

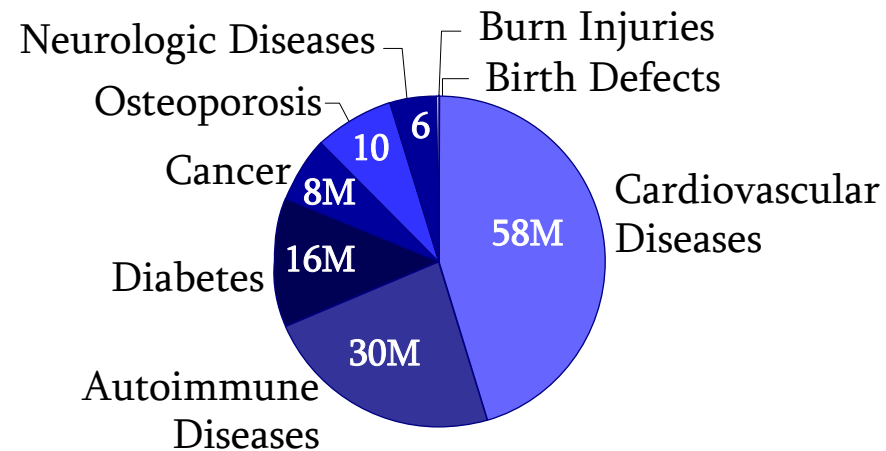
# Manufacturing Cell and Gene Therapy Products

Scott R. Burger, MD  
Advanced Cell & Gene Therapy

# Cell Therapies - Potential, Promise, and Plenty of Challenges

- Numerous potential applications, often for unmet needs
  - Potentially definitive therapies
- Novel uses of cells/genes
  - Difficult to evaluate efficacy, predict clinical risks
- Complex cell/gene engineering
  - Risk of manufacturing problems, product/process characterization challenges

Potential Patients (USA)



# Cell and Gene Therapy Applications

*Immune, hematopoietic replacement*

Cancer, autoimmune, immunodeficiency disorders

Blood, bone marrow cord blood, HPC, HSC, MSC, cord tissue cells

*Immune effector cell therapy*

Cancer, autoimmune, infectious diseases

Dendritic cells, NK cells, lymphocytes, macrophages

*Tissue repair, regeneration*

Cardiovascular, neurologic, orthopedic disorders, wound healing

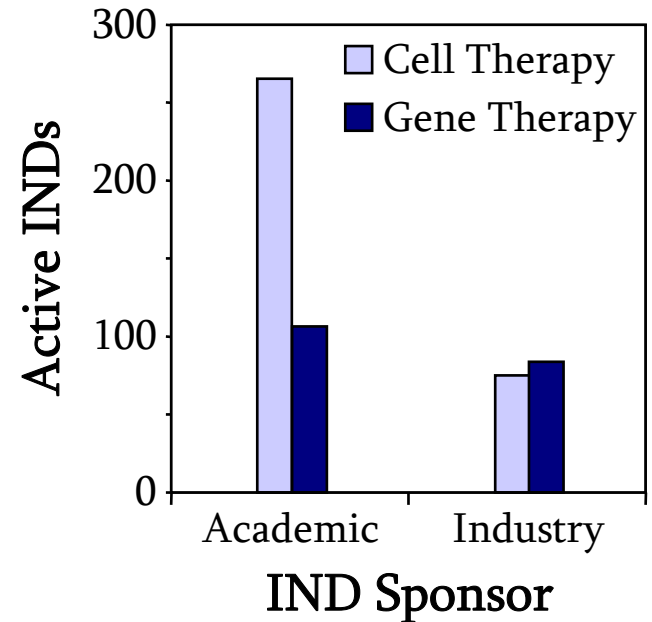
Bone marrow MSC, other stem cells, neural cells, cardiomyocytes, macrophages, chondrocytes, keratinocytes, dermal fibroblasts

*Metabolic replacement, support*

Diabetes, renal, liver failure, other metabolic disorder

Islet cells, stem cells, bioartificial liver, bioartificial kidney, hepatocytes

# An Emerging Cell Therapy Industry



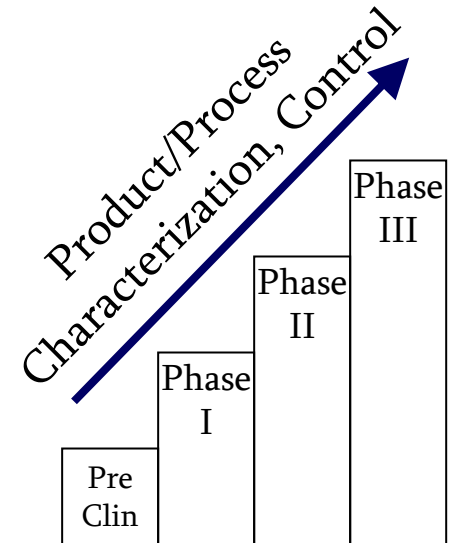
- Over 400 cell or gene therapy companies worldwide
- Over 500 cell or gene therapy products in clinical development
- Over 1,000 gene therapy clinical trials worldwide
- Industry sponsors 25% of cell therapy INDs

