Oncology for Scientists

Christopher Choi, PhD
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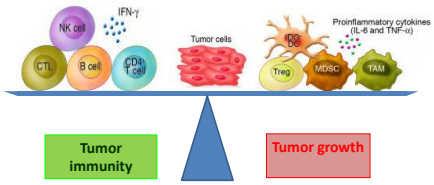
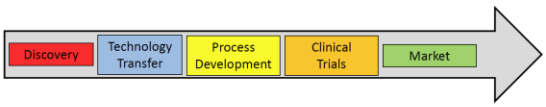
Assistant Professor of Oncology

Immunological Battle Ground

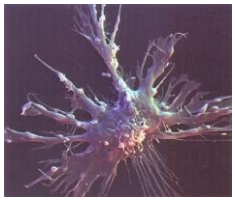


The tumor environment is an immunological battle ground: **Good vs. Bad**

RPCI CFI TCPF "cGMP Facility"

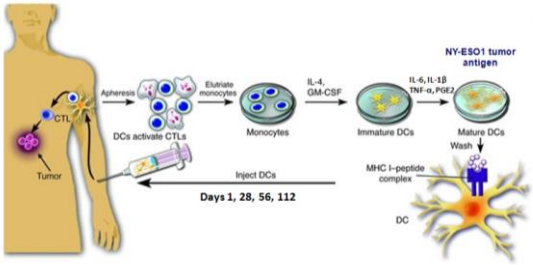


How do we identify DCs?



CD 80+ CD86+ CD83+ CD14-

NY-ESO-1 DC Vaccine Manufacture Process



Clinical Trial Phases

Clinical trials are made up of distinct parts called phases.

- Phase I clinical trials are used to show that a new treatment is safe for a small group of people.
- Phase II clinical trials provide more information about the safety of the new treatment and how well it works to treat cancer.
- Phase III clinical trials compare the new treatment with the standard treatment in a large group of people.

Chemistry, Manufacturing, & Control: (Un)related/Autologous/Allogeneic, UCB-/PB-/BM-Derived, (insert cell type) Therapy

I. Product Manufacturing & Characterization Information

A. General
- -Product type, derivation
- -Where processed?
- -Relevant accreditations (FACT, AABB, CAP,CLIA)
- -Type V MF reference (if filed)

B. Procurement
- -Starting material
- -Apheresis (mobilized/non-mobilized), UCB, marrow aspirate
- -Where collected?
- -Process description

i.

I. Product Manufacturing & Characterization Information (con't)

C. Infectious Disease Testing & Prevention of Cross-Contamination
- -Donor suitability per cGTPs
- -Medical history
- -List of testing
- -Quarantine if positive result
- -Process if product with positive result to be infused

D. Cell Processing
- -Description of processing methods
- -Flow diagram outlining processing and testing

E. Reagents
- -Table indicating reagent, manufacturer, status (reference to FDA-approval, C of A, MF, existent IND)
- -HSA (from countries considered free of vCJD risk?)
- -Reference and include C of As for reagents not approved for human infusion

ii.

II. Product Testing

A. Microbiological Testing
- -Sterility testing
  - -Method/test (e.g., BACTEC, USP)
  - -When tested? Final product? In process? Days held?
  - -Indicate sample will not be washed or manipulated before testing
- -Mycoplasma testing
  - -Method/test (e.g., PCR, culture)
  - -When tested? Final product? In process? Days held?
  - -Indicate sample will not be washed or manipulated before testing
- -Gram stain
- -Reference to donor infectious disease testing (Section I.C.)

B. Identity
- -Labeling, segregation, any test methods employed

iii.

II. Product Testing(con't)

C. Purity
- -Make-up of final suspension (e.g., washed cells in 5% HSA)
- -Analysis (e.g., flow cytometry, endotoxin, etc.)

D. Potency
- -Analysis (e.g., flow cytometry as in vitro surrogate, in vivo clinical assessment, other functional assays such as MLR-based)

E. Additional Testing

i. Viability
- -Method (e.g., microscopy, flow cytometry)
- -When?

ii. Cell Dose
- -Method (e.g., hematology analyzer)
- -Actual doses (always provide range)
- -Minimum dose to allow for infusion?

iii. Other
- -Retain aliquot?

iv.

