Gene Therapies in the Clinic: A Product Perspective

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Clinical Investigator's Course 2012

Presentation outline

- Products regulated by the Office of Cellular, Tissues and Gene Therapies (OCTGT) in CBER
- Introduction to gene therapy, gene therapy products and gene delivery approaches
- Manufacture of gene therapy products
- Gene therapy products in the clinic

Products regulated by OCTGT

CELL THERAPY PRODUCTS

- Stem cells and stem cell-derived products
  - Examples: Hematopoietic, mesenchymal, embryonic, umbilical cord blood
- Cancer vaccines and immunotherapies
  - Examples: Dendritic cells, activated T lymphocytes (TILs), B cells, monocytes, peptides, recombinant proteins
- Somatic cells
  - Examples: Allogeneic pancreatic islets, chondrocytes, myoblasts
- Cell lysates and extracts
- Cells plus scaffold matrix
  - Examples: Encapsulated cells, tissue engineering products

Products regulated by OCTGT

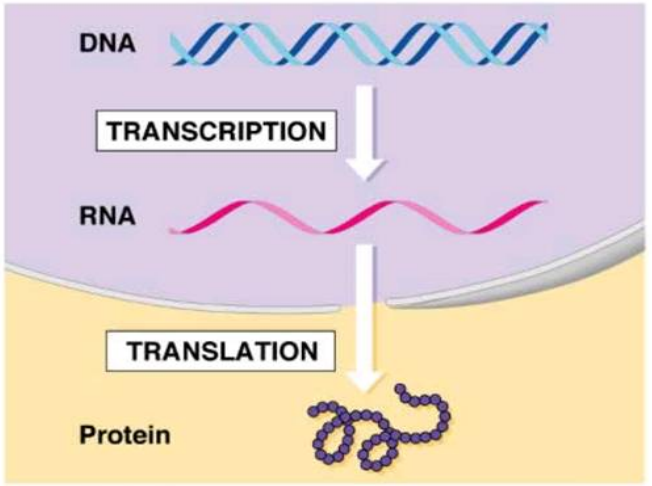
GENE THERAPY PRODUCTS

- Recombinant Vectors
  - Plasmids
  - Viral
    - Examples: Adenoviruses, Adeno-associated Virus (AAV), Retroviruses & Lentiviruses, Herpes Simplex Virus, Poxvirus
  - Bacterial
    - Examples: Listeria, Salmonella, Clostridium
- Gene modified cells
  - Modified T cells (CAR-T), dendritic cells, fibroblasts, stem cells

Gene therapy (GT): Definition

All products that:

- Mediate their effects by transcription and/or
- Translation of transferred genetic material and/or
- By integrating into the host genome, and
- Are administered as nucleic acids, viruses, or genetically engineered microorganisms.



- 2006 Guidance for Industry-Gene Therapy Clinical Trials- Observing Subjects for Delayed Adverse Events.

The GT product may be used to modify cells *in vivo* or transferred to cells *ex vivo* prior to administration to the recipient.

Delivery of GT products

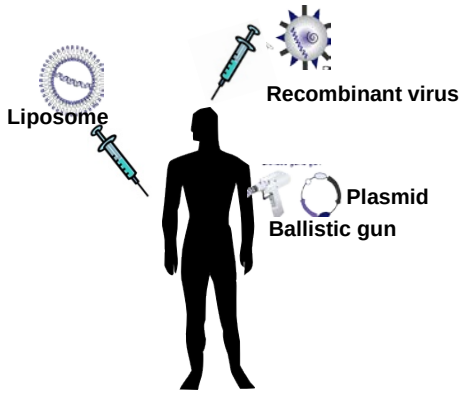
Viral Vectors

- Retrovirus/Lentivirus
- Adenovirus
- Adeno-Associated Virus
- Herpes Simplex Virus
- Vaccinia Virus