# Challenges of Cell-Based Therapy

	<b><i>Biotechnology</i></b>	<b><i>Cell Therapy</i></b>
<b><i>Product</i></b>	Cultured cells generate product	Living cells <i>are</i> product
<b><i>Raw Material</i></b>	Seed cell lines	Unique, primary tissue
<b><i>Variability, Heterogeneity</i></b>	Limited	Substantial
<b><i>Product Definition</i></b>	Well-defined, definable products	Product defined through trials Full definition likely unattainable
<b><i>Process, Testing</i></b>	Established early	Evolve through trials
<b><i>Process Scale</i></b>	Bulk processes predominate	Patient-specific products common

# Development Throughout Clinical Trials

- Evolution of manufacturing process, characterization profile
  - Processes, specifications refined based on experience
- FDA expects  $\uparrow$  control/characterization as clinical development progresses
  - Preclinical - basic process control, characterization
  - Phase III - full characterization, GMPs, GTPs



# Manufacturing Processes

- Cryopreservation
- Cell selection
- *Ex vivo* culture
  - Expansion, maturation, selection, other
- Cell activation
- Genetic modification
- Tissue processing
- DNA/RNA purification, amplification

# Cell Therapy Product Manufacturing Strategies

- Manufacturing process must protect product, patient
- Focus on product characterization, process control
  - Controlled, consistent processes → controlled, consistent products
  - Rigorous, ongoing process development and characterization
- High throughput, parallel processing to achieve scale
  - Functionally-closed processing systems, automation

# Automated, Functionally-Closed Systems: Making Coffee One Cup at a Time

Individualized, cup-specific brewing of a variety of coffees, teas, cocoa, *even mochaccino with extra foam*.



Preloaded, disposable,  
individualized raw  
material sets



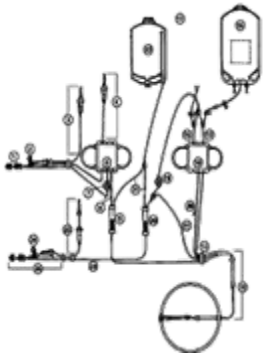
Separate process  
environment  
for each product



Automated  
processing  
device

# Automated, Functionally-Closed Systems: High Throughput Cell Therapy Manufacturing

Individualized manufacturing, run in parallel for high throughput - cell selection, expansion, activation, centrifugation, cryopreservation.



Preloaded, disposable,  
individualized raw  
material sets



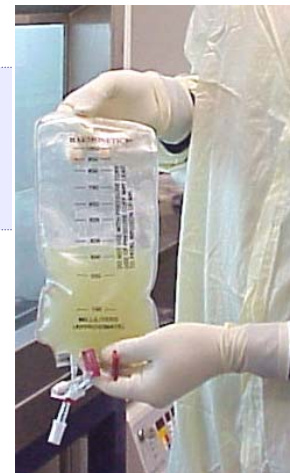
Separate process  
environment  
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Automated  
processing  
devices

# Open vs. Closed-System Manufacturing

	<u>Open</u>	<u>Closed</u>
<i>Contamination Risk</i>	↑	↓
<i>Cell Yield</i>	↓	↑
<i>Manufacturing Space</i>	Cross-contamination risk limits options	Maximal effective use
<i>Consistency, Control</i>	Limited	↑ ↑ ↑
<i>Throughput Potential</i>	↓ ↓ ↓ Patient-specific	↑ ↑ ↑ Parallel processing Readily automated Presterilized, disposable



# FDA Requirements - GCPs, GTPs, GMPs

Good Manufacturing Practices (GMPs)	Ensure consistent manufacture of safe, pure, potent products
Good Tissue Practices (GTPs)	Prevent infectious disease transmission Donor screening and testing
	Prevent cross-contamination, mixups Product recovery, processing, storage, labeling, distribution
Good Clinical Practices (GCPs)	Ethical, scientific quality standards Protect trial subjects rights, safety, confidentiality Assure credibility of clinical trial data

# GMP, GTP Systems Needed

## GMPs

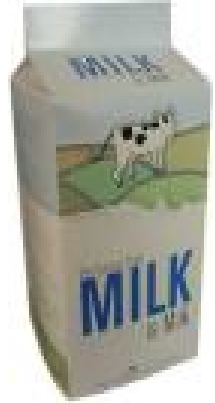
- Organization, personnel, training, evaluation
- Buildings and facilities
- Equipment, reagents and supplies
- Procedures
- Production and process controls
- Finished product control
- Laboratory controls
- Records and reports

## GTPs

- Organization, personnel
- Facilities, monitoring
- Equipment, supplies and reagents
- Quality program
- Procedures
- Process validation, controls, changes
- Storage, receipt, distribution
- Tracking
- Labeling controls, records, complaint file

