Development and Integration of New Analytical Technologies in Review of Biologics by FDA Center for Biologics Evaluation and Review

Fourth AIMBE/NIH Workshop on Validation and Qualification of New In Vitro Tools and Models for The Pre-clinical Drug Discovery Process

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Outline

- CBER Organization
- CBER Regulated Products
- BLA Regulatory Environment
- OVRR product in cell substrate area
- OCTGT research in MSC area
- Concluding remarks

CBER Organization

- Three “Product” Offices
  - –Office of Vaccines Research and Review
  - –Office of Blood Research and Review
  - –Office of Cellular, Tissue, and Gene Therapies
- Supporting Offices

CBER Activities

- Regulatory review
- Mission-relevant Research
- Regulatory policy and guidance development
- Outreach to Stakeholders

What OVRR Regulates

- Antitoxins, antivenoms, most enzymes, venoms
- Vaccines (bacterial, viral, parasitic - therapy and prophylaxis)
- Adjuvants
- Allergenics

What OBRR Regulates

- Blood (collection and processing)
- Blood components (whole and cellular)
- Blood fractionation products (Ig, albumin, HGB, clotting factors)
- Diagnostic kits (HIV, hepatitis)

What OCTGT Regulates

- Stem cell and stem cell-derived products
- Somatic cell therapies
- Gene therapies
- Therapeutic vaccines and other antigen-specific active immunotherapies
- Devices and combination products

Regulatory Framework

Governing Regulations

- Code of Federal Regulations, Section 21, subchapter F
  - part 600, Biological Products
- Defines a biological product as

  "...any virus, therapeutic serum, toxin, antitoxin, protein or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man…"

  Provides the legal basis for enforcement

Regulatory Considerations for All Biologics

- Safety, efficacy, purity, potency
- Oversight of both product and process
- Quality control of product and intermediates
- Reproducibility of lots

Regulatory Flexibility 21 CFR 610.9

- Provides for modification of any particular test method or manufacturing process or the condition under which it is conducted as required in Part 600 if:
- The applicant presents evidence demonstrating that the modification is at least equal to the methods (to measure safety, purity, potency, effectiveness) in the regulations

The IND Review Process

- Emphasis of review is on data to support:
  - Product safety and characterization
  - Manufacturing and quality control issues
  - Scientific rationale
- Sound scientific principles
  - Pre-clinical studies
  - Product development
  - Clinical protocol

Goals of Preclinical Safety Evaluation

- Discern mechanism of action
- Terminate potentially unsuccessful development programs early
- Provide data to support use in IND and BLA clinical studies
- Provide data to support labeling

Goals of Preclinical Safety Evaluation

- Recommend safe starting doses and escalation schemes for humans
- Identify potential target organ(s)
- Identify parameters for clinical monitoring
- Identify “at risk” patient populations (inclusion/exclusion criteria)

Selected Differences Between Drugs and Biologics

Traditional Drugs	Biologic Therapies
Guidelines	Guiding principles
Previous examples	Unique
Historical data base	Concurrent controls
Maximal tolerated dose	Optimal biologic dose
Species-independent	Species-specific
Metabolized	Degraded
Specific mechanisms	Pleiotropic mechanisms

CBER Approach to Preclinical Safety and Toxicity Testing

- Creative, problem-solving
- Data-driven
- Should be based on best available science, technology to date
- Careful design and judicious use of animals
  - should allow early initiation of clinical studies
  - should allow uninterrupted clinical development

Critical Issues for Optimizing Predictive Value of Testing

- Review of current technologies
  - Availability
  - Appropriateness
  - Usefulness
- Consideration of new technologies
  - Identification
  - Development
  - Application
- All technologies
  - Fit for purpose

CBER Research on Innovative Products and Product Testing

OVRR Challenge

Introduction of novel cell substrates for vaccine production poses new questions of safety assessment