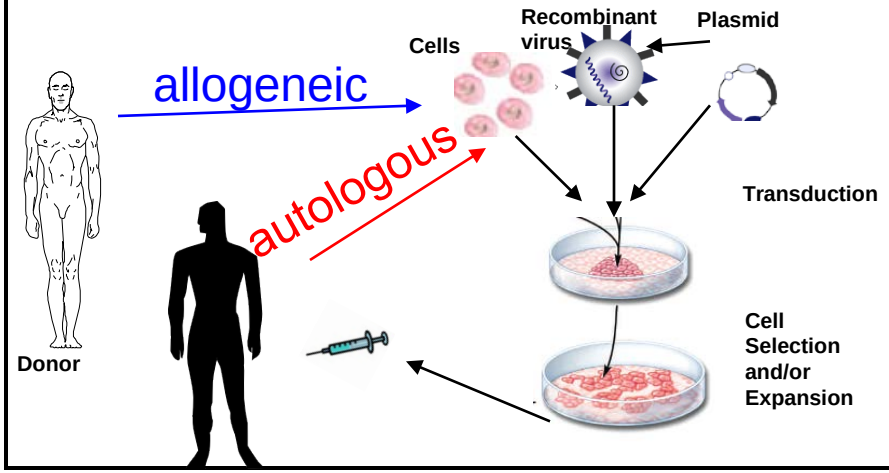
Non-viral Vectors

- Naked DNA
- plasmids
- Liposomes
- Molecular conjugates

In vivo (direct)

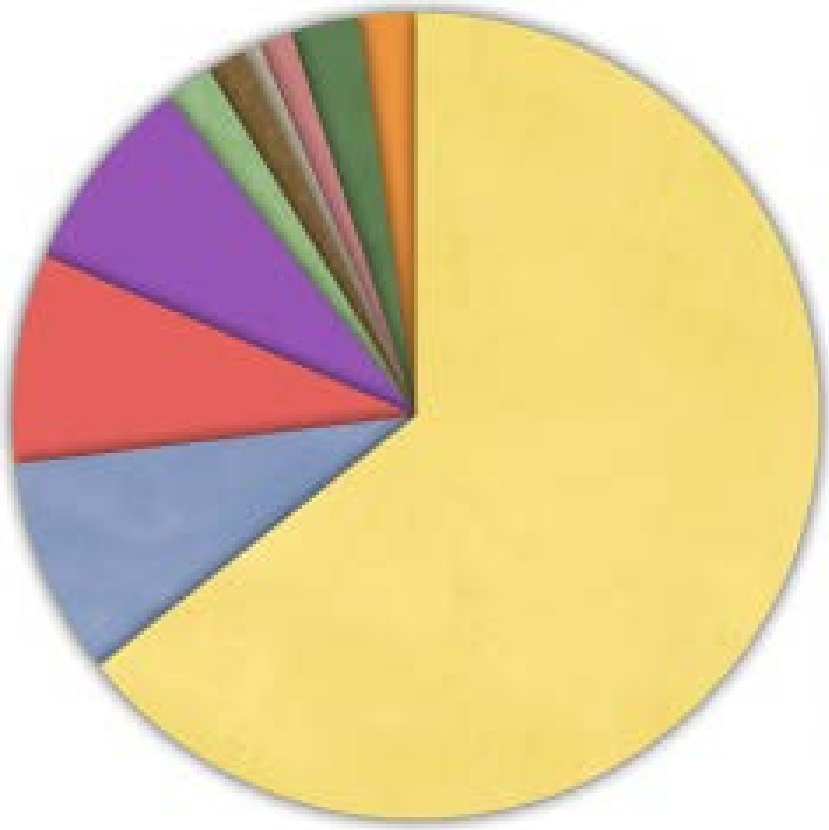


Ex vivo (via cells)



