

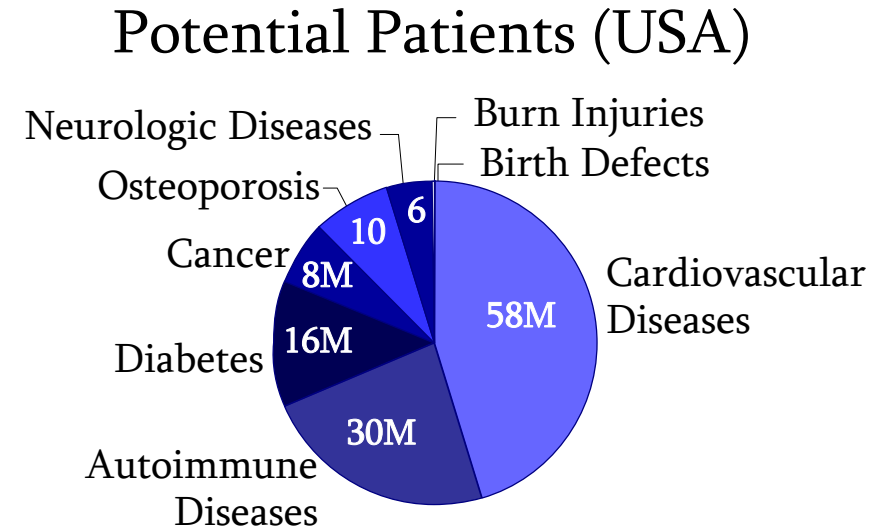
Commercialization of Cell and Gene Therapy Products: When and How?

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Advanced Cell & Gene Therapy

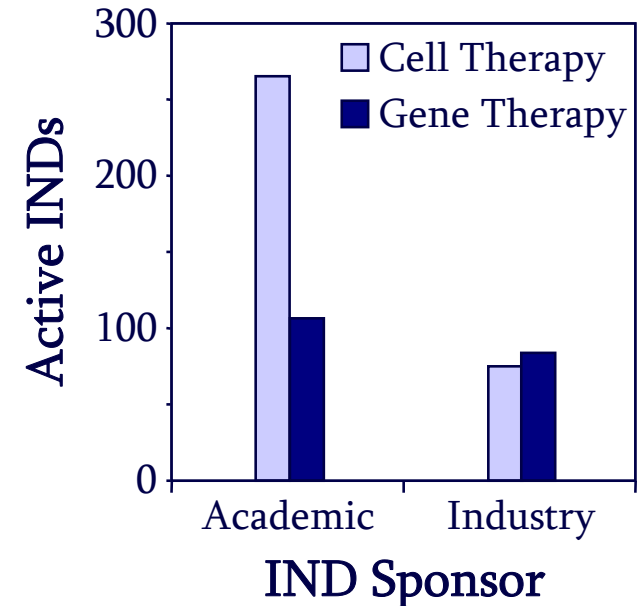
Promise, Potential, and Plenty of Challenges

- Novel, potentially definitive therapies, with numerous potential applications
- Novel uses of cells/genes
 - Difficult to predict clinical risks
- Complex cell, gene engineering
 - ↑ Risk of manufacturing problems
 - Challenges in product and process characterization

