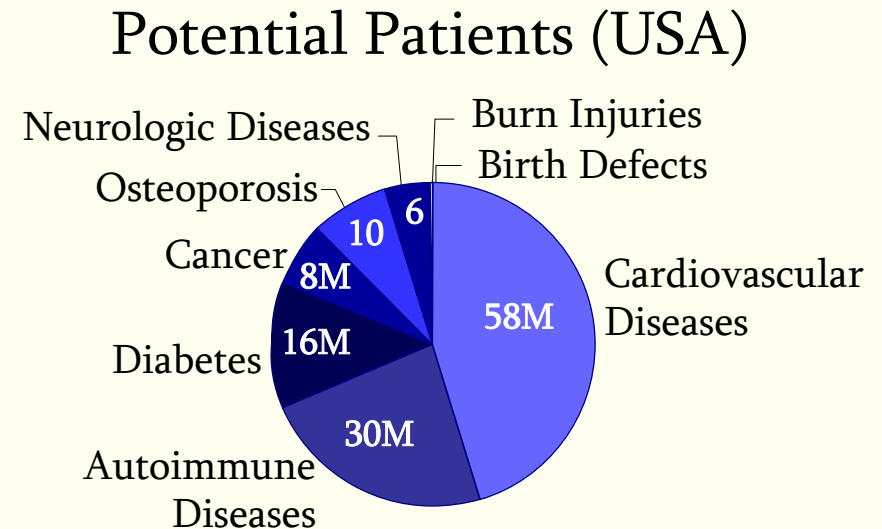


Developing Cell Therapy Product Manufacturing: Avoiding the Pitfalls

Scott R. Burger, MD
Advanced Cell & Gene Therapy

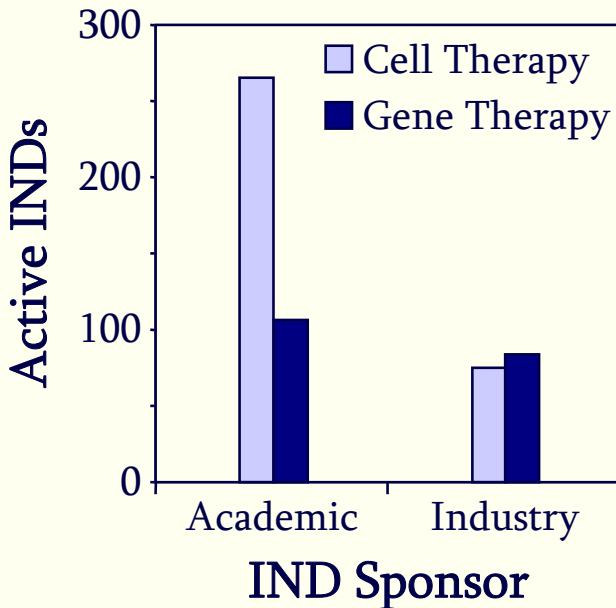
Cell and Gene Therapies - Promise, Potential, and Plenty of Challenges

- Numerous potential applications, often for unmet needs
 - Potentially definitive therapies
- Novel uses of cells/genes
 - How does the product function?
 - Difficult to evaluate efficacy, predict clinical risks
- Complex cell/gene engineering
 - ↑ Risk of manufacturing problems
 - Challenges in product and process characterization