GT products: Indications

Indications Addressed by Gene Therapy Clinical Trials



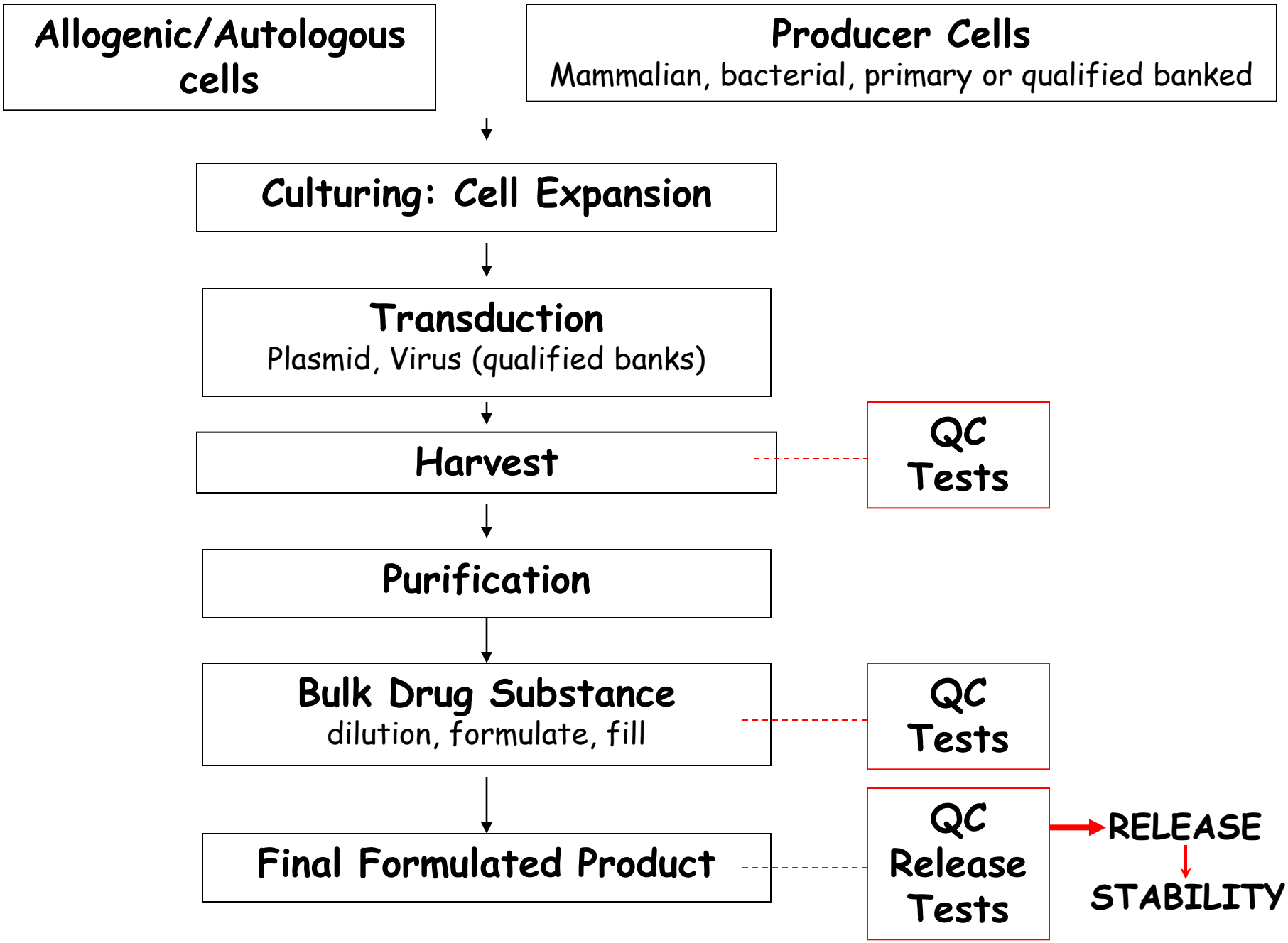
- Cancer diseases 64.4% (n=1186)
- Monogenic diseases 8.7% (n=161)
- Cardiovascular diseases 8.4% (n=155)
- Infectious diseases 8% (n=147)
- Neurological diseases 2% (n=36)
- Ocular diseases 1.5% (n=28)
- Inflammatory diseases 0.7% (n=13)
- Other diseases 1.4% (n=25)
- Gene marking 2.7% (n=50)
- Healthy volunteers 2.3% (n=42)

n=number of trials

Factors affecting safety and efficacy of gene therapy vectors

- Delivery and efficiency of gene transfer
- Target specificity
- Ability to infect dividing/non-dividing cells
- Immunogenicity and toxicity
- Long term Vs short term expression
- Genotoxicity: Insertional mutagenesis