Parallel Evolution of Cell Substrates and Regulatory Approach

- **Primary Tissues or Cell Cultures (1950's)**
  - *21 CFR 600 series*
  - Chicken embryonated eggs; embryo fibroblasts
- **Diploid Cell Strains (1970's)**
  - *Guidelines: J. Biol. Stand., 1981*
  - Human MRC-5 and WI-38
- **Continuous Cell Lines (1980's)**
  - *Points to Consider: 1984; 1987; 1993*
  - *Guidance for Industry, 2006*
  - African green monkey VERO (non-tumorigenic)

Currently Novel Cell Substrates

- Naturally-occurring
  - Mammalian: tumorigenic cell lines and tumor-derived cells
  - Avian cell lines: embryonic stem cells
  - Insect cells
  - Plants and plant cells
  - Bacteria
- Genetically-engineered
  - new, well-characterized cell line from primary or diploid cells
  - packaging cell lines
  - a specific cell line for complementation of vectored
  - viruses

General Safety Issues Associated with Cell Substrates

- Intact cells
  - Tumorigenicity
- Residual cellular components
  - DNA (oncogenicity, infectivity)
  - Proteins (allergenic reactions)
- Adventitious Viruses
  - Exogenously-acquired (replicating viruses and latent viruses)
  - Genetically-inherited (endogenous retroviruses)
  - *de novo*-generated (novel recombinant viruses)
  - VLPs containing co-packaged “unwanted” RNA or DNA
  - Reverse transcriptase (RT) activity produced from avian and insect cells (retroviral particles/retrotransposons?)

Strategies to Mitigate Risk of Adventitious Viruses

- Identify potential safety concerns to enable development of a comprehensive testing plan and risk mitigation strategy
- Cell banking and use of qualified raw materials
- Incorporation of steps during manufacture for viral clearance and purity
- Testing
  - Extensive testing for known and unknown agents in the starting materials
  - Adventitious agent testing at different stages in manufacturing
  - Using various sensitive and broad detection assays

New Technologies for Broad/Novel Virus Detection

- Microarrays
  - Array consists of virus-specific oligos based upon known and related virus sequences: use of long primers allows for some mismatch
  - Technology uses direct application of nucleic acid to arrays or a random PCR step prior to application
- Broad-range PCR with mass spectrometry (PLEX-ID)
  - Long PCR primers that are specific for virus families
  - Amplicons are detected and sized by mass spectrometry (MS)
  - Mass of amplicons are compared with a database to identify the organism
- Massively parallel (deep) sequencing (MPS)
  - Sequencing without prior knowledge of sequences for known and novel viruses
  - Several high-throughput sequencing platforms are currently available and some are emerging

OCTGT Research

OCTGT Challenge

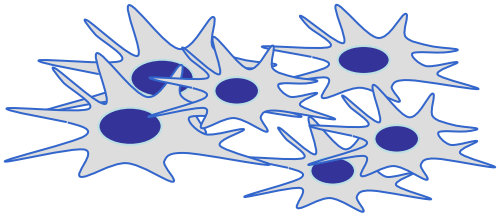
Characterization of novel cellular therapeutic “product class” with inherent and manufacturing-induced variability

Challenges for MSC Clinical Translation

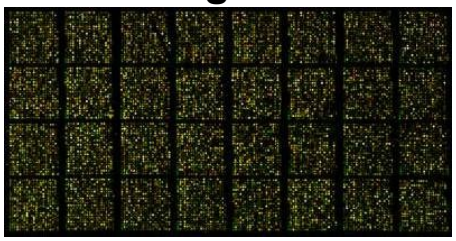
- MSCs are diverse
  - Source
  - Characterization
  - Manufacturing
- Need to better understand how these factors influence product characteristics and performance in clinical trials
- FDA reviews each regulatory submission based on its own merits, no FDA requirement for consistent nomenclature, manufacturing method, characterization method

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

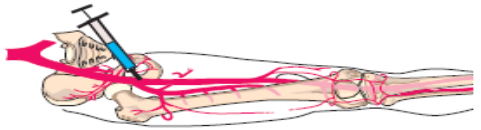
Multipotent Stromal Cell Characterization