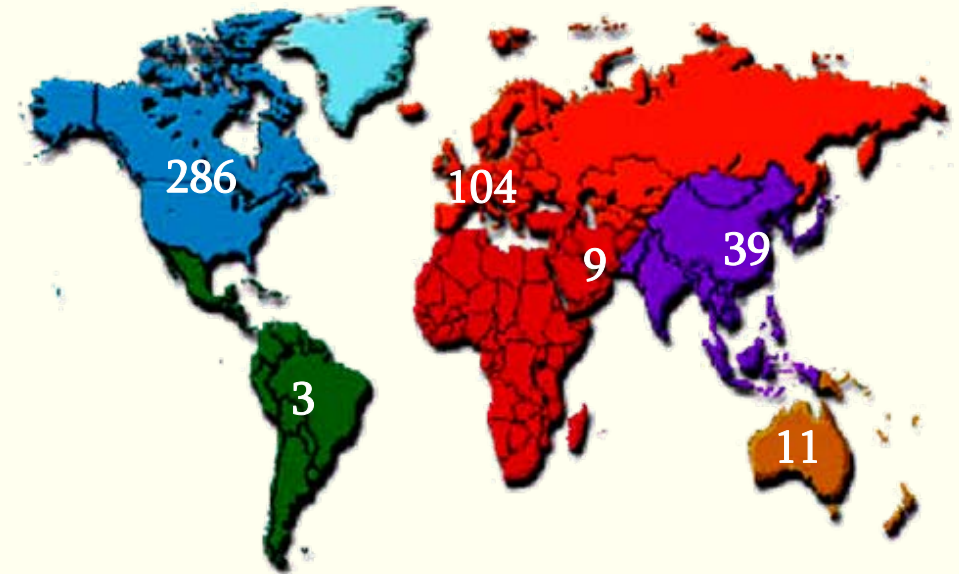


An Emerging Cell and Gene Therapy Industry

Industry sponsors 25%
of cell therapy INDs

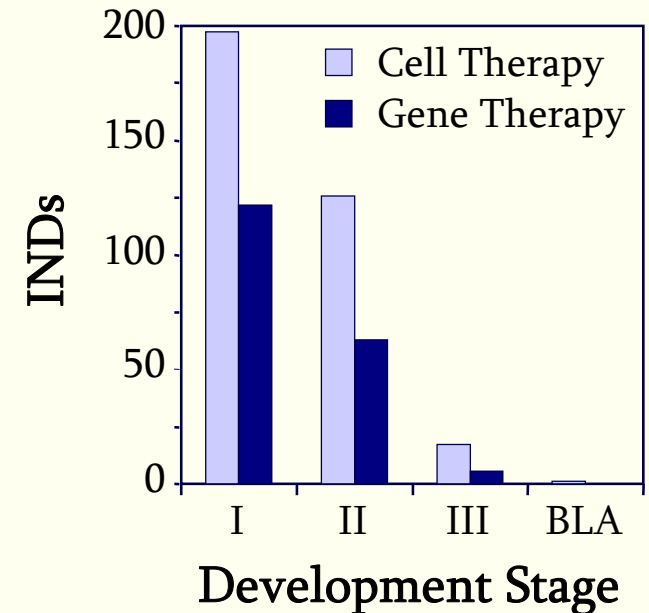


>400 cell and gene therapy
firms worldwide



Why Do Cell and Gene Therapy Products Fail in Clinical Development?

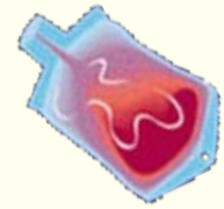
- Major drop-off post-Phase II
- Damage is often self-inflicted - common root causes of failure
 - Inability to manufacture, deliver product (inadequate/undeveloped processes)
 - Inability to adequately characterize product (inadequate/undeveloped characterization)
 - Inability to evaluate efficacy - animal model limitations, problematic clinical endpoints
 - Lack of critical enabling infrastructure
 - Financial considerations



Cell Therapy Products - Intrinsic Challenges

- Product definition
 - Living, functional cells, not the products of cells
 - Biological variability/heterogeneity
 - Product function?
- Process scale
 - Immune compatibility → patient-specific products
 - Commercialize at 1 lot per patient?
- Limited infrastructure/technology/reagents
 - Novel therapies and therapeutic strategies
- Evolving, iterative development
 - Processes, specifications refined through trials