General manufacturing scheme


Allogenic/Autologous cells
Producer Cells
Mammalian, bacterial, primary or qualified banked
Culturing: Cell Expansion
Transduction
Plasmid, Virus (qualified banks)
Harvest
QC Tests
Purification
Bulk Drug Substance
dilution, formulate, fill
QC Tests
Final Formulated Product
QC Release Tests
RELEASE
STABILITY

Final product testing

Safety

- Sterility, mycoplasma, adventitious agent testing

Purity

- Endotoxin, residuals

Identity

Potency

Objective?

- Demonstrate product safety and quality
- Show lot-to-lot consistency

GT product manufacturing is a complex biological process

Starting material

Cells
Fastidious and diverse

Vector
Unique make-up and growth requirements

Biological Process
Complex and Variable

Raw Materials
Complex (quality and source)
Animal-derived (adventitious agents)

Manufacturing process

- Complex biologicals
  - Limit cell and process impurities
  - Limit process variability
- No terminal sterilization
  - Aseptic processing throughout manufacture
  - Closed manufacturing systems wherever feasible
- Patient specific
  - Limited product for testing
  - Need to prevent product mix-ups
  - Limited shelf life (due to cell viability)

GT products:
Common regulatory challenges

- Potency
  - Mechanism of action not defined, potency assay does not provide a meaningful measurement of biological activity
- Stability
  - Formulation, cryopreservation -> viability, potency??
- Lot size
  - Patient specific, small scale
- Characterization/Purity
  - Limited purification process, heterogeneity, cell-derived impurities
- Scale-up
  - Undefined variables due to complex biology of production process
- Storage/shipping
  - Some GT products are not 'off the shelf' products, i.e., these products are patient-specific, not always frozen and require special handling and shipping

GT products:
Challenges in the clinic

- Dose
  - Manufacturing limits, volume limits, dose does not always correlate with toxicity and efficacy
- Vector delivery (route of administration, device) and vector targeting
  - Imaging, monitoring for related AEs
- Immune reactions: anti-vector, anti-transgene, autoimmune
  - Vector clearance -> ineffective repeat dosing
  - Off target effects, cytokine storm ->SAE
  - Vector purity -> high antigenic load, low effective dose

- Vertical vector transmission and vector shedding
  - Monitoring in the clinic
- Vector integration and latency
  - Long-Term Follow-Up (LTFU)
- Mechanism of action: not elucidated
  - Selection of endpoints, surrogate measures of efficacy

Progress in the clinic: Recent reports

AAV-vectored gene therapy in Hemophilia B

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2011 VOL. 365 NO. 25

Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B

Amit C. Nathwani, M.B., Ch.B., Ph.D., Edward G.D. Tuddenham, M.B., B.S., M.D., Savita Rangarajan, M.B., B.S., Cecilia Rosales, Ph.D., Jenny McIntosh, Ph.D., David C. Linch, M.B., B.Chir., Pratima Chowdary, M.B., B.S., Anne Riddell, B.Sc., Arnulfo Jaquilmac Pie, B.S.N., Chris Harrington, B.S.N., James O'Beirne, M.B., B.S., M.D., Keith Smith, M.Sc., John Pasi, M.D., Bertil Glader, M.D., Ph.D., Pradip Rustagi, M.D., Catherine Y.C. Ng, M.S., Mark A. Kay, M.D., Ph.D., Junfang Zhou, M.D., Yunyu Spence, Ph.D., Christopher L. Morton, B.S., James Allay, Ph.D., John Coleman, M.S., Susan Sleep, Ph.D., John M. Cunningham, M.D., Deokumar Srivastava, Ph.D., Etiena Basner-Tschakarjan, M.D., Federico Mingozzi, Ph.D., Katherine A. High, M.D., John T. Gray, Ph.D., Ulrike M. Reiss, M.D., Arthur W. Nienhuis, M.D., and Andrew M. Davidoff, M.D.

