro* quantitative differentiation



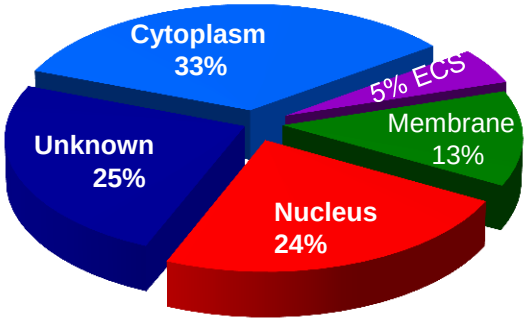
PRODUCT CHARACTERISTICS

CORRELATE CANDIDATE ATTRIBUTES WITH ASSAY OUTCOMES

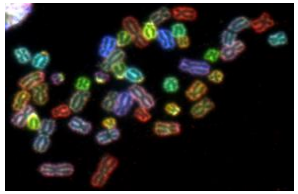
Moos Lab: gene expression, qRT-PCR, single cell PCR, NGS

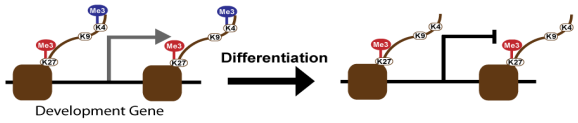


