

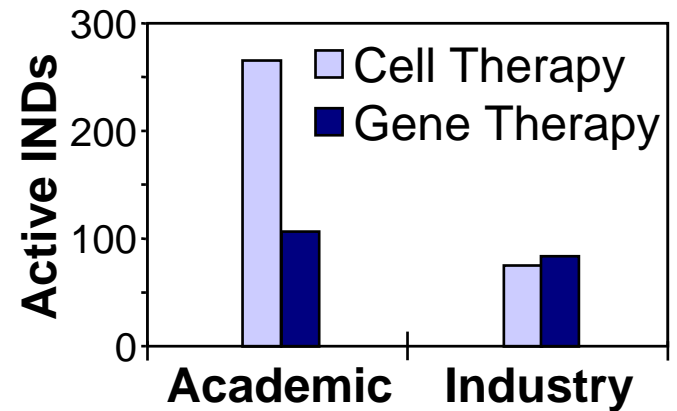
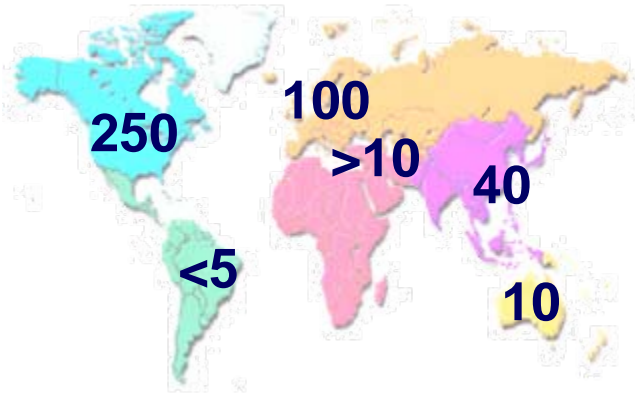
Technology Transfer

The First Step in Process Development

Scott R. Burger, MD
Advanced Cell & Gene Therapy

Cell/Gene Therapy Industry, 2007

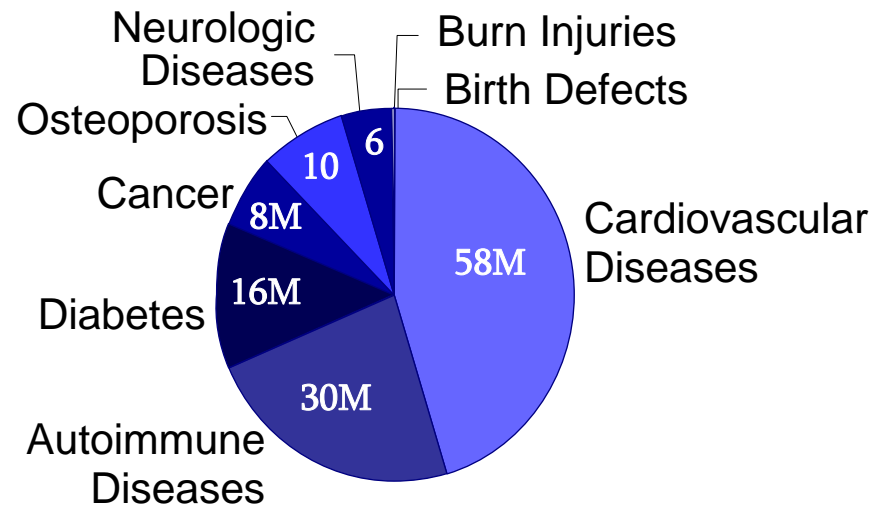
- Industry sponsoring 25% of cell therapy INDs
 - >300 cell/gene/tissue therapy companies
 - >500 cell/gene therapy INDs, >1000 gene therapy trials
- Increasing Big Pharma involvement
 - Internal ventures, external partnerships
- BLA filing (!), others expected



Coming Through the Pipeline...

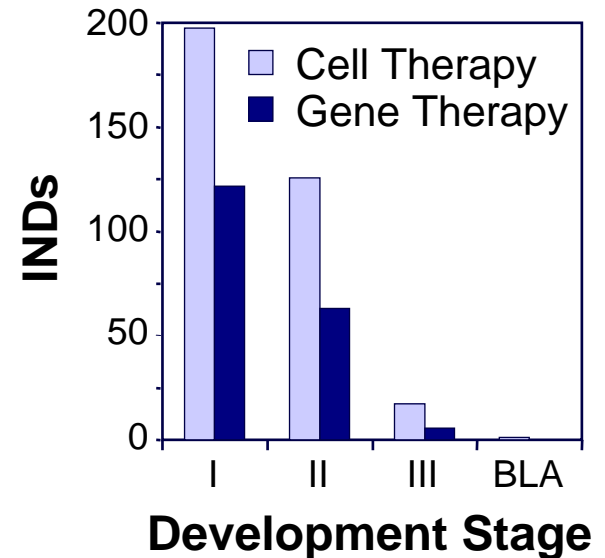
- Immunotherapies, gene therapies for cancer
- Regenerative medicine, broad range of applications
- Cell/tissue therapies for orthopedic applications
- Cell and gene therapies for neurological, metabolic disorders
- Cardiovascular cell therapies, development continues

