

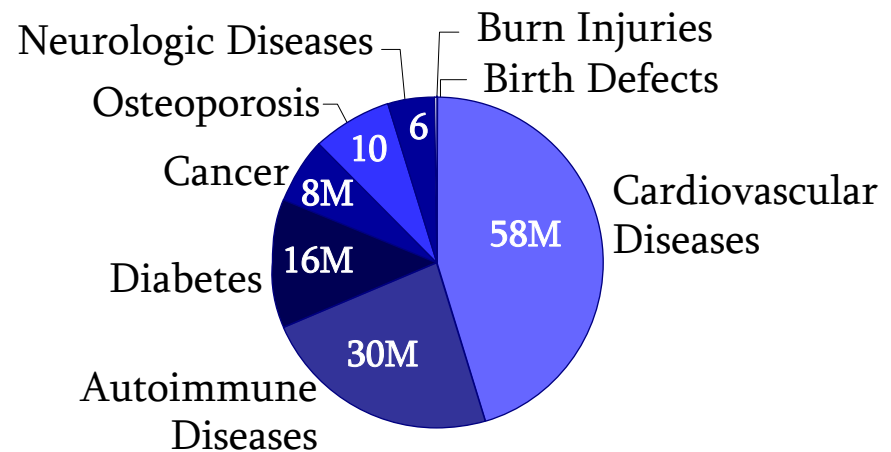
Manufacturing Cell and Gene Therapy Products: Overcoming the Obstacles

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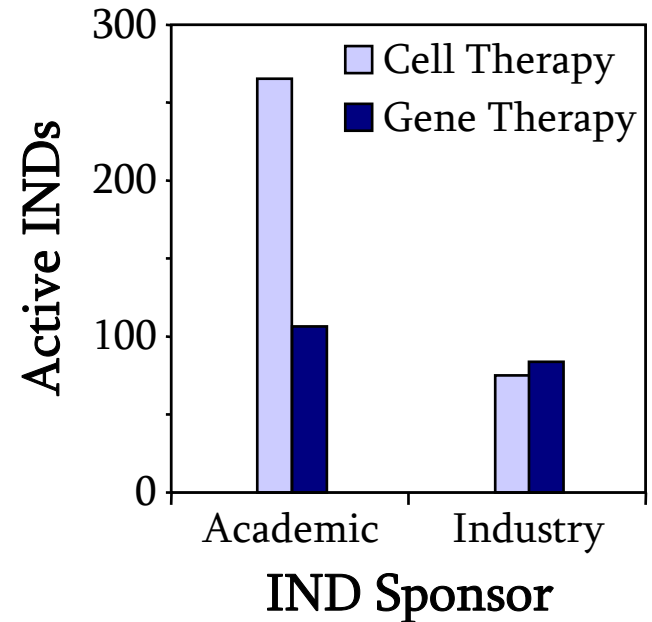
Cell Therapies - Potential, Promise, and Plenty of Challenges

- 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)



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

Unique Challenges of Cell Therapy

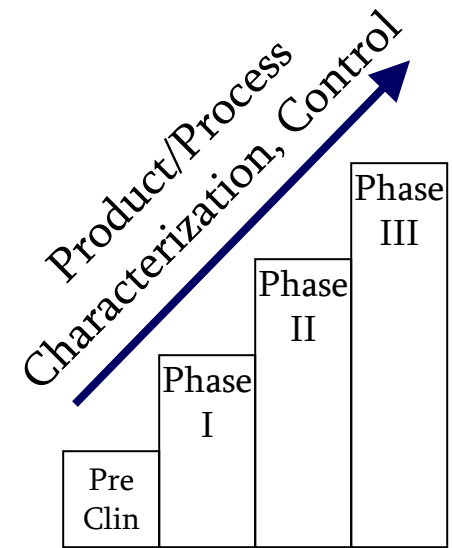
	<i>Biotechnology</i>	<i>Cell Therapy</i>
<i>Product</i>	Cultured cells generate product	Living cells <i>are</i> product
<i>Raw Material</i>	Seed cell lines	Unique, primary tissue
<i>Variability, Heterogeneity</i>	Limited	Substantial
<i>Product Definition</i>	Well-defined, definable products	Product defined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

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

Process/Analytical Development Throughout Clinical Trials

- Ongoing, iterative development of manufacturing process and characterization profile
 - Refine processes, specifications based on clinical manufacturing experience, characterization data
- FDA expects increasing control, characterization as clinical development progresses
 - Preclinical - basic process control, characterization
 - Phase III - full product characterization, full GMPs, GTPs



Cytotherapy 2003 5:289-298
Cell & Gene Therapy 2004 1:16-22
FDA-CBER Draft Guidance for CMC
Reviewers of Cell Therapy INDs.