III. Product Release Criteria Testing and Additional Testing
- One table with lot release testing (assay, method, where tested, specification)
  - -E.g., Endotoxin, LAL Method (manufacturer of kit), cell therapy lab, $\leq$ 5EU/kg; Viability, Flow Cytometry (7-AAD), clinical flow cytometry lab, $\geq$ 70%
- Second table with additional (not lot release) testing
  - -E.g., Sterility/Mycoplasma testing on final product that will not be available prior to release; research-type assays (MLR-based)

IV. Product Stability
- Stability testing to support post-production clinical use
- Fresh? Cryopreserved? Transit time/conditions

v.

V. Other Issues
A. Product Tracking
- -Labeling per standards/regs
- -Unique identifiers (#, name)
- -Confirmation prior to administration
- -Segregation system

B. Labeling
- -Per standards/regs
- -Additional items on label
- -Include "Caution: New Drug – Limited by Federal Law to Investigational Use" per 21 CFR 312.6
- -Attach sample label/hangtag

C. Container/Closure
- -Bags, tubing sets, flasks, etc.
- -Indicate compatibility with cells

vi.

V. Other Issues (con't)
D. Environmental Impact
- -"The sponsor claims categorical exclusion [under 21 CFR25.31(e)] for the study under this IND. To the sponsor's knowledge, no extraordinary circumstances exist."

E. Validation and Qualification of the Manufacturing Process and Facility
- -Indicate process validation performed prior to clinical use
- -Reference Facility MF if on file

vii.

History of Good Manufacturing Practices (GMPs)

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- 1906 Pure Food and Drug Act
- 1938 Federal food, Drug and Cosmetic (FD&C) Act
- 1941 Two Unrelated Events
- 1944 Public Health Services Act
- 1962 Kefauver-Harris Drug Amendments
- 1963 GMPs for Drugs (28 FR 6385)
- 1975 cGMPs for Blood and Blood Components Final Rule
- 1976 Medical Device Amendments
- 1978 cGMPs for Drugs and Devices (21 CFR 210-211 and 820)
- 1979 GLPs (21 CFR 58) Final Rule
- 1980 Infant Formula Act
- 1982 Tamper-Resistant Packaging Regulations Issued for OTC Products
- 1983 Two Unrelated Regulatory Events
- 1987 Guideline on General Principles of Process Validation
- 1990 Safe Medical Devices Act
- 1992 Generic Drug Enforcement Act
- 1996 Two Unrelated Events
- 1997 cGMPs for Medical Devices (Quality System Regulation) Final Rule
- 1997 Electronic Records Final Rule (21 CFR 11)
- 1998 Draft Guidances
- 1999 QSIT Inspection Handbook
- 2001 ICH Q7A API guidance
- 2002 Drug Manufacturing Inspections Compliance Manual
- 2008 Guidance for Industry: Phase I Clinical Trials

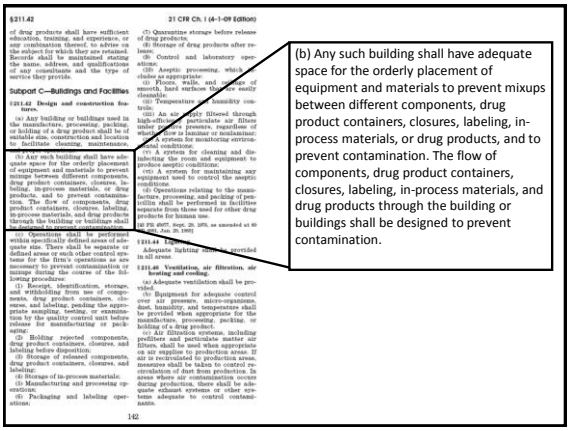
Barbara Kimmel, A Brief History of the GMPs

History of Good Manufacturing Practices (GMPs)

- GMPs were developed out of a need for consistent methods to develop and manufacture drugs, devices, and food in the United States
- GMP regulations are promulgated and enforced by the FDA and primarily housed within the Federal Food, Drug, and Cosmetic Act
- GMPs are based on industry best practices that continually evolve as science, technology, and manufacturing techniques change
  - Commonly referred as Current Good Manufacturing Practices (cGMP)s

GMPs Defined

GMPs are methods, facilities, or controls used in the production of drugs, devices, foods, and biologics. These manufacturing practices are designed to ensure the safety, identity, strength, quality, and purity of such products, driven by Standard Operating Procedures (SOPs)



§211.42 21 CFR Ch. I (4–1–09 Edition)

of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Subpart C—Buildings and Facilities

§211.42 Design and construction features.