ABSTRACT

CONCLUSIONS

Peripheral-vein infusion of scAAV2/8-LP1-hFIXco resulted in FIX transgene expression at levels sufficient to improve the bleeding phenotype, with few side effects. Although immune-mediated clearance of AAV-transduced hepatocytes remains a concern, this process may be controlled with a short course of glucocorticoids without loss of transgene expression. (Funded by the Medical Research Council and others;

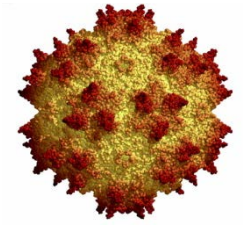
The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Merry Christmas for Patients with Hemophilia B

Katherine P. Ponder, M.D.

In sum, this gene therapy trial with an AAV8 vector for hemophilia B is truly a landmark study, since it is the first to achieve long-term expression of a blood protein at therapeutically relevant levels. If further studies determine that this approach is safe, it may replace the cumber-



Note: The first AAV-vectored gene therapy Phase I/II trial for hemophilia started in 1999

Challenges:

- Immune clearance and toxicity
- Sustained expression
- Optimized dosing

Autologous CAR-T cells in cancer treatment

Science Translational Medicine AAAS

T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia
Michael Kalos *et al.*
Sci Transl Med **3**, 95ra73 (2011);
DOI: 10.1126/scitranslmed.3002842

Editor's Summary

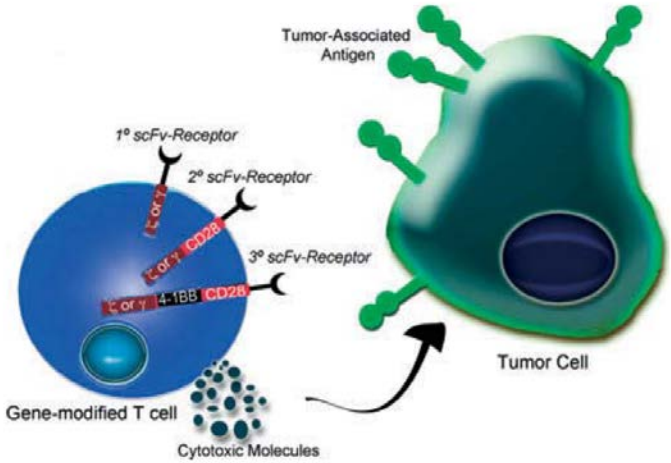
Go CAR-Ts in the Fast Lane

LEUKEMIA

T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia

Michael Kalos,[1,2]* Bruce L. Levine,[1,2]* David L. Porter,[1,3] Sharyn Katz,[4] Stephan A. Grupp,[5,6] Adam Bagg,[1,2] Carl H. June[1,2]†

syndrome. Here, we show that the CART19 cells mediated potent clinical antitumor effects in all three patients treated. On average, each infused CAR T cell and/or their progeny eliminated more than 1000 leukemia cells in vivo in patients with advanced chemotherapy-resistant chronic lymphocytic leukemia (CLL). CART19 cells underwent robust in vivo T cell expansion, persisted at high levels for at least 6 months in blood and bone marrow (BM), continued to express functional receptors on cells with a memory phenotype, and maintained anti-CD19 effector function in vivo.



Berry *et al.*, Tissue Antigens (2009) 74: 277-289

Challenges:

- Persistence
- Trafficking
- Toxicity
- Manufacturing

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Thank you!

We used to think that our fate was in our stars, but now we know that, in large measure, our fate is in our genes

-James Watson