Potential Patients (USA)



Why Do Cell Therapy Products Fail in Clinical Development?

- Major drop-off post-Phase II
 - Damage often self-inflicted
- Common root causes of failure
 - Inability to manufacture/deliver product
 - Inadequate/inappropriate process development
 - Inadequate product characterization
 - Inability to evaluate efficacy
 - Inadequate scientific/technical foundation



Technology Transfer

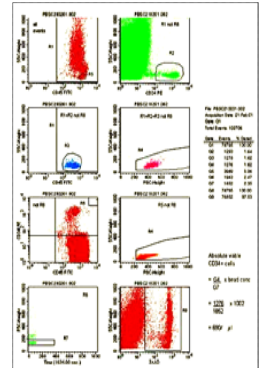
- “Process of developing practical applications for the results of scientific research”
 - Technology Transfer Society
- Establishing a complete, accurate understanding of processes, analytical methods, and specifications to enable further development
- Critical first step in development pathway
- Effective technology transfer and process development are crucial if cell therapy is to fulfill its great promise

Technology Transfer Overview

- Identify what is (and is not) to be transferred, from whom, to whom
 - Confidentiality, IP considerations
- Review process, analytical methods *in detail*
- Establish draft description, specifications
 - Review and sign-off
- Source materials, devices for To site
- Test runs at From site and To site
 - Review results, sign-off
- Revise descriptions, repeat sequence as needed

Review Process, Analytical Methods

- Written procedures, laboratory notebooks, summary reports
- Deviation reports (*very* useful)
- Identify customs and unwritten traditions
- Observe process closely
 - Ask questions, and distinguish fact from folklore
 - Total n of experience? Who can do this process successfully? How often does the process fail?
 - What goes wrong? What doesn't work?



Establish Draft Description

- Detailed description of process, analytical methods
 - To evolve into Batch Record
- Specifications
 - Materials, devices, conditions
 - Expected results (means, ranges, S.D.)
 - Establish criteria for successful transfer
 - Acceptability specifications? Test methods? n runs?
 n staff trained?
- Review and sign-off by From and To staff
 - Operations staff and QA

Prepare the To Site

- Source materials, devices and equipment
- Establish analytical capabilities, internal or send-out
- Prepare process facilities
- Send staff to and fro
- Review preparations, summarize and sign off

Test Runs

- To staff at From site, with From staff
 - Optional, but very useful
- To staff at To site
 - Helpful for From staff to observe
- Review results, troubleshooting, sign-off
 - From and To operations staff and QA
 - What went wrong? “This never happened at the From lab!”
- Revise procedures, materials as needed
- Repeat

Completing Technology Transfer

- Ideal: target criteria are met, the From site has the new process/analytical method up and running
 - Tech transfer summary report
 - Review and sign-off, From and To staff, QA