(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall include size, construction and location to facilitate cleaning, maintenance

(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall

(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures:

(1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;

(2) Holding rejected components, drug product containers, closures, and labeling before disposition;

(3) Storage of released components, drug product containers, closures, and labeling;

(4) Storage of in-process materials;

(5) Manufacturing and processing operations;

(6) Packaging and labeling operations;

(7) Quarantine storage before release of drug products;

(8) Storage of drug products after release;

(9) Control and laboratory operations;

(10) Aseptic processing, which

(i) Floors, walls, and

smooth, hard surfaces that are easily cleaned;

(ii) Temperature and humidity controls;

(iii) An air supply filtered through high-efficiency particulate air filters under

whether flow is laminar or nonlaminar;

(iv) A system for monitoring environmental conditions;

(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;

(vi) A system for maintaining any equipment used to control the aseptic conditions.

(d) Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4086, Jan. 20, 1995]

§211.44 Lighting.

Adequate lighting shall be provided in all areas.

§211.46 Ventilation, air filtration, air heating and cooling.

(a) Adequate ventilation shall be provided.

(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.

(c) Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contamination.

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(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.

Characteristics of GMP regulations and interpretations

GMP regulations are largely general and open for interpretation

Benefit:

- Manufacturers and researchers are able to interpret and apply the regulations in ways that may work best for their unique situations

Risk:

- The flexibility may lead to confusion during the interpretation of the regulation and misapplied control mechanisms

cGMP Composite elements

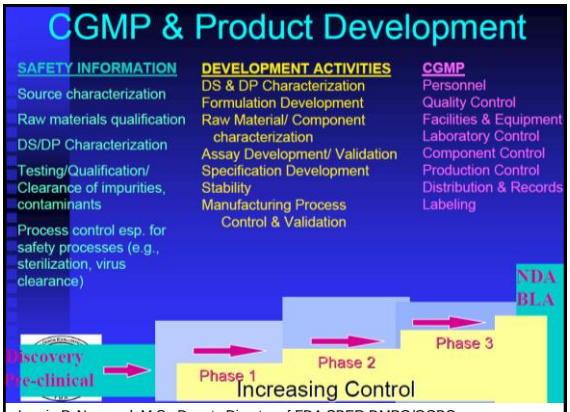
GMP regulations cover the following areas

- Documentation
- Validation
- Facilities
- Equipment
- Personnel
- Training
- SOP management
- Error management
- Labeling
- Auditing
- Process control

Cell Therapy Products fall under cGMP for Finished Pharmaceuticals

- General provisions
- Organization & personnel
- Buildings & Facilities
- Equipment
- Control of Components & Product Containers & Closures
- Production & Process Controls
- Packaging & Labeling Control
- Holding & Distribution
- Laboratory controls
- Records & reports
- Returned & Salvaged Drug Products

CGMP & Product Development



Laurie P. Norwood, M.S.; Deputy Director of FDA CBER DMPQ/OCBQ

QC/QA Program

Current industry practice generally divides the responsibilities of the quality control unit (QCU), as defined in the CGMP regulations, between quality control (QC) and quality assurance (QA) functions.