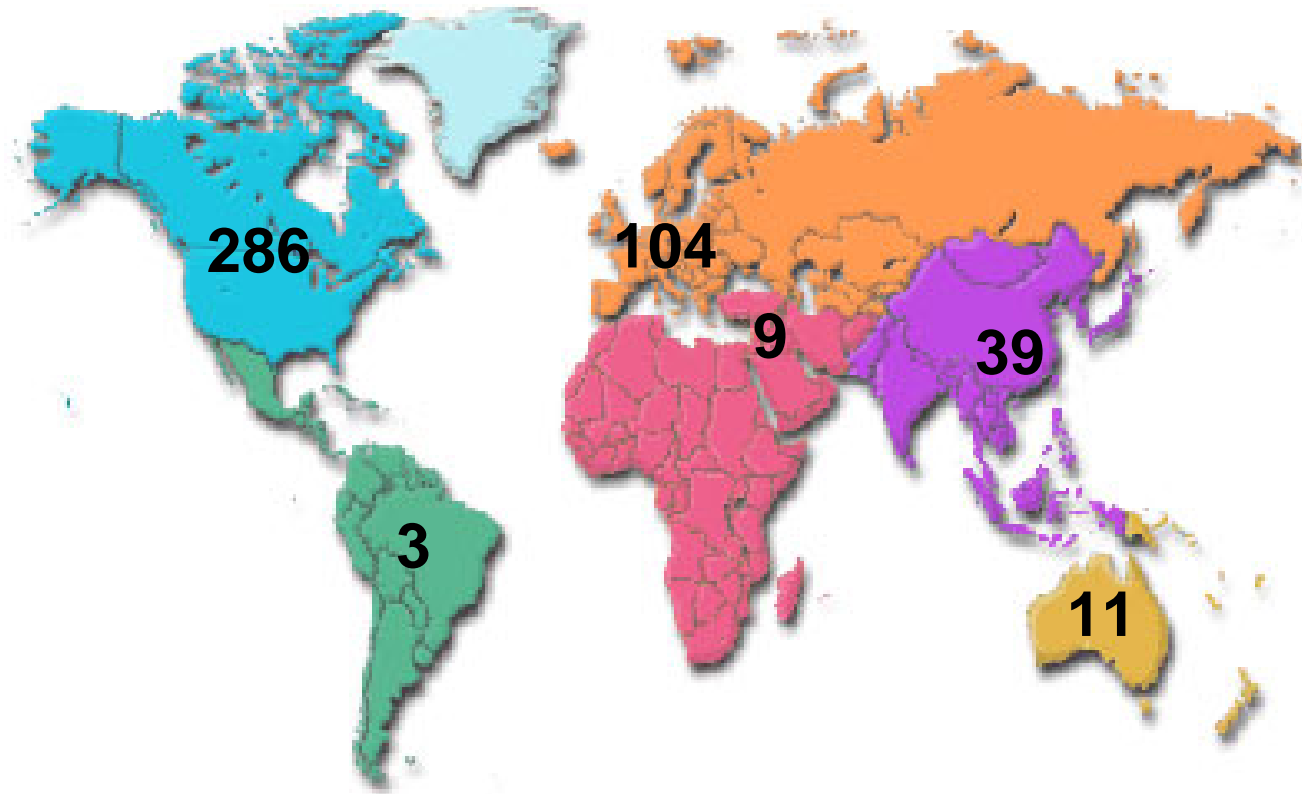


An Emerging Cell and Gene Therapy Industry

- ↑ Clinical development activity
 - 340 cell therapy products
 - 190 gene therapy products
 - Over 1,000 gene therapy clinical trials worldwide
- ↑ Industry-sponsored clinical trials
 - 25% of cell therapy INDs
 - 45% of gene therapy INDs

