Regulatory Perspective on Combination Therapy of Cancer

Ashok Batra, M.D., F.R.C.S, F.A.C.S.

Director

Division of Clinical Evaluation and Pharmacology/Toxicology

OCTGT,CBER,USFDA

1 November , 2007

Overview

- Office of Cellular, Tissue, and Gene Therapies -Organization, CBER/CDER Biologic Products incl. Cancer Vaccines and immunotherapy
- Combination products : Regulations and Examples
- Review of combination Products
- Challenges in the clinical Development of the combination products
- OCTGT Collaborations
- Communications

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Stephanie Simek, Ph.D. Deputy Director

Division of Cellular and Gene Therapies

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Division of Human Tissue Products

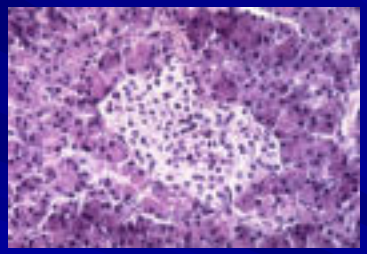
Ruth Solomon, M.D., Director

Division of Clinical Evaluation and Pharmacology/Toxicology

Ashok Batra, M.D., F.R.C.S, F.A.C.S. , Director

Products Regulated by CBER

- Blood, blood components and derivatives
- Vaccines (preventive and therapeutic)
- Allergenics



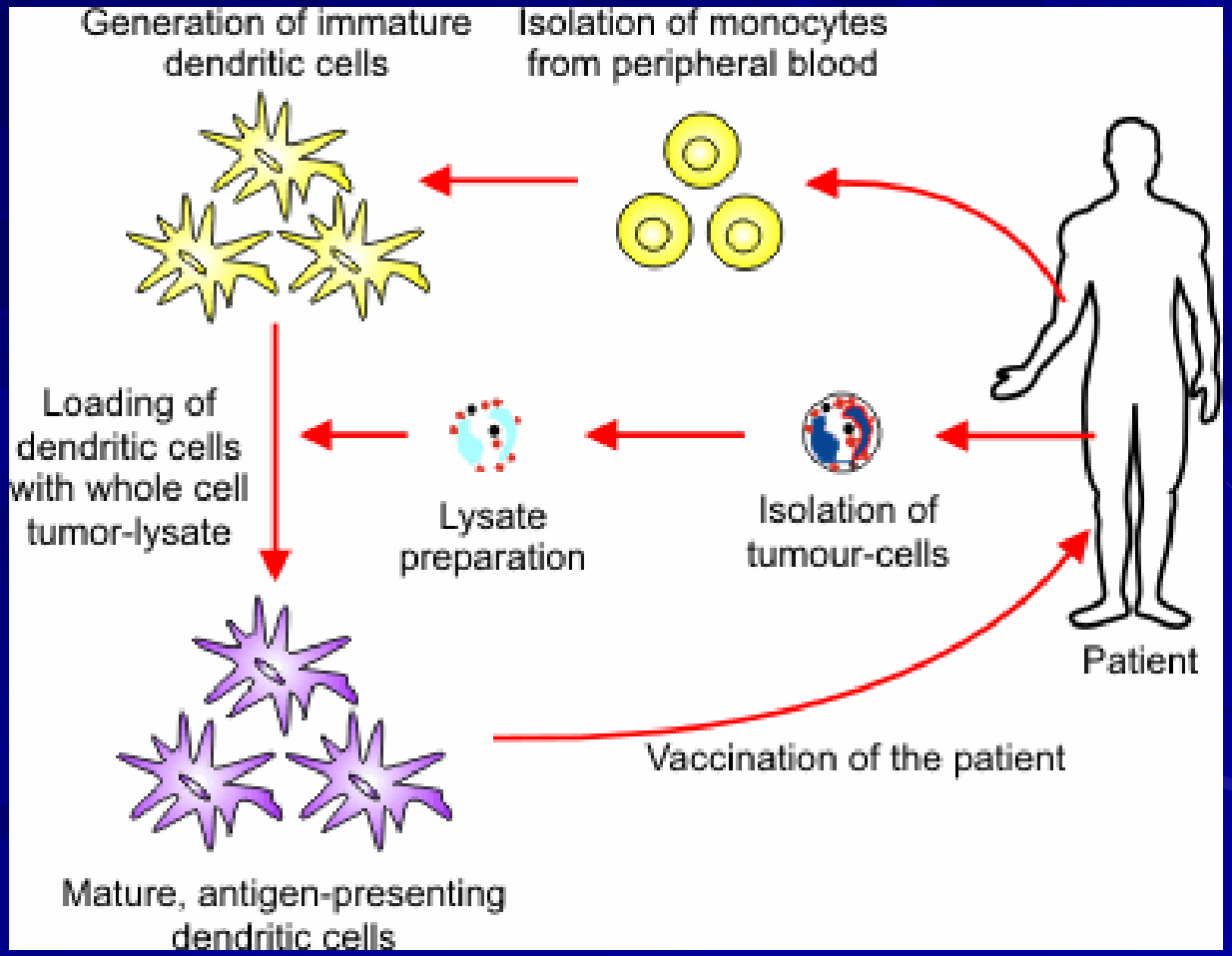
- Cell and Gene Therapies
- Tissues
- Xenotransplantation
- Related Devices (including certain IVDs)