Puri Lab: genomics

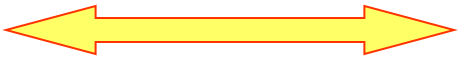


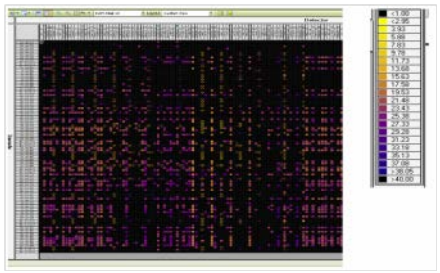
McCright Lab: *in vivo* model of critical hind limb ischemia



Bauer Lab: *in vitro* quantitative proliferation and differentiation

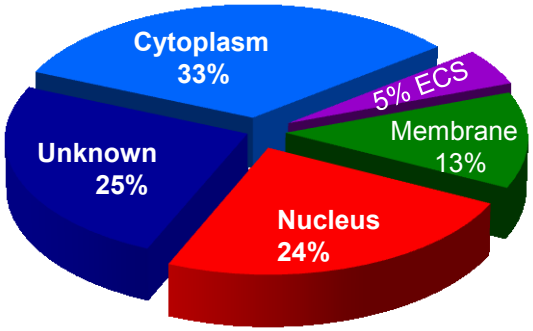
Correlate candidate attributes with assay outcomes



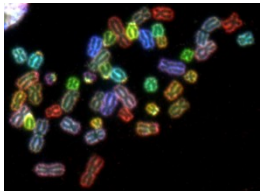


Moos Lab: gene expression, qRT-PCR, single cell PCR

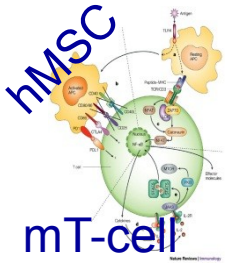
Alterman Lab: proteomics



Hursh lab: epigenetics, karyotypes



Wei Lab: *in vitro*, *in vivo* immunosuppression



ISCT proposed an industry standard to help harmonize MSC product characterization