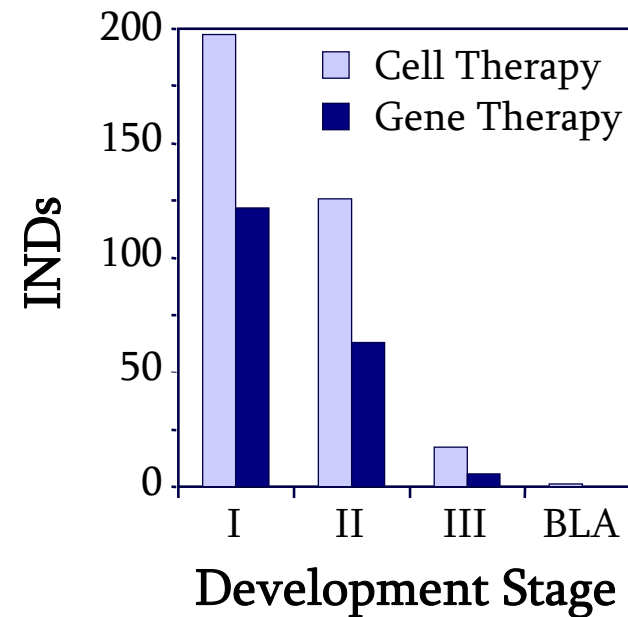
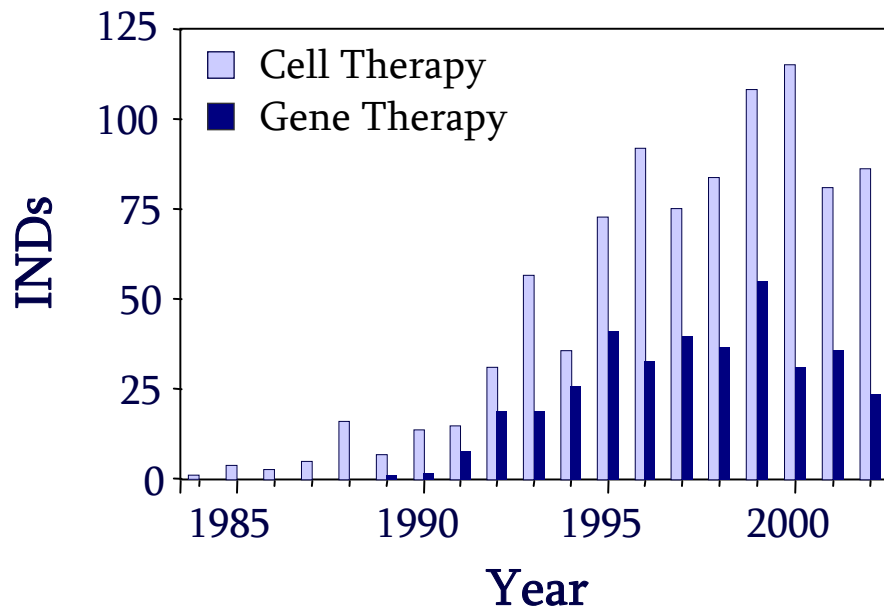


Over 400 Cell or Gene Therapy Firms Worldwide



Products Entering Late-Stage Development

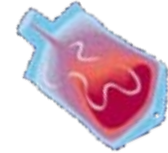
- 22 cell or gene therapy Phase III trials in 2003



Cell and Gene Therapies - Intrinsic Challenges

- Product definition
 - Manufacture living, functional cells, not the products of cells. Inherent biological variability, heterogeneity, known and unknown subpopulations.
- Process scale
 - Need for immunologic compatibility → patient-specific products, autologous or matched-allogeneic cells. How to commercialize at 1 lot per patient?
- Evolving, iterative development
 - Inevitable changes as processes, testing, specifications are refined
- Limited infrastructure, technology, reagents
 - Novel therapies and therapeutic strategies

>99% CDX⁺ cells



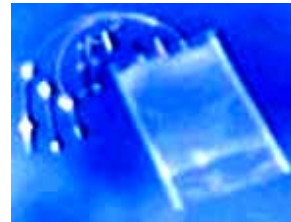
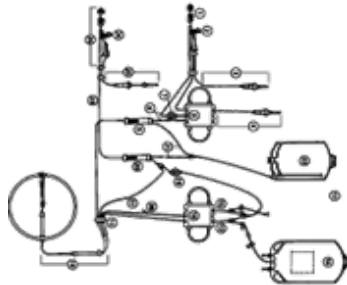
?% CDY⁺ cells