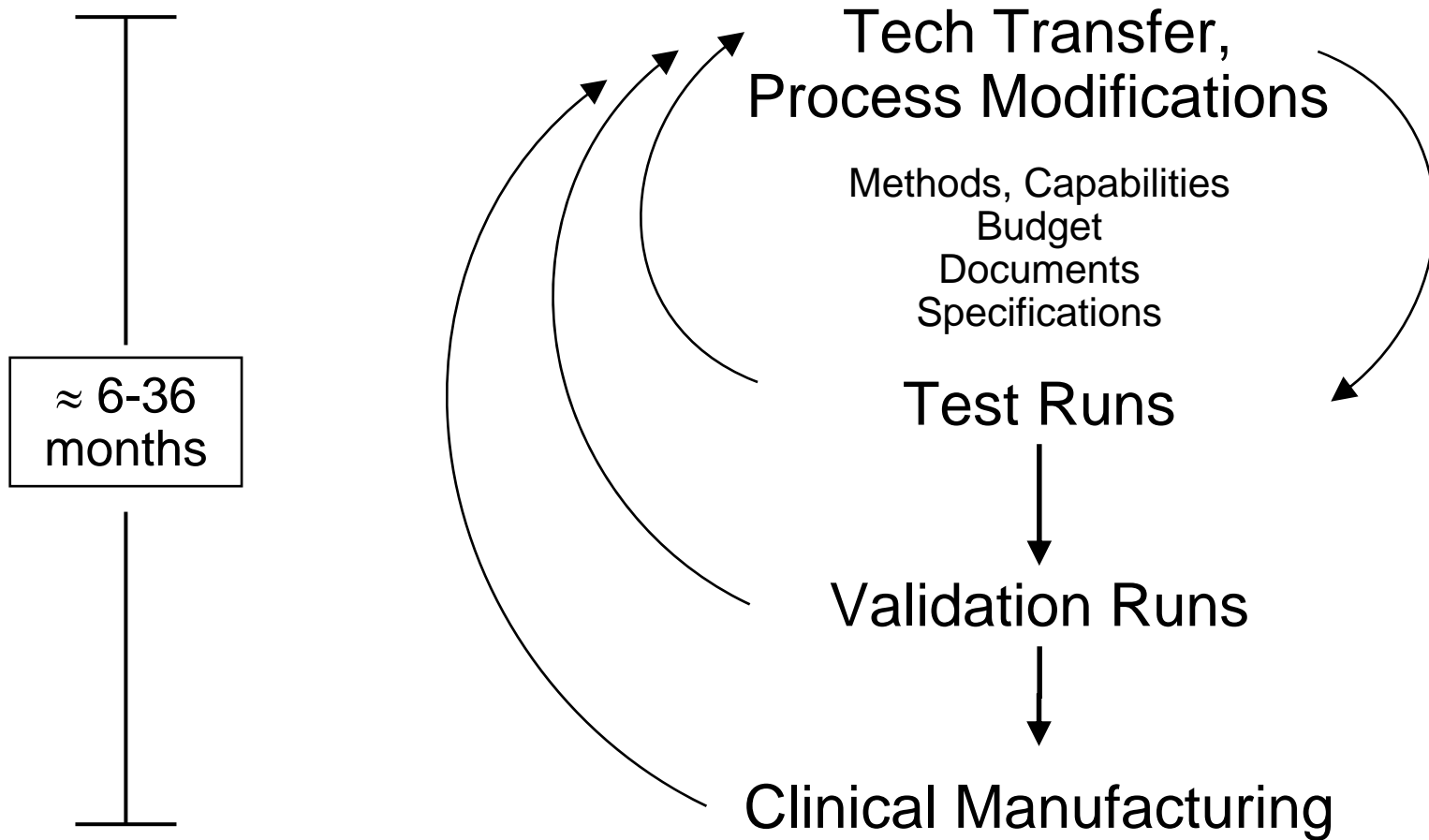
OR

- The new process is so variable or poorly understood that true transfer is not feasible.

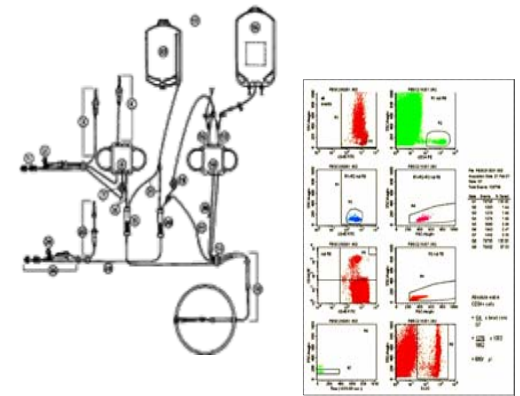
Options:

- Leave it in the From lab and hope they improve it
- Transfer what one can, and begin process development to fix things up

Process Development



Key Issues in Cell Therapy Process Development



- Reagents, Materials
 - Research-grade, small-scale → GMP, qualified, clinical-scale
- Processes, Devices
 - Manual, open-system → Qualified, closed-system, automated
- Characterization
 - Moderate → Extensive, and growing
- Documentation, Control
 - Notebooks → Batch records, qualified processes



Cell Therapy Product Commercialization Strategies

- Rigorous process development, characterization
 - Product definition, relevant biological function
- Focus on manufacturing process control
 - Controlled, consistent processes → controlled, consistent products
- High throughput, parallel processing to achieve scale, reduce costs
 - Functionally-closed processing systems, automation
 - Closed-system manufacturing replaces process cleanroom

Development Throughout Clinical Trials

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