Alterman Lab: proteomics

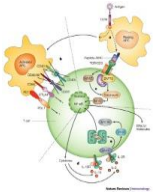


Hursh lab: epigenetics, karyotypes



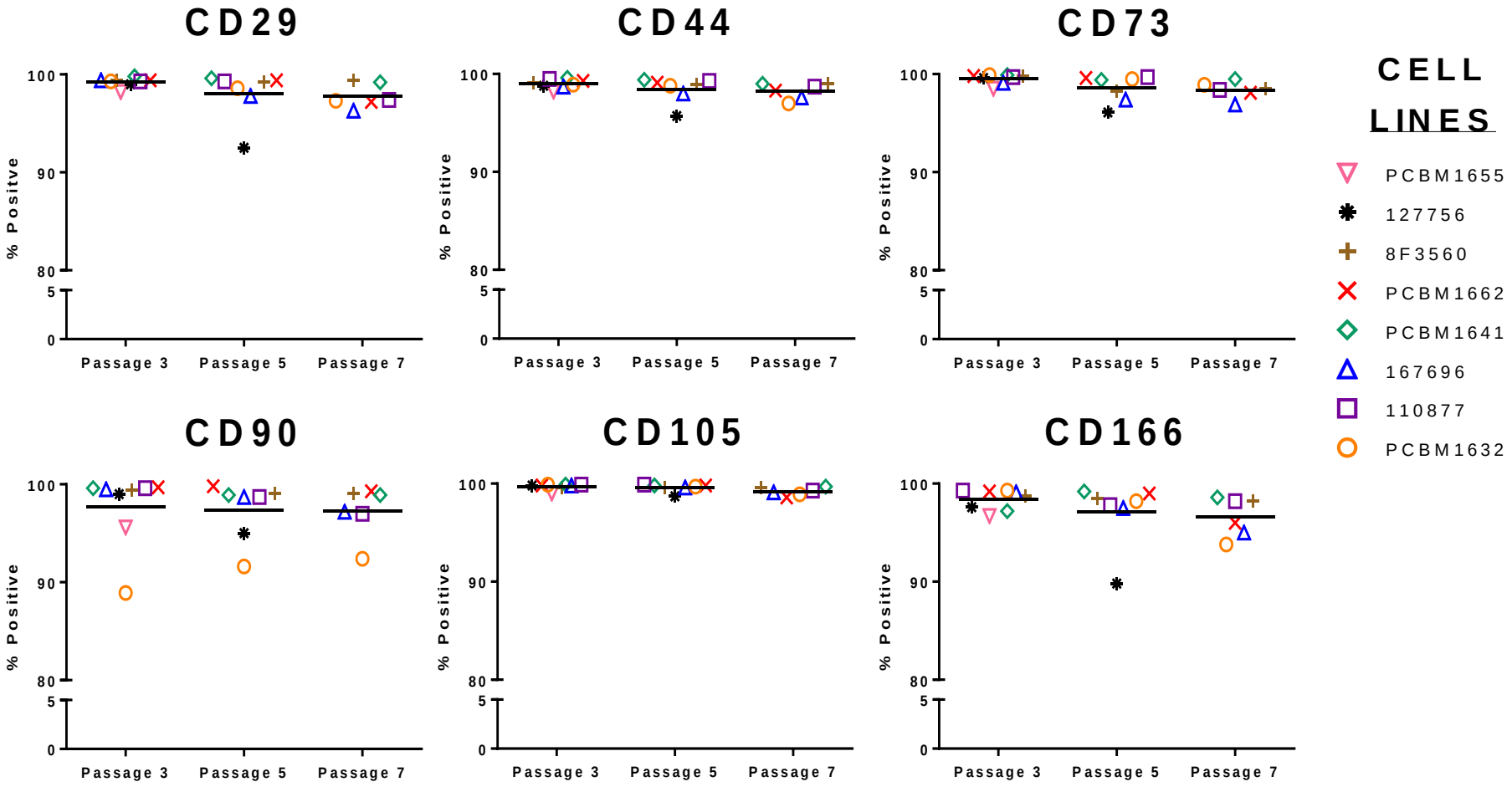


Wei/Bauer Labs: *in vitro, in vivo* immunosuppression



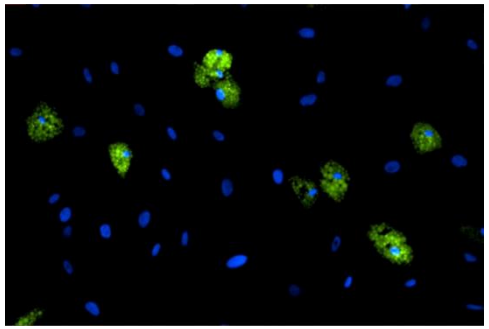
Sung Lab: *3D in vitro* tissue/organ microfluidic models