?% CDY⁻ cells

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

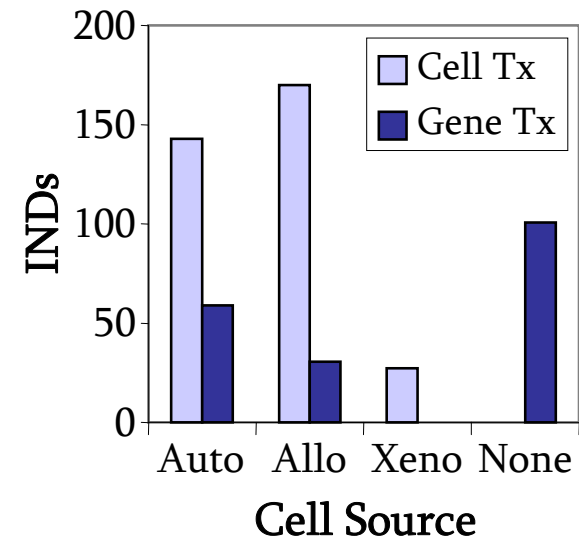
Strategies for Cell and Gene Therapy Product Manufacturing

- 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



Cell Source - Autologous, Allogeneic, Other?

- Autologous
 - Immunologic compatibility, but \uparrow variability
 - Logistics - tracked/traceable collection, transport, manufacturing, administration
 - Patient-specific products - process scale
- Allogeneic
 - Normal-donor cells, but risks of immune response.
 - Immunosuppression? May \downarrow product function, other risks
 - Donor-patient matching - patient-specific products, or nearly so
- The allure of "off-the-shelf" products
 - Non-cell-mediated gene therapy
 - Immunologically privileged cells, perhaps. Define practical limits of mismatch. Need robust animal models, analytical tools.



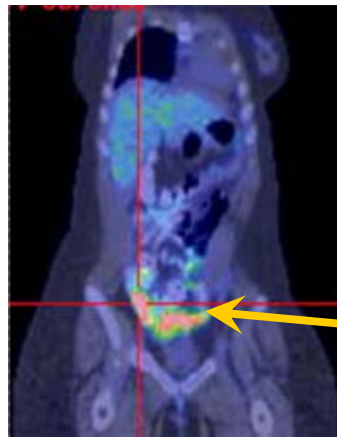
Contract Services for Cell and Gene Therapy

- Academic-based laboratories n <5
 - >20 years experience in cell therapy development, production
 - State-of-the-art cell therapy technology
 - Cell therapy GMP usually well established, GTP in progress
 - Not primarily contract service labs, but external contracts help support facility
- Commercial laboratories n <5 worldwide
 - Experience typically emphasizes cell line and vector production, banking, rather than clinical cell therapy
 - Generally GLP, some offer GMP capabilities
 - Contract services are primary mission
- Vendor audit, qualification - essential

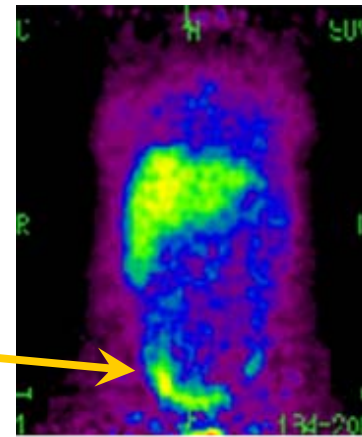


Distribution and Fate of Administered Cells

- *In vivo* cell tracking studies
 - *In vivo* product evaluation across manufacturing changes
 - Patient monitoring
 - Imaging technologies
 - Magnetic particle-based
 - Isotopic imaging - PET-CT, SPECT



Pre-Rx PET imaging



FDG-labelled cellular immunotherapy
PET-CT, 3 hrs post-administration

Raw Materials for Cell and Gene Therapies

- Viable, functional biological raw material
 - Cell/tissue source for development studies?
- Reagents and supplies
 - Cytokines, vectors, genes, culture media, supplements, mAbs
 - GMP manufactured reagents
 - Complex biologicals, often unique to product
 - Availability, need for qualification
 - Limited market, high cost of goods

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

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.
 - Evolving characterization and rigorous process control are especially vital to counter the intrinsic heterogeneity, variability, and incomplete definition of cell therapy products.
 - Processes, analytical methods, and product definition must evolve over multiple clinical trials.
 - Manufacturing in functionally-closed systems can overcome process scale limitations of patient-specific cell therapy products by enabling automated, parallel processing at high throughput.