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



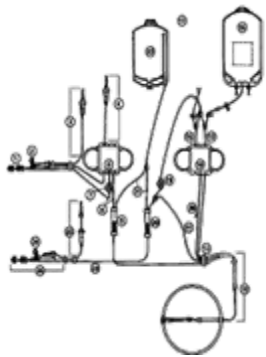
Separate process
environment
for each product



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,
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Separate process
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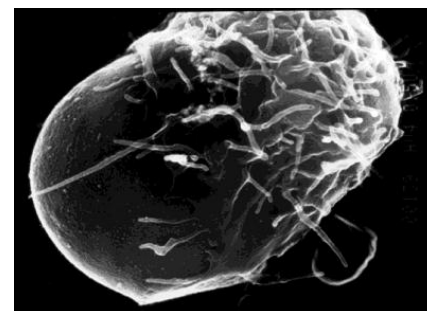


Automated
processing
devices

Raw Materials

- Viable, functional biological raw material
 - Cell/tissue source for development studies?
- Reagents and supplies
 - Complex, often unique - cytokines, vectors, genes, culture media, supplements, mAbs...
 - Need for GMP manufactured reagents
 - Develop reagent specifications, qualify
 - Physical characteristics, quality control, qualification tests, storage conditions, expiration
 - Manufacturer Service Level Agreements

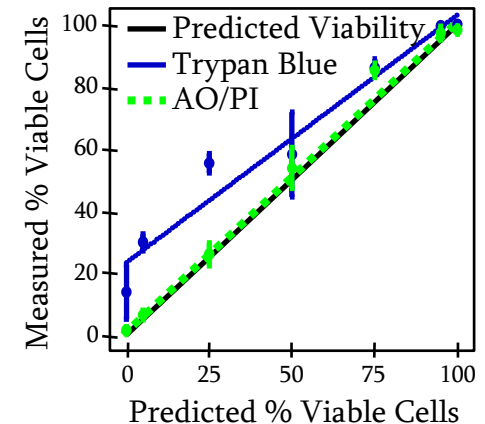
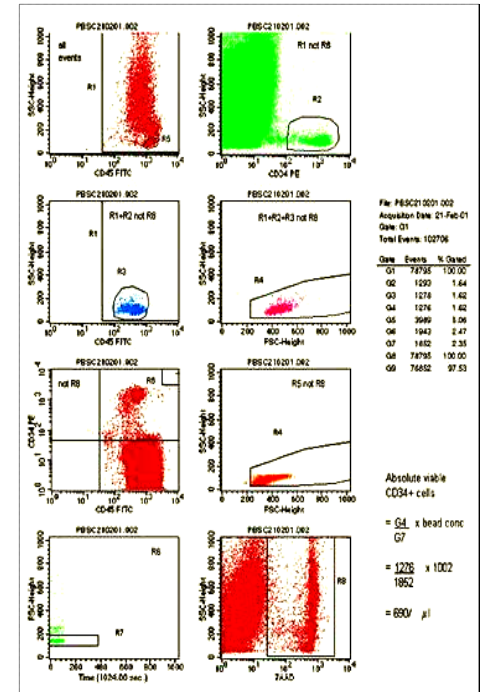
Human serum (AB-, autologous)
Fetal calf serum, horse serum
Monoclonal antibodies
Recombinant vectors
G-CSF, GM-CSF, EPO, TPO
IL-1 α , IL-1 β , IL-2, IL-3
IL-4, IL-6, IL-7, IL-8,
TNF- α , PG-E₂
SCF, FL, Flt3, VEGF
BMP-4, EGF, IGF
PDGF-BB, MIP-1 α , MCP-1
TGF- β 1, aFGF, bFGF
N-desulfated O-sulfated heparin