>99% CDX⁺ cells



?% CDY⁺ cells

?% CDY⁻ cells

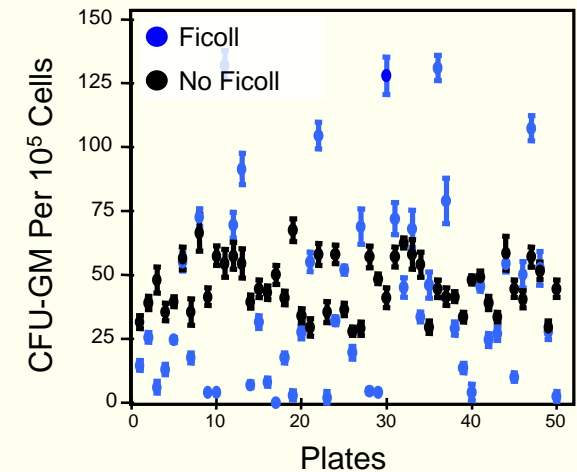
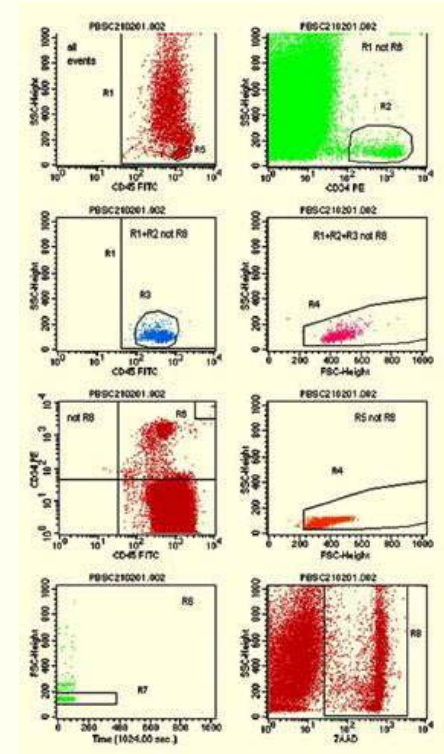
	<u>INDs</u>	<u>Amendments</u>
Cell Tx	903	13,527
Gene Tx	372	8,090

Strategies for Cell and Gene Therapy Product Manufacturing

- Manufacturing *process* must protect product, patient
 - Focus on product characterization, process control
 - Controlled, consistent processes → controlled, consistent products
 - Process qualification (PQ) studies to bridge process changes
- High throughput, parallel processing to achieve scale
 - Functionally-closed processing systems, automation
- Ongoing process development, and rigorous product characterization

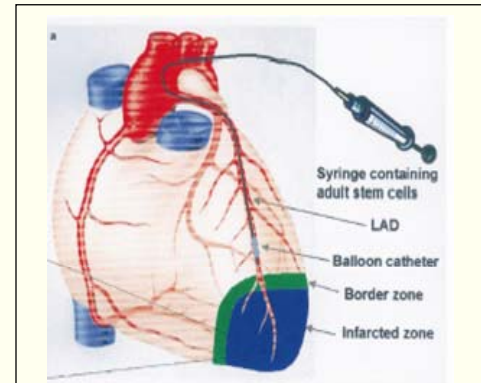
Product Characterization

- Safety
 - Sterility, endotoxin, mycoplasma, adventitious agents
- Purity, Identity
 - Cell viability, concentration, morphology, immunophenotype...
- Potency
- 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

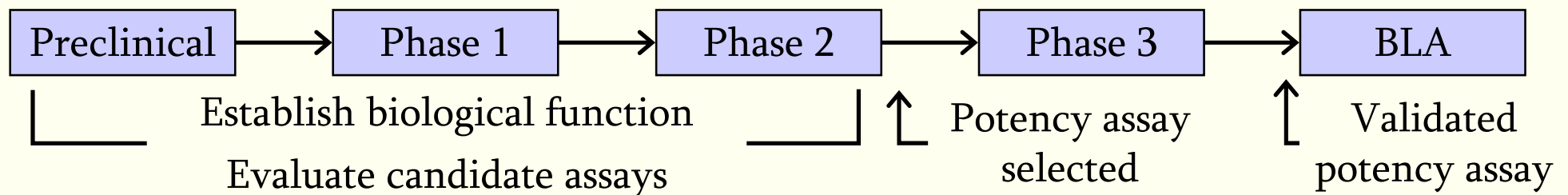


Potency Testing

- Testing “relevant biological function”
 - Understanding product function refined from preclinical to Phase III
- Potency assays
 - Evaluate candidate assays across Phase I, II trials, assess in light of clinical data
 - Functional assay turnaround time problematic, qualify real-time surrogate assays

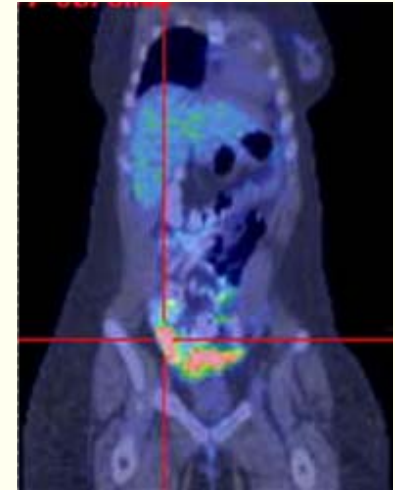


Direct or indirect repair? Humoral factors?
In vitro correlates for % fractional shortening by echo?