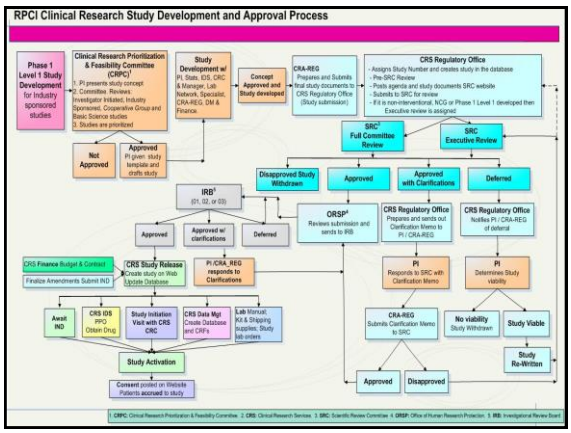
• QC usually involves
(1) assessing the suitability of incoming components, containers, closures, labeling, in-process materials, and the finished products
(2) evaluating the performance of the manufacturing process to ensure adherence to proper specifications and limits
(3) determining the acceptability of each batch for release

• QA primarily involves
(1) review and approval of all procedures related to production and maintenance
(2) review of associated records
(3) auditing and performing/evaluating trend analyses

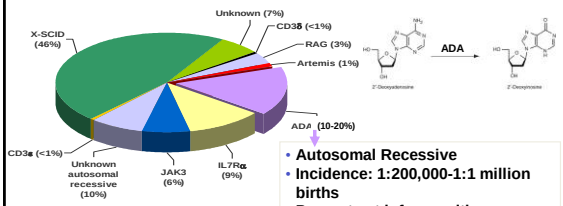
Excerpt from the Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations

QC/QA Program

• Maintenance of a Quality Control Unit
• Training of operators
• Developing, maintaining and ensuring adherence to the SOPs
• Room clearance/change-over procedures
• Maintaining manufacturing records
• Change controls
• Equipment/instrument qualification, calibration and maintenance
• Facility and equipment cleaning/sanitization
• Environmental monitoring
• QC testing and in-process and final product release testing
• Approval of contract services and vendor qualifications
• Rejection and approval of in-coming materials and final products
• Deviation and out of specification (OOS) reports, investigations, corrective and preventative actions



ADA-SCID



Conventional Treatments

- Allogeneic BMT
  HLA-identical
  Haplo-identical
- Enzyme replacement therapy
  PEG-ADA

- **Autosomal Recessive**
- **Incidence: 1:200,000-1:1 million births**
- **Presents at infancy with:**
  - Recurrent opportunistic infections
  - Failure to thrive
  - Pan-lymphopenia (T-,B-, NK-)
  - Absent cellular and humoral immunity

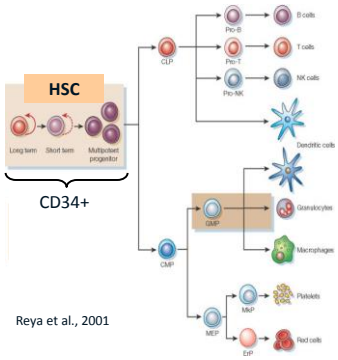
PEG-ADA Enzyme Replacement

- **Injections must be administered life-long**
- **Expensive (~$200,000-$400,000 per year)**
- **Only partial immunity is restored in some cases**

Why SCID is a good Candidate Disease to be Used for Gene Transfer

- **A monogenic disease**
- **It is believed that a small number of corrected HSCs can be curative.**
- **Therefore, even if only a small number of cells receive the therapeutic gene, the patient may derive some benefit.**

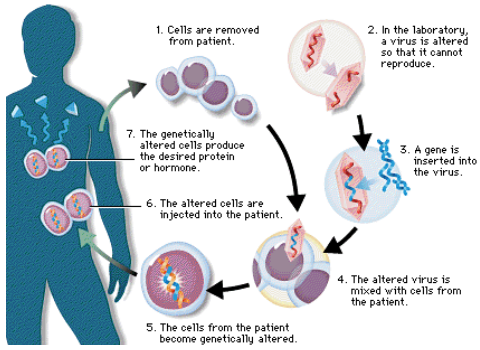
Hematopoietic Stem Cells (HSC)



Reya et al., 2001

- The common ancestor to all types of blood cells
- Have the ability to perpetuate themselves through self-renewal
- Generate mature cells of a particular tissue through differentiation
- One of the best-characterized stem cells in the body and the only stem cell that is clinically applied in the treatment of diseases for example, leukemias and congenital immunodeficiencies

Hematopoietic Stem Cells (HSC)



Hematopoietic Stem Cells (HSC)

news feature

Nature **420**, 116-118 (14 November 2002) | doi:10.1038/420116a

Gene therapy: A tragic setback

Erika Check[1]

With one French gene-therapy patient having developed a form of cancer, a frantic detective effort is under way to determine what went wrong — and to assess the risks faced by others. Erika Check reports.