Therapeutic Biological Products Evaluated by CDER

- Monoclonal antibodies for in vivo use.
- Proteins intended for therapeutic use, including cytokines (e.g. interferons), enzymes (e.g. thrombolytics), and other novel proteins, except for those that are specifically assigned to CBER (e.g., vaccines and blood products). This category includes ther. proteins derived from plants, animals, or microorganisms, and recombinant versions of these products.
- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response).
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo

Cancer Vaccines and Immunotherapy Products Evaluated by OCTGT

- **Cells**
- **Lysates**
- **Proteins, peptides**
- **Gene therapies**
- **Idiotypic and anti-idiotypic antibodies**



Types of Combination Products

- 21 CFR 3.2(e)
  - A product comprised of two or more regulated components that are physically, chemically or otherwise combined or mixed as a single entity
  - Two or more separate products packaged together (e.g., drug and device products)
  - Provided separately but intended for use together where both are required to achieve the intended use, indication, or effect and where mutually conforming labeling is needed.

Combination Products
21 CFR 3.2(e)(1)

- Comprised of two or more regulated components (Single Entity, Packaged Together or Separately)
  - Drug/device
  - Biologic/device
  - Drug/biologic
  - Drug/biologic/device
- Physically, chemically, or otherwise combined or mixed

Combination Products :Packaged Together
21 CFR 3.2(e)(2)

- Two or more separate products packaged together
  - Drug/device package (e.g., drug-eluting stent, condom with spermicide etc.)
  - Device/biologic package (e.g., artifical bladder)
  - Biologic/drug package (e.g., monoclonal antibody combined with a therapeutic drug)

Combination Products : Packaged Separately
21 CFR 3.2(e)(3)

- Packaged separately
  - One is already approved
- Based on investigational plan or labeling are intended for use only with an approved individually specified article
- Both are required to achieve intended use, indication, or effect
- Cross-labeling is needed

Combination Products
21 CFR 3.2(e)(4)

- Packaged separately
  - Both investigational
- Based on proposed labeling to be used with another investigational article
- Both are required to achieve the intended use, indication, or effect
- Cross-labeling is needed

Specifically Intended For Use Together

Example

Myeloablative therapy plus Cells

- Myeloablative drugs not specified
  - Not a combination product
- Why? 21 CFR 3.2(e)(3)
  - Need to meet all three criteria
    - Approved specified drug
    - Both required to achieve effect
    - Cross-labeling needed

Example

- Specific myeloablative drug(s) plus Cells
  - Combination product
- Why? 21 CFR 3.2(e)(3)
  - Meets all three criteria
    - Approved specified drug
    - Both required to achieve effect
    - Cross-labeling needed

What is not a Combination Product?

- Drug-drug, device-device, or biologic-biologic combinations, such as:
  - Fixed combination drug products
  - Products comprised of two biologics, even if review responsibility shared between CDER and CBER
- Most concomitant use of drugs, devices and biologics
- General drug or biologic delivery devices (e.g., unfilled syringe or infusion pump) not intended for use with specified drug or biologic product

What is not a Combination Product?

- Dendritic cells pulsed with tumor antigens, peptides, purified or recombinant proteins, cell lysates, nucleic acids or transduced with gene transfer vectors
- Cells cultured and expanded in growth factors or cytokines and administered as such or mixed with growth factors
- Tumor antigens or cells mixed with adjuvant (BCG, KLH, CPG, GM-CSF etc.) either injected separately or together
- Antibody, tumor antigen and adjuvant (anti-CTLA-4 Ab, peptide and montanide)

How does FDA assign jurisdiction for review of combination products?