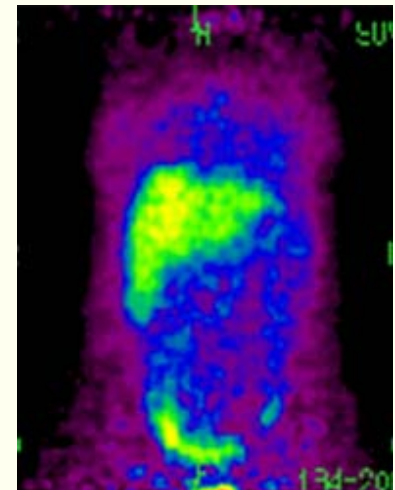


Cell Distribution *In Vivo*

- 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

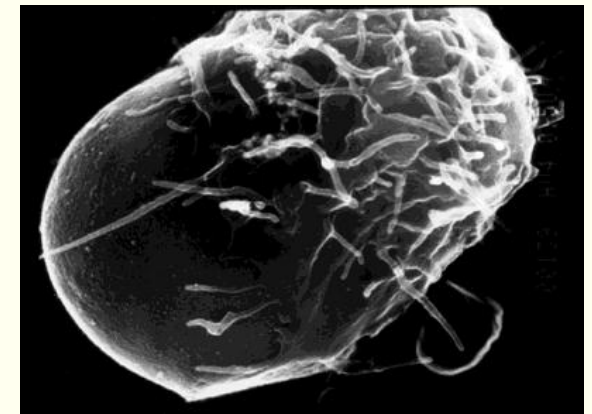


FDG-labelled MAK cells
t = 3 hr., PET-CT

Raw Materials for Cell and Gene Therapies

- Viable, functional biological raw material
 - Cell/tissue source for development studies?
- Reagents, supplies
 - Complex, often unique - cytokines, vectors, genes, culture media, supplements, mAbs...
 - GMP manufactured reagents needed
 - Develop reagent specifications, qualify
 - Physical characteristics, QC, qualification testing, storage conditions, expiration
 - Manufacturer Service Level Agreements
 - Helpful reference
 - USP Chapter 1043, Ancillary Materials for Cell, Gene, and Tissue-Engineered Products

Human serum (AB-, autologous)
Fetal calf serum, horse serum
Monoclonal antibodies
Recombinant vectors
G-CSF, GM-CSF, EPO, TPO
IL-1 α , IL-1 β , IL-2, IL-3
IL-4, IL-6, IL-7, IL-8,
TNF- α , PG-E₂
SCF, FL, Flt3, VEGF
BMP-4, EGF, IGF
PDGF-BB, MIP-1 α , MCP-1
TGF- β 1, aFGF, bFGF
N-desulfated O-sulfated heparin



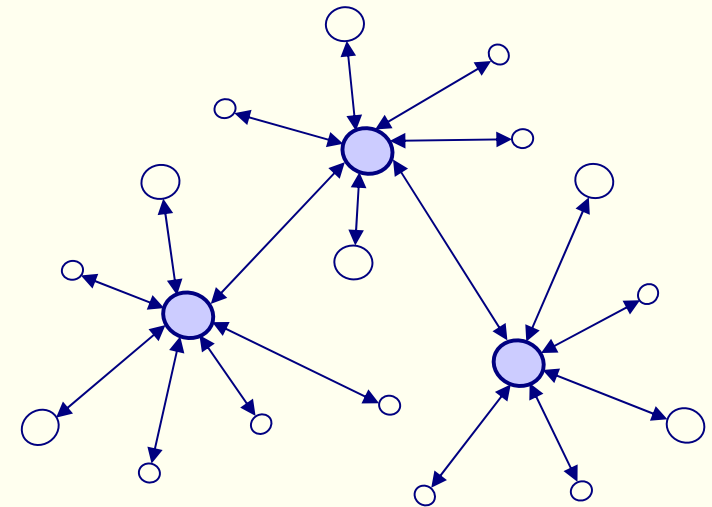
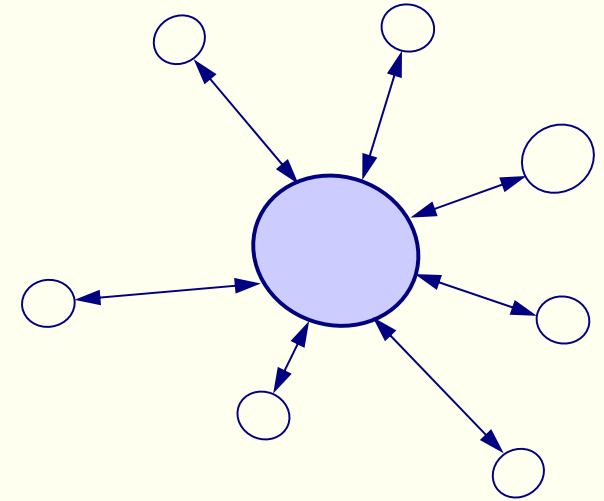
Manufacturing in Open vs. Closed Systems