Top

Until a few weeks ago, a three-year-old boy whose identity remains confidential was a beacon of hope for gene therapists. He is one of 11 children with severe combined immune deficiency (SCID) to receive a pioneering treatment from a team led by Alain Fischer and Marina Cavazzana-Calvo of the Necker Hospital for Sick Children in Paris. It worked, providing the first proof that gene therapy can cure a life-threatening disease[1].

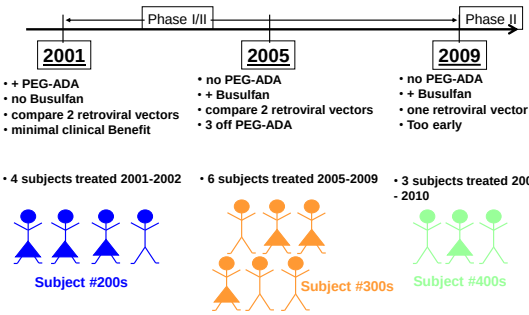
Clinical Trials of Gene Transfer for ADA-Deficient SCID

- In the early 1990s, retroviral vectors were used to transfer a normal human ADA cDNA to T cells collected by leukopheresis (US, Italy, Japan)
- Later, investigators started to use progenitors from the bone marrow (Netherlands, Milan) for gene transfer.
- In 1993, 3 infants, who were diagnosed *in utero,* had gene transfer to their umbilical cord blood CD34+ cells, which were reinfused when the babies were 4 days old (CHLA, NIH)
- In all cases, T cells with the normal gene were produced, but at levels too low to restore immunity.
- All subjects continued to receive PEG-ADA enzyme and did not receive any cytoreductive conditioning.
- Minimal clinical benefit seen.

New Gene Therapy Trial for ADA-deficient SCID – first performed in Milan, Italy

- In 2002, a group in Milan, Italy published a paper in *Science* on 2 patients who were treated by retroviral-GT to their bone marrow CD34+ cells and who derived benefit
- The patients were not on PEG-ADA at the time and received 4mg/kg busulfan (an alkylating agent, which destroys predominantly stem cells)
- This group has now treated ~15 patients, the majority of who have derived benefit (Data on first 10 has been published.)
- Subsequent GT studies for ADA-SCID [in London (data on 1 subject has been published) and the US] have been designed similarly

U.S. Trial of Gene Therapy for ADA-SCID Using CD34+ cells from Bone Marrow



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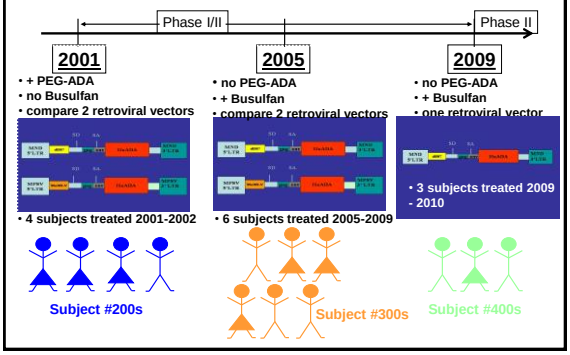
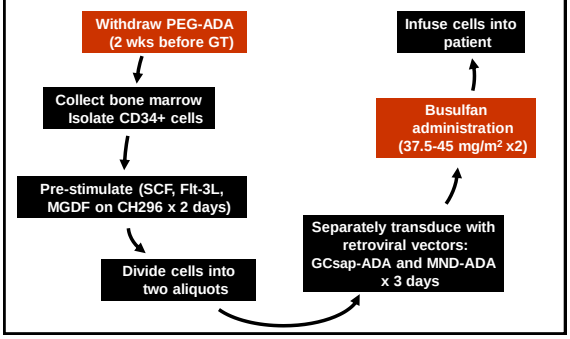
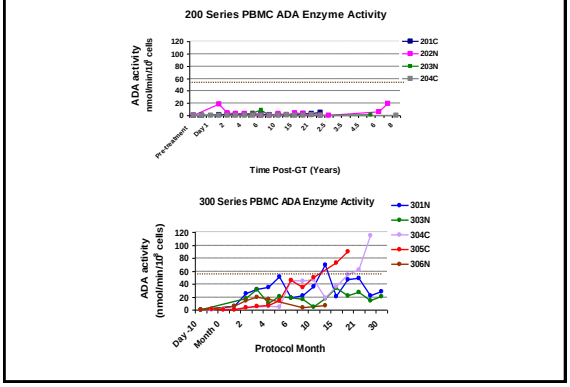
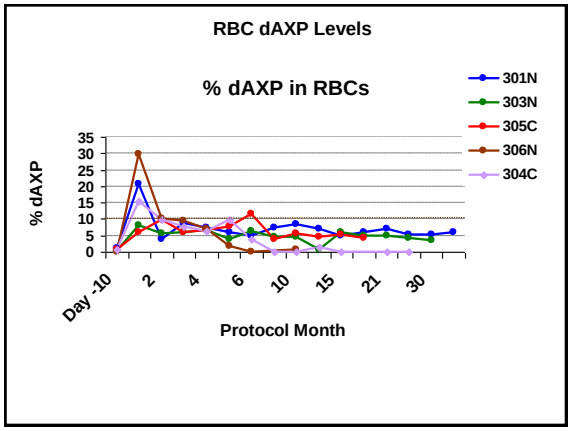