International Society for Cellular Therapy ISCT

Cytotherapy (2006) Vol. 8, No. 4, 315–317

Taylor & Francis
Taylor & Francis Group

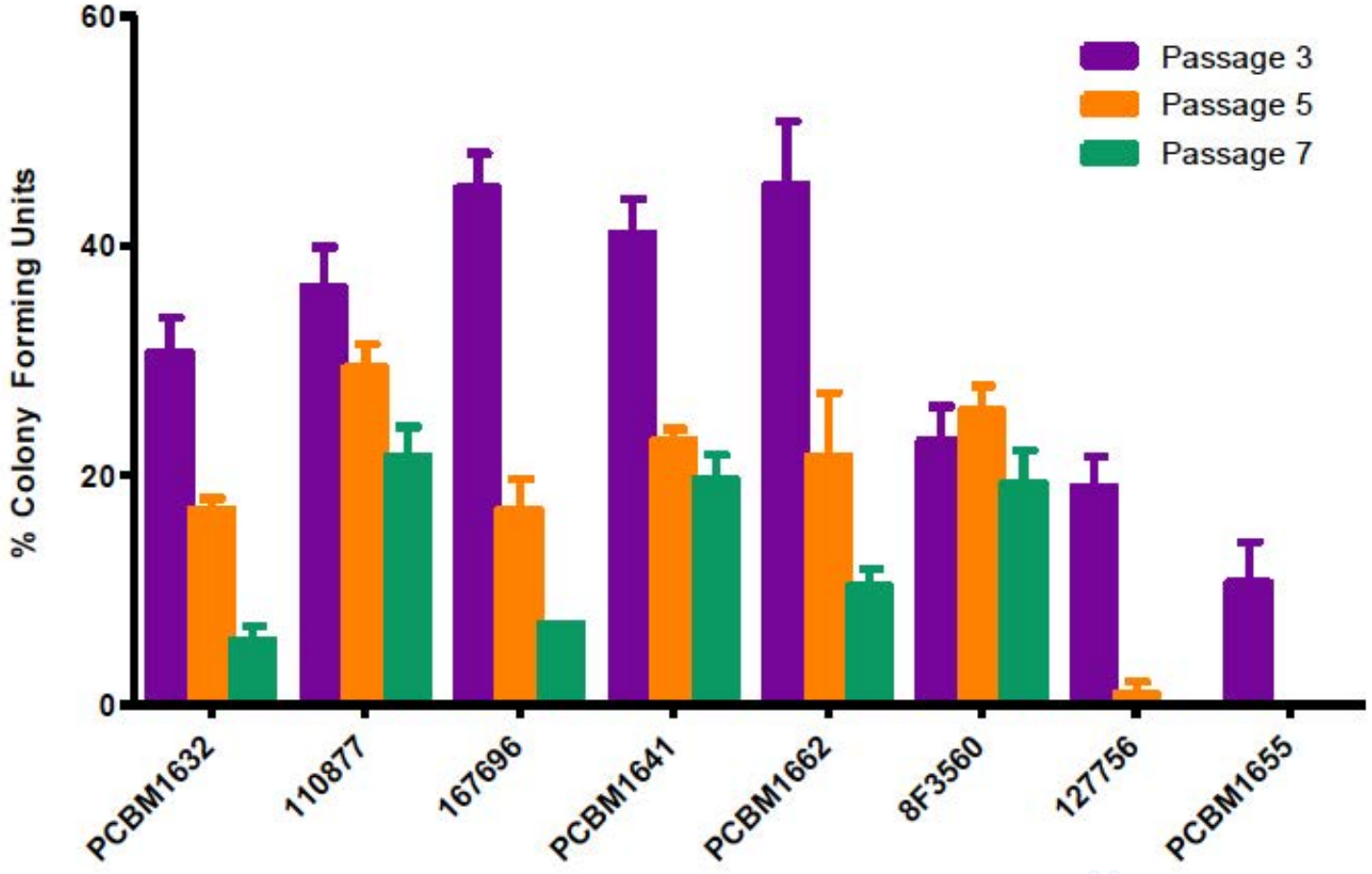
POSITION PAPER

Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement