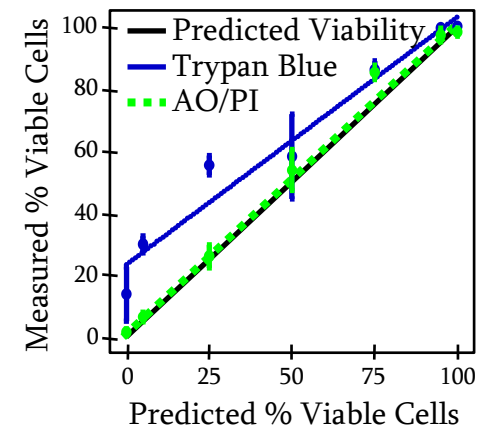
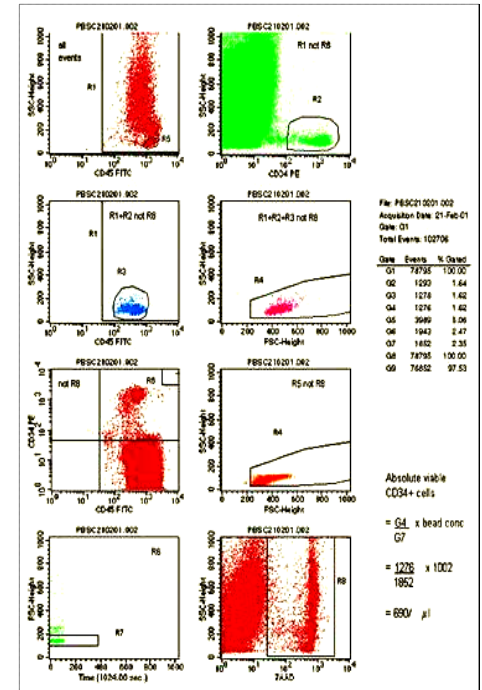
# Formulation - Stability - Shelf-Life

- Fresh (non-cryopreserved) products
  - Product stability drives release, distribution, administration
  - Release on 24/48 hr sterility culture, endotoxin, Gram stain
  - Need effective rapid sterility testing
- Cryopreserved products
  - Manufacturing and administration flexibility, but...
  - Thaw and administer product with cryoprotectant
  - Thaw, wash, administer - manufacturing at clinical site
    - Post-wash, stat Gram stain and endotoxin
    - *Need functionally-closed device for thaw/wash/resuspension*
- Novel preservation alternatives
  - Possibilities for DMSO-free, non-frozen preservation



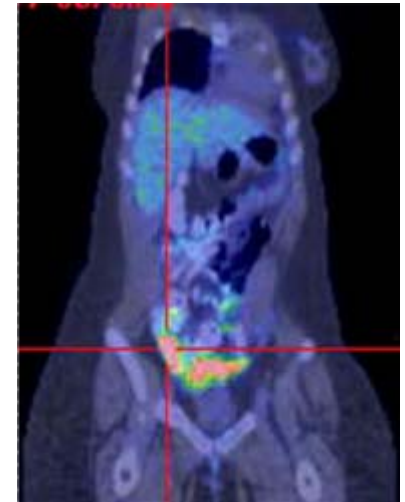
# Product Characterization

- Characterization strategy
  - Test multiple parameters, establish *pattern* of product characterization data, *refine over time*
  - May need novel analytical tools
  - Robust, qualified analytical methods
    - Documented reproducibility, predictive value, sensitivity, specificity
- Safety, Purity/Identity, Potency

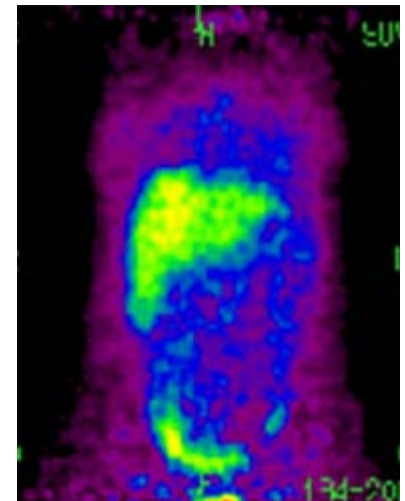


# Cell Distribution *In Vivo*

- Imaging technology for *in vivo* cell tracking
  - Cell distribution, kinetics
  - Fluorescence, magnetic particle-based imaging
  - Isotopic imaging - PET-CT, SPECT
- Development and regulatory applications
  - Clues to biological function
  - Animal model qualification
    - Human cells? Animal cells?
  - Bridge manufacturing changes
    - Fresh *vs.* frozen/thawed? Serum *vs.* serum-free?
  - Patient monitoring



Pre-Rx PET



FDG-labelled MAK cells  
t = 3 hr., PET-CT

# Summary

Unprecedented numbers of cell therapy products are in development for a remarkable range of clinical applications. These living biological products present unique challenges in development, manufacturing, characterization, and delivery

- Rigorous, evolving characterization and process control vital to address biological heterogeneity, variability, incomplete definition.
- Begin preparing for manufacturing *early*, and expect changes. Processes/analytical methods/product definition must evolve over multiple clinical trials.