	Open	Closed
Contamination Risk	↑	↓
Cell Yield	↓	↑
Manufacturing Space	Limited options X-contamination	Maximizes effective use
Consistency, Control	Limited	↑ ↑ ↑
Throughput Potential	↓ ↓ ↓ Patient-specific	↑ ↑ ↑ Parallel processing Readily automated Presterilized, disposable



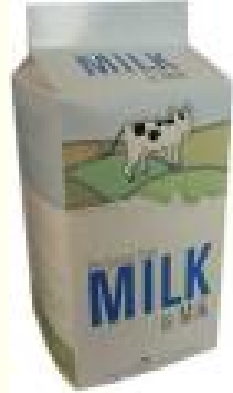
Centralized or Distributed Manufacturing?

- Centralized
 - One facility to control
 - Robust, controlled, validated transport, and environmental monitoring during shipping
 - Raw material and product stability
- Distributed
 - Multiple manufacturing facilities to control, liability concerns
 - Shorter-range transport, but shipping still must be controlled, qualified, monitored
 - Manufacturing at clinical site - very problematic unless extensively automated



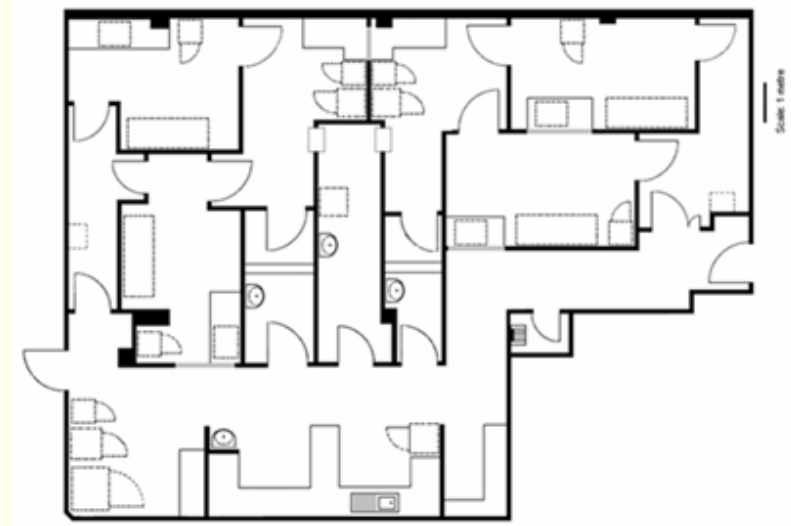
Formulation - Stability - Shelf-Life

- 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
 - DMSO-free, non-frozen preservation?



Contract Services

- Academic-based laboratories, n <5
 - Decades of experience in cell therapy, state-of-the-art cell therapy technology
 - Cell therapy GMP usually well established, GTP in progress
 - Not primarily contract service labs, use external contracts to help support facility
- Commercial laboratories, n <5 worldwide
 - Experience emphasizes cell line/vector production, not clinical cell therapy
 - Most are GLP, some GMP capabilities
 - Contract services are primary mission
- Vendor audit, qualification - essential



Summary

- Cell therapy products - living biologicals - present unique challenges in development, manufacturing, characterization, and delivery.
 - Evolving characterization and rigorous process control needed to address intrinsic heterogeneity, variability, and incomplete definition.
 - Begin preparing for manufacturing *early*, and prepare for changes. Processes/analytical methods/product definition must evolve over multiple clinical trials.
 - Manufacturing in functionally-closed systems enables automated, parallel processing at high throughput - overcomes process scale limitations of patient-specific products.