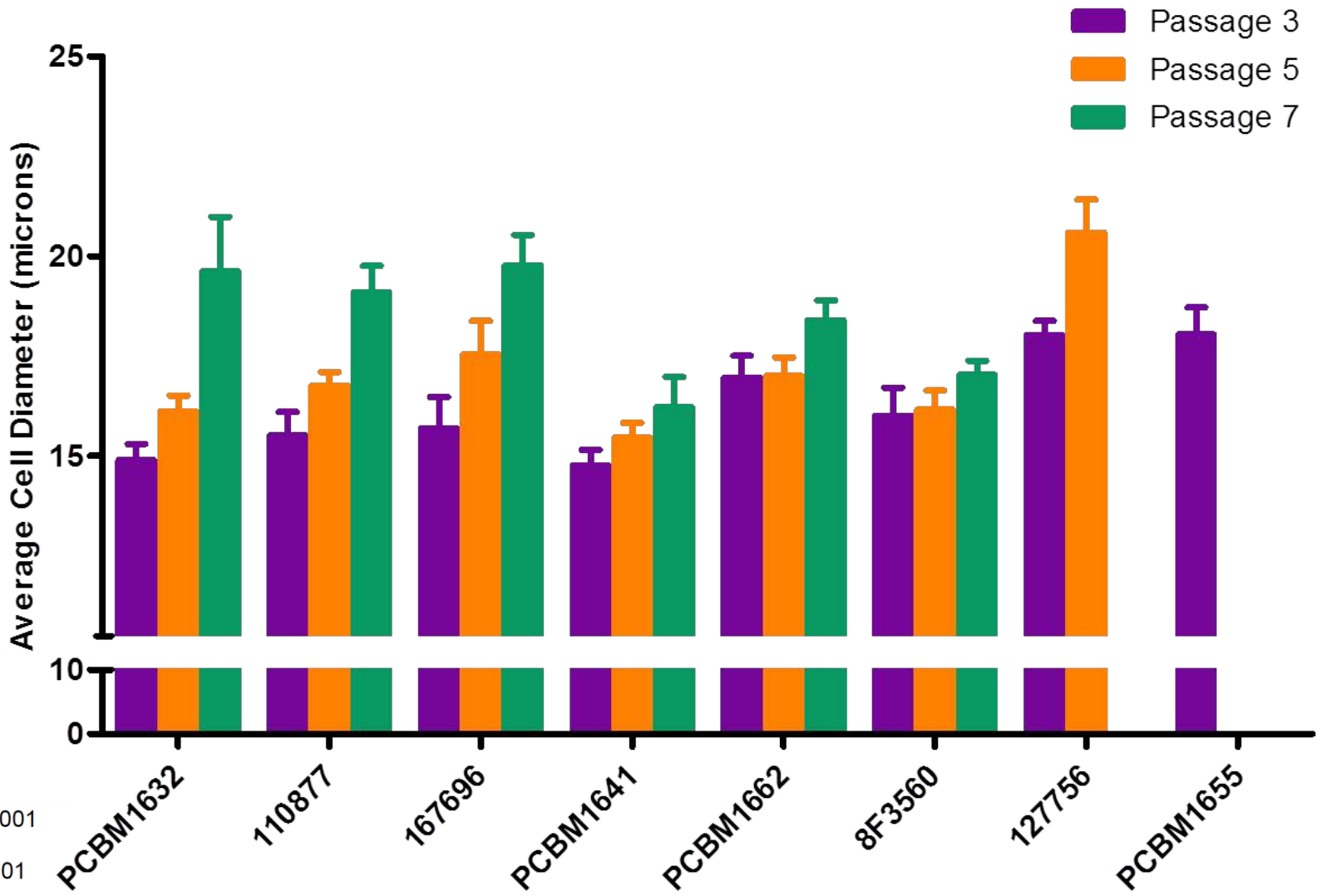
Table 1. Summary of criteria to identify MSC

1	Adherence to plastic in standard culture conditions
	[redacted]
3	*In vitro* differentiation: osteoblasts, adipocytes, chondroblasts (demonstrated by staining of *in vitro* cell culture)