J Immunol Methods 2001

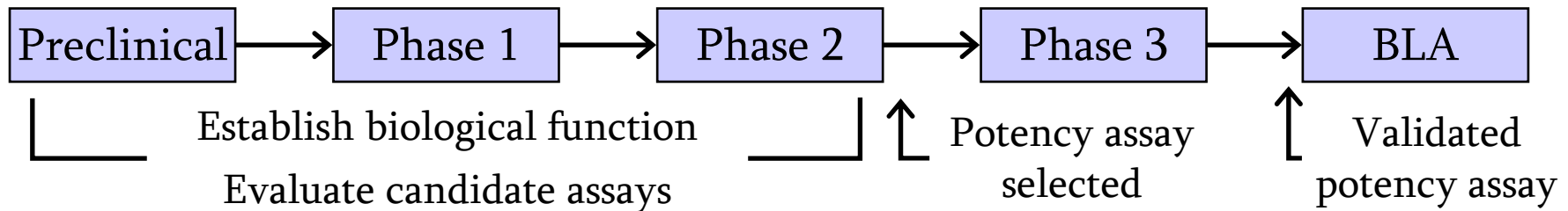
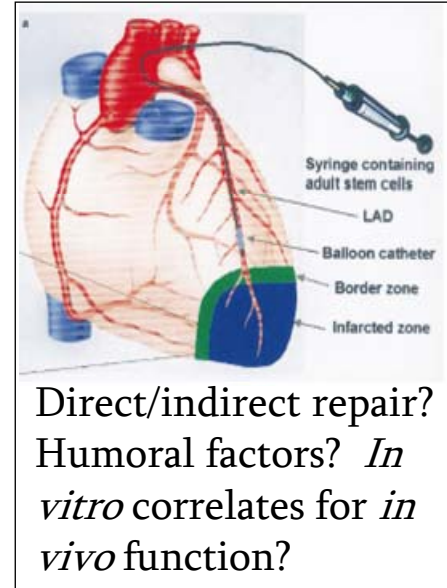
Product Characterization

- 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
 - 21 CFR 610 methods, *or demonstrate equivalence*
 - BLA - 21 CFR 610 methods or validated alternative methods



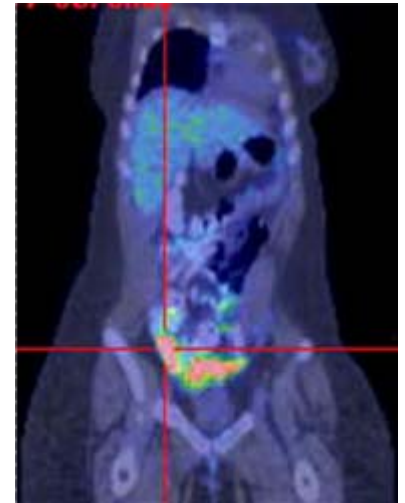
Product Characterization - Potency

- 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
 - Qualify surrogate assays giving real-time results

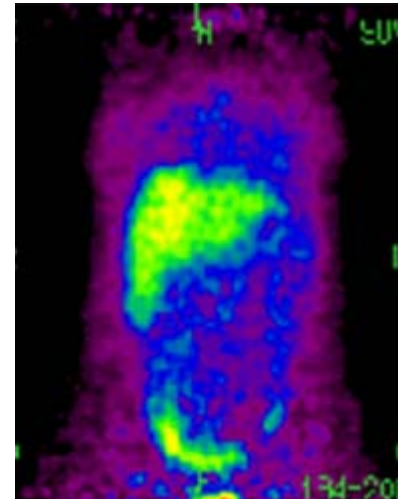


Cell Distribution *In Vivo*

- 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

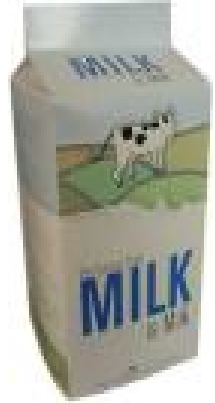
Contract Services

- Academic-based laboratories
 - Decades of experience in cell therapy development, production, state-of-the-art cell therapy technology
 - Not primarily contract service labs, use external contracts to help support facility
- Commercial laboratories
 - Experience emphasizes cell line and vector production, banking, rather than clinical cell therapy
 - Contract services are primary mission
- Look for cell therapy-specific experience, capabilities, GMP/GTP and QA infrastructure



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



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.
- Manufacturing in functionally-closed systems enables automated, parallel processing at high throughput, can overcome scale limitations of patient-specific products.