Consensus MSC Surface Markers Do Not Reveal Significant Differences

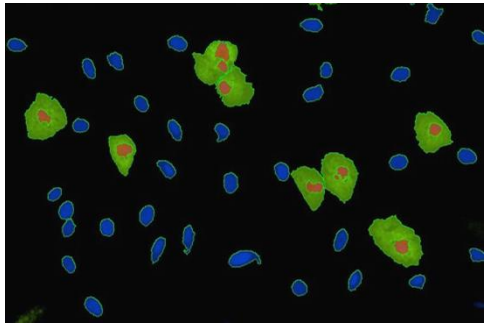


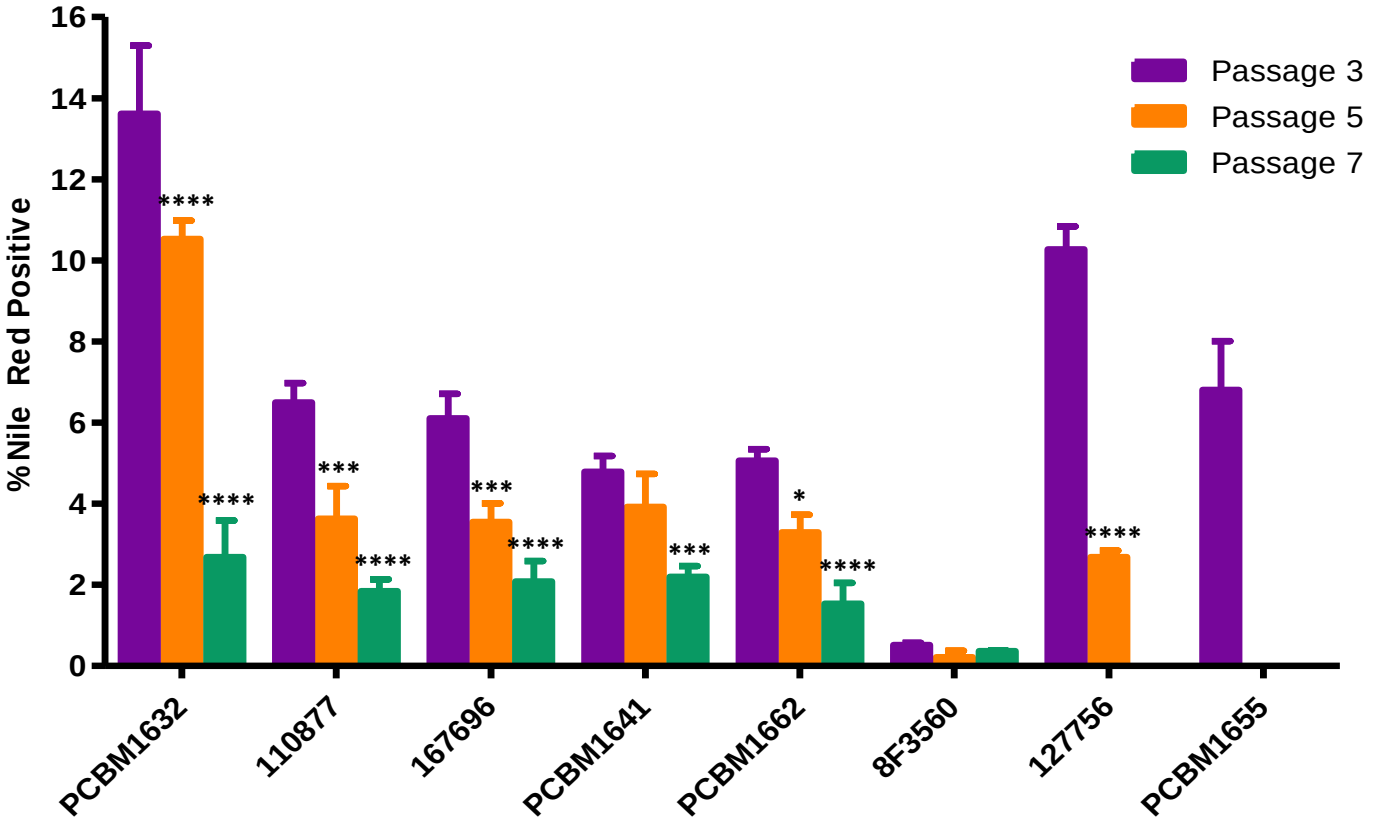
Lo Surdo JL et al., Cytotherapy, 2013.