CFU-F Activity Decreases with Tissue Culture Passage: Donor Differences



Cell Size Increases with Tissue Culture Passage: Donor Differences

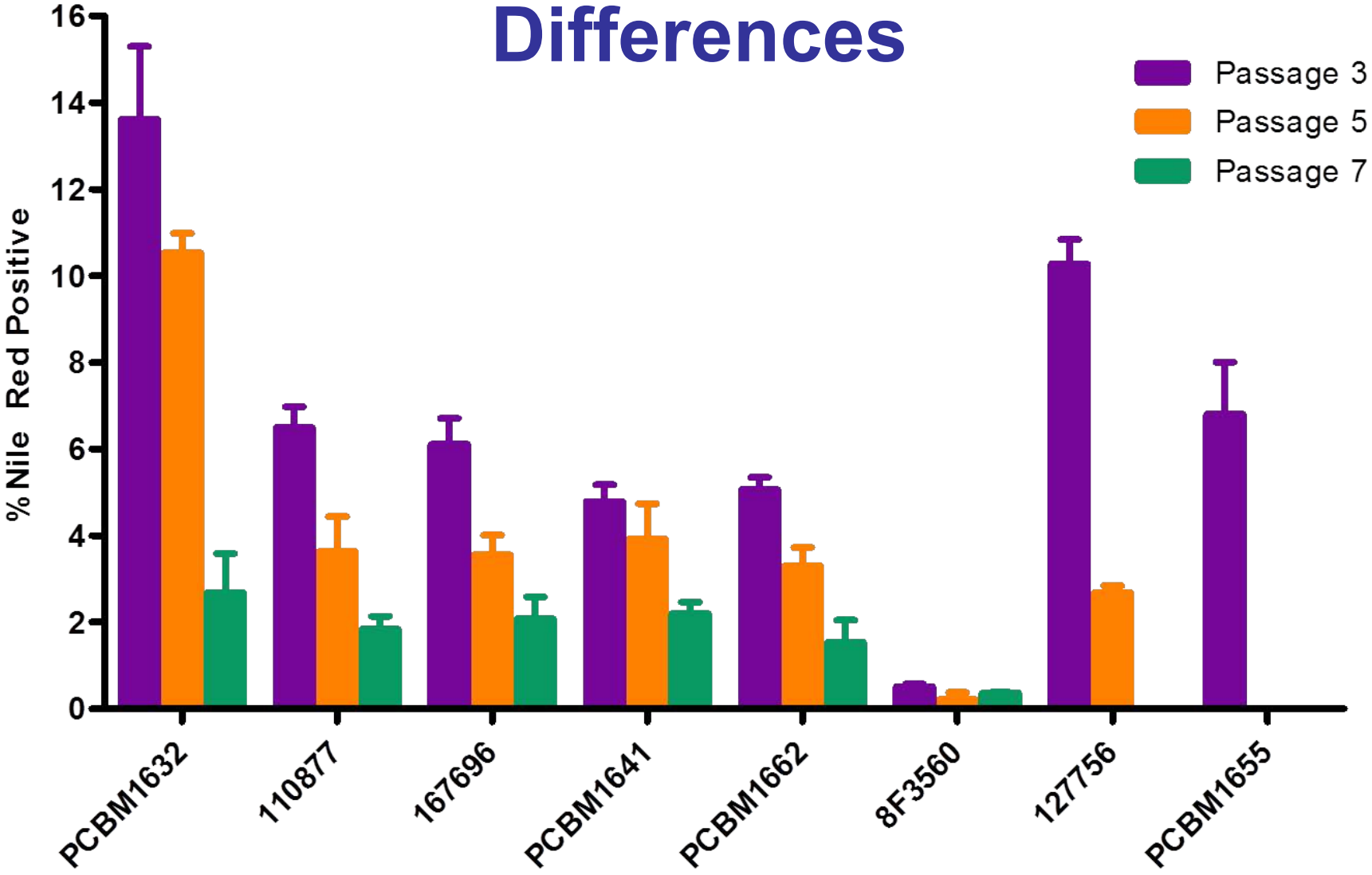


*** = p<0.001

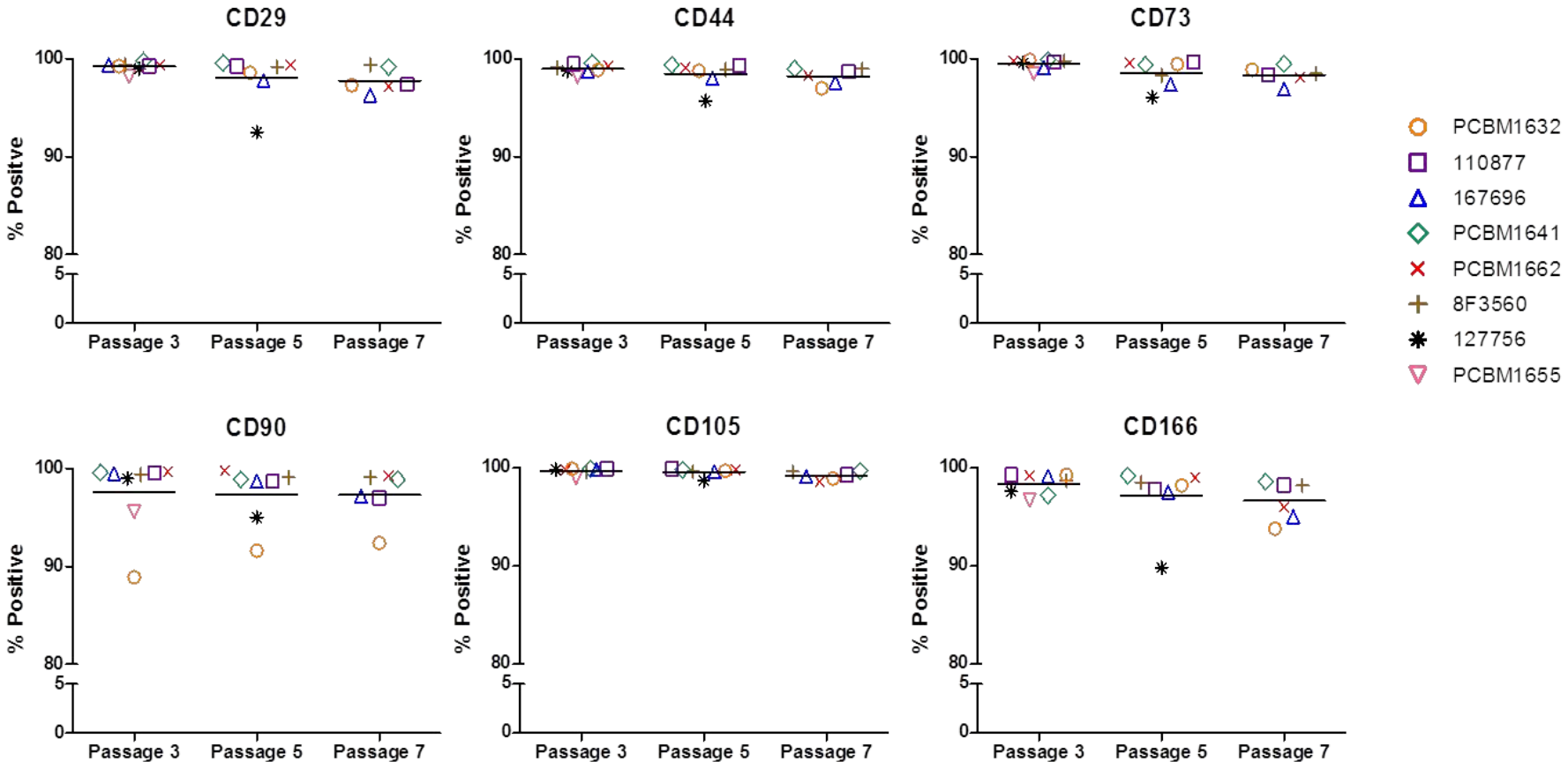
** = p<0.01

* = p<0.05

Adipogenic Activity Decreases with Tissue Culture Passage: Donor Differences



Consensus MSC Markers do not Correlate with Functional Heterogeneity, Donor or Tissue Culture Age Differences



International Society for Cell Therapy: Cytotherapy (2006) Vol. 8, No. 4, 315-317. MSCs are characterized as being adherent to plastic, capable of tri-lineage differentiation, ≥95% of the MSC population must express CD105, CD73 and CD90, as measured by flow cytometry. Additionally, these cells must lack expression (≤ 2%positive) of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA class II.

Conclusion

- CBER regulates an heterogeneous group of biologic products
- The IND and BLA regulations provide flexibility to allow use of innovative in vitro testing to support investigational and marketing of these biologics when these technologies are shown to be fit for purpose
- Research into manufacturing and safety issues of some CBER products may be informative for development of cell-based in vitro assay

Public Access to CBER

CBER website:
http://www.fda.gov/BiologicsBloodVaccines/default.htm

Phone: 1-800-835-4709 or 301-827-1800

Consumer Affairs Branch (CAB)
Email: ocod@fda.hhs.gov
Phone: 301-827-3821

Manufacturers Assistance and Technical Training Branch (MATTB)
Email: industry.biologics@fda.gov
Phone: 301-827-4081

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