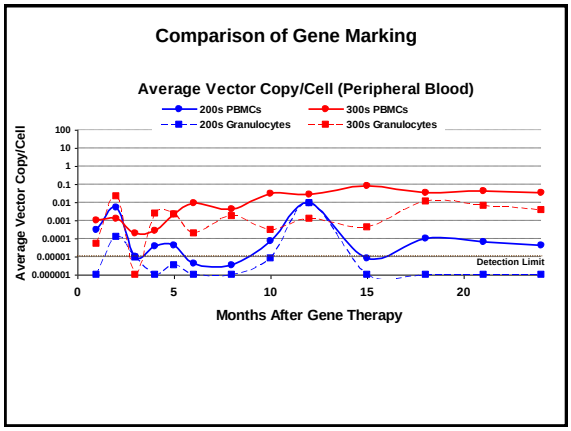
2001-2009 Phase I/II Gene Transfer Clinical Trial (CHLA & NIH)



PBMC ADA Enzyme Activity







Plenary paper

Gene therapy for adenosine deaminase–deficient severe combined immune deficiency: clinical comparison of retroviral vectors and treatment plans

Fabio Candotti,[1] Kit L. Shaw,[2] Linda Muul,[1] Denise Carbonaro,[2] Robert Sokolic,[1] Christopher Choi,[2] Shepherd H. Schurman,[1] Elizabeth Garabedian,[1] Chimene Kesserwan,[1] G. Jayashree Jagadeesh,[1] Pei-Yu Fu,[2] Eric Gschweng,[2] Aaron Cooper,[3] John F. Tisdale,[4] Kenneth I. Weinberg,[5] Gay M. Crooks,[6] Neena Kapoor,[7] Ami Shah,[7] Hisham Abdel-Azim,[7] Xiao-Jin Yu,[1] Monika Smogorzewska,[7] Alan S. Wayne,[8] Howard M. Rosenblatt,[8] Carla M. Davis,[10] Celine Hanson,[10] Radha G. Rishi,[11] Xiaoyan Wang,[12] David Gjertson,[6,12] Otto O. Yang,[13] Arumugam Balamurugan,[13] Gerhard Bauer,[14] Joanna A. Ireland,[7] Barbara C. Engel,[15] Gregory M. Podsakoff,[16] Michael S. Hershfield,[17] R. Michael Blaese,[18] Robertson Parkman,[7] and Donald B. Kohn[2,19]

Takeaways:

1. The phases of a clinical trial
2. Knowledge that you need to prepare an Investigational New Drug Application (IND)
3. The IND - Chemistry Manufacturing and Controls section
4. Know the challenges of getting an IND approved by the FDA, eg.
   1. Infrastructure
   2. Testing