Adipogenic Potential Varies Between Cell Lines and Decreases with Passaging



Automated microscopy-based quantification

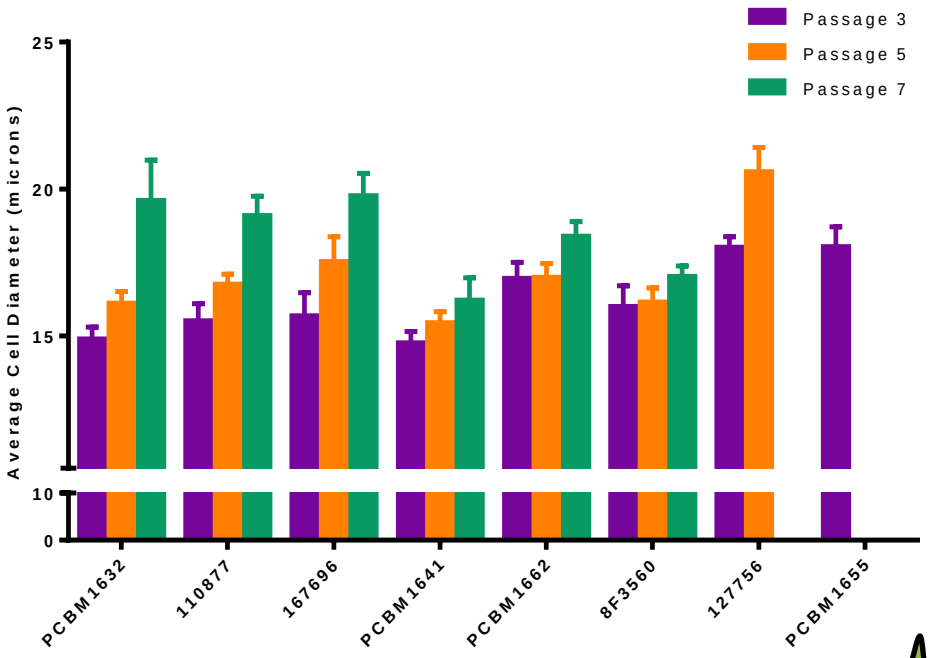


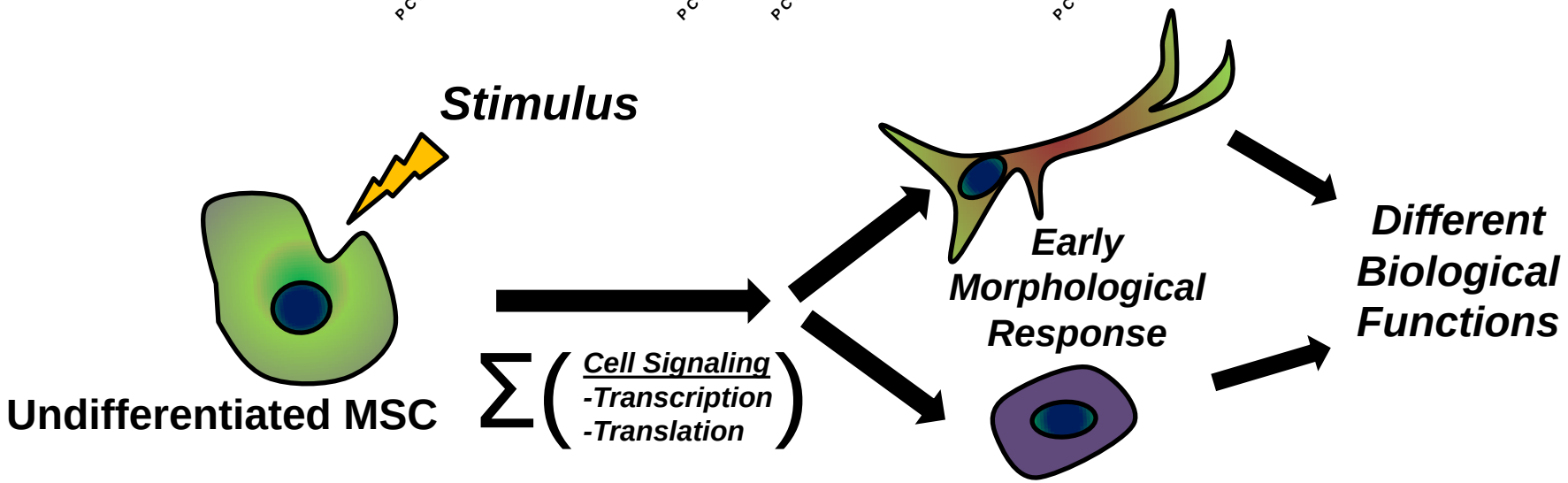


Lo Surdo JL et al., *Cytotherapy, 2013.*

Are Morphological Differences Associated With Different Biological Functions?

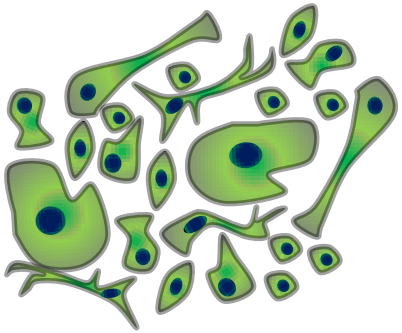
Lo Surdo JL et al., *Cytotherapy, 2013.*

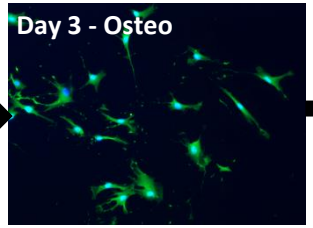


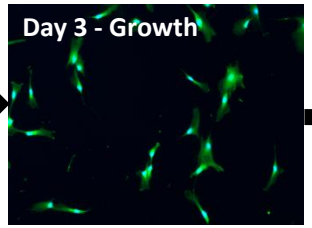


MSC Morphology Predicts Osteogenic Activity

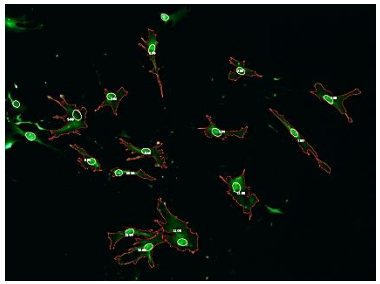
CULTURE-EXPANDED hMSCs







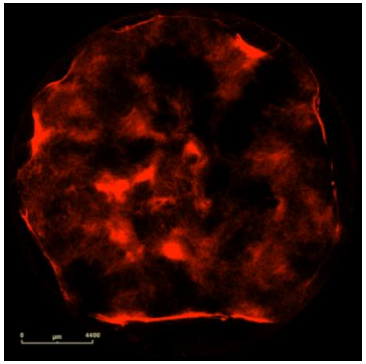
CellProfiler



Extract Cell Shape and Nuclear Shape Features (96 total)

Long-Term Osteogenic Induction (35 Days)

Short-Term Morphology Characterization (3 Days)



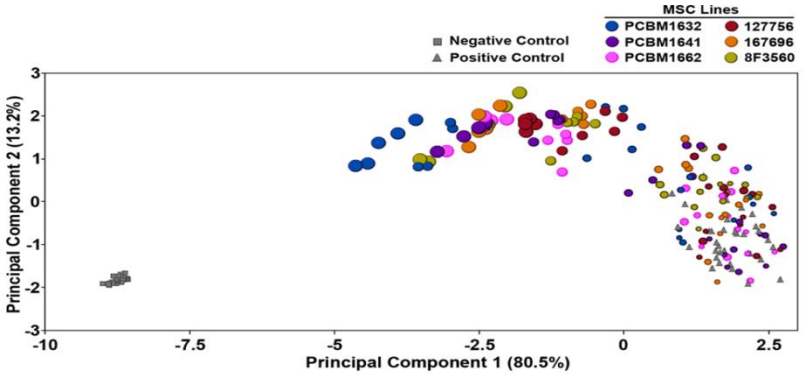
Mineralization

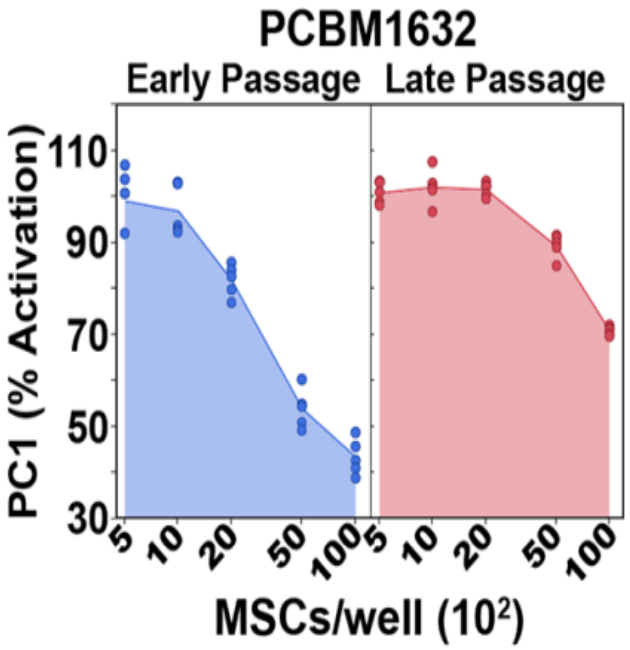
Principal Component Analysis (PCA)

Morphological 'signature' at day 3 predicts mineralization at day 35

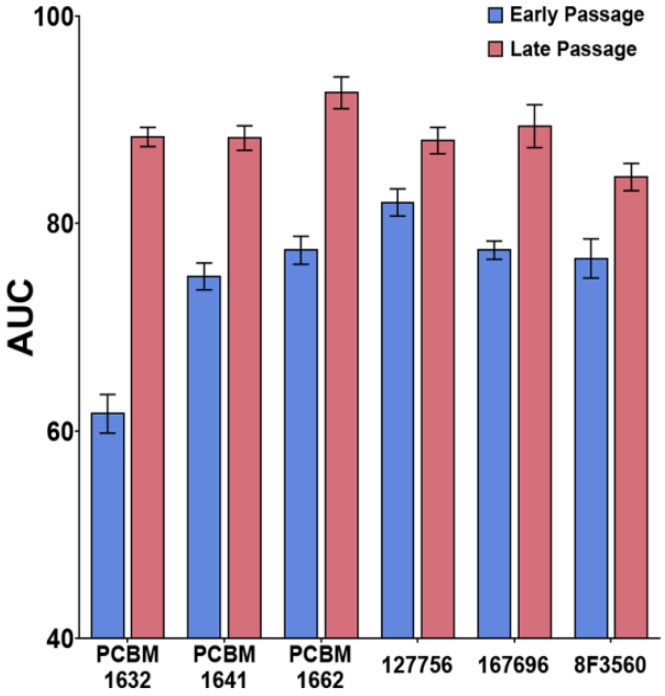
Marklein et al, Stem Cells 2016

Immunosuppressive Capacity Varies Between Cell Lines and with Culture Duration



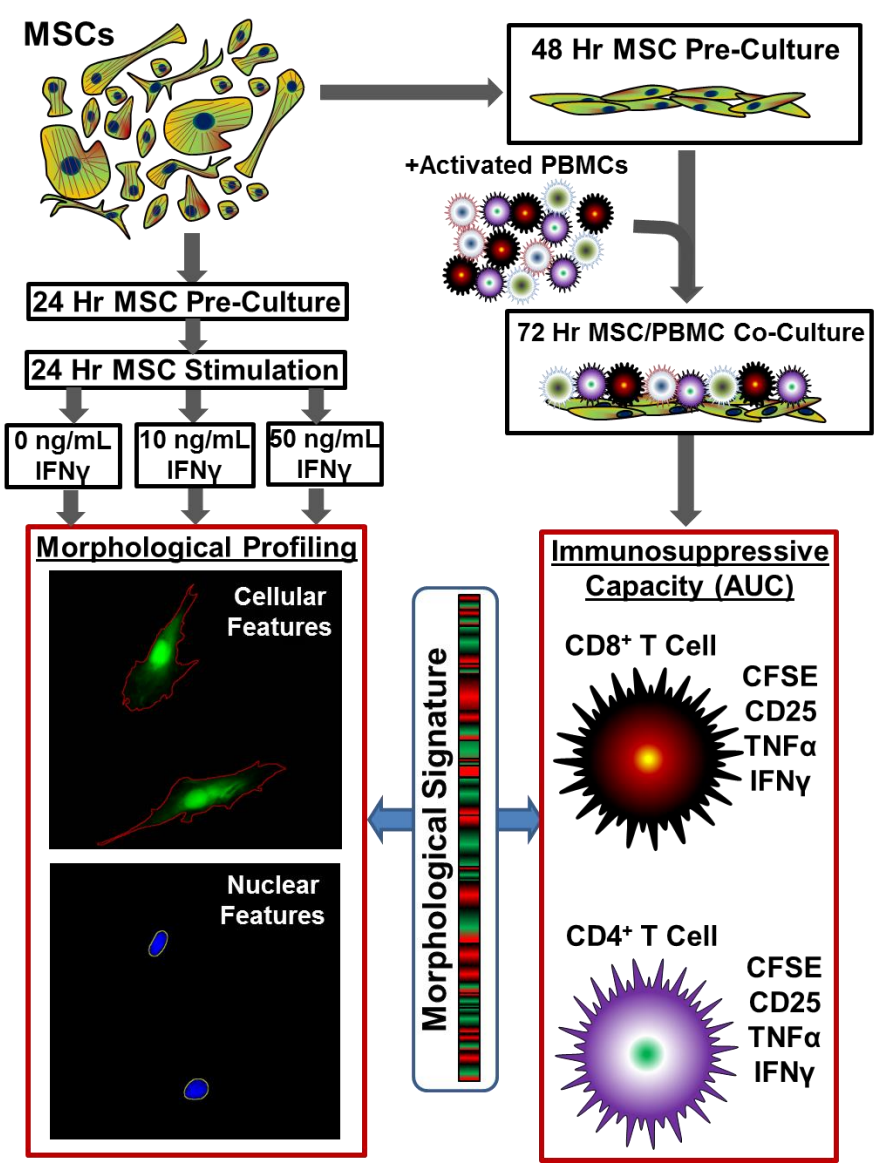


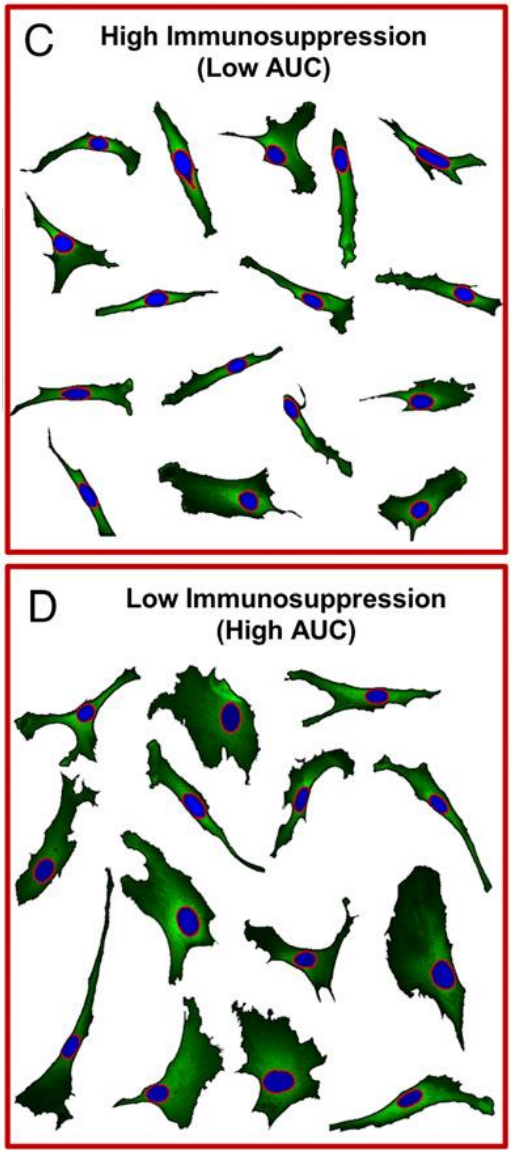
↑AUC ↓Immunosuppressive Capacity



Klinker, et al. PNAS 2017

IFNγ-Stimulated MSC Morphology Predicts Immunosuppressive Activity





MSC Consortium Outcomes

- **Demonstrated that consensus markers do not predict functional biological heterogeneity of MSCs**
- **Identified cellular characteristics that predict relevant biological properties of MSC preparations**
  - **Functionally relevant morphology**
  - **Gene expression**
- **Published findings**
  - **Sector Overview**
  - **Quantitation of Differentiation**
  - **Proteomics**
  - **Immunomodulation**
  - **Genomics**
  - **Genetic and Epigenetic Stability**

Potential Applications (1)

- Cell Source/Donor
  - Screen samples for desired biological activity
- Manufacturing
  - Evaluate impact of manufacturing process
    - Tissue culture conditions and duration
- Cell Characterization
- Identify Quality Attributes
  - Activity/Potency
    - Quantitative Bioassays
    - Molecular markers correlated with bioassay outcomes
- Guide cell enrichment techniques

Potential Applications (2)

- Standards Development
  - Quantitative bioassays
    - Osteogenesis
    - Adipogenesis
    - Immunosuppressive Capacity
    - Others?
      - Angiogenesis
      - Wound repair

MSC Consortium

Michail Alterman
- Samuel Mindaye
- Kristin Shultz-Kuszak
- Natalia Pripuzova

Steve Bauer
- Jessica Lo Surdo
- Heba Degheidy
- Ross Marklein
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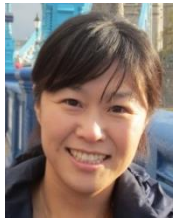
- Katie Steers



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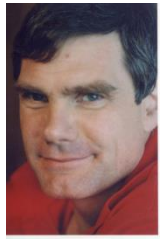
- Jennifer Mateshaytis
- Elaine Thompson
- Alexa Bianchi



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- CBER/OTAT/DCGT
- FDA Targeted Research Funds
- BARDA

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- **OCTGT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
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