- If possible on the basis of primary mode of action, which is defined in the Code of Federal Regulations
- If primary mode of action cannot be used, then the selection is based on precedents and experience with similar products
- If no precedents exist, then the selection is based on expertise in the therapeutic questions

FDA Review of Combination Product

- FDA center with lead review responsibility
  - PMOA dependent upon biologic – CBER
  - PMOA dependent upon drug – CDER
  - PMOA dependent upon device – CDRH
    - [see 21 CFR 3.4]
- Consult reviews for secondary components will be performed by center with component expertise

FDA Review of Combination Product

- Collaborative review:
  - Combination product and some non combination products - cancer vaccines and immunotherapy products – each Center provides independent review. Comments consolidated by the lead Center - determined by PMOA - IND filed at lead Center
- Consultative review:
  - Expertise – CBER requesting consults on the issues of proteins, antibody, enzymes or catheters, device

Cell/Tissue Combination Products Regulation

- Primary mode of action dictates

  if regulated as:

  - IND or IDE, HDE...
  - BLA or PMA / 510(k)

- Consult Reviews for secondary components will be performed by Center with component expertise

Combination product vs. Combinatorial therapy

- Combination product --- 2 or more therapeutic components (drug, device, or biological product) required for intended effect

- Combinatorial therapy --- therapy containing multiple components

Cancer Vaccines in Combination Therapies

CMC Challenges

- Manufacturers will not provide access to or develop products for combination use
- CMC data may reside in Master Files or cross-referenced file not accessible to investigator; FDA cannot discuss/divulge CMC issues without authorization

Cancer Vaccines and Immunotherapy in Combination Therapies

CMC - Possible Solutions

- Role of Master Files in protecting confidential information
- Education of sponsor-investigators regarding FDA confidentiality
- Education of manufacturers regarding adverse reaction reporting requirements and FDA approach to review of marketing applications

Considerations for Pharmacology/Toxicology Testing

- Preclinical testing paradigm is influenced by:
  - Data from previous preclinical studies on all components and combination
  - Data from previous clinical studies (pre- and post-marketing) on all components and combination
  - Regulatory status of each component
- Provide safety and activity data for individual components and combination in appropriate animal models by intended clinical route of administration
- Challenges: Lack of appropriate Models

Considerations for Cancer Vaccine and Immunotherapy -Clinical Studies: Efficacy Standard

- For initial approval, more than one phase 3 study necessary unless highly significant survival benefit shown
- For supplemental approval,activity in the initial approval may be supportive of activity in the new setting

Cancer Vaccines and Immunotherapy in Combination Therapies: Challenges

Clinical development

- Establish that each component is *required to achieve the intended use, indication, or effect*
- Generate sufficient data to write adequate directions for use
- Conducted with product in which each component adequately characterized (GMP)

Cancer Vaccines and Immunotherapy in Combination Therapies: Efficacy

- A Randomized controlled trial (Standard)
- A well planned , carefully thought out , prospectively planned adaptive trial that controls type I error and in which the integrity of the trial is maintained can be considered for review.

Cancer Vaccines and Immunotherapy in Combination Therapies: Adaptive Designs

- Unique Issues in Cancer Vaccines and Immunotherapy – Uncertainty

- Utilize accumulating data from the ongoing trial to modify certain aspects of the study without undermining the validity and integrity of the trial.

Cancer Vaccines and Immunotherapy in Combination Therapies- Clinical Studies

- Multi-arm trials
  - Vaccine A combined with one or more adjuvants or immunomodulators
  - Choice of control (comparator) arm dependant upon
    - Availability of active therapy
    - Evidence that investigational agent(s) is/are active
    - Apparent risks of investigational agent(s)

Cancer Vaccines and Immunotherapy in Combination Therapies- Clinical Studies

- Example: One component (Vaccine A) has been shown to be safe and effective

  Add-on trial designs:

  - Vaccine A vs. Vaccine A + Invest Drug B
  - Standard therapy C + Vaccine A vs. Standard therapy C + Vaccine A + invest drug B
  - Designed to verify superiority of combination to single agent, thus establishing contribution of Drug B

Common Questions: Single dose Studies for Each Component

- Is there a need for single dose initial clinical studies for each component of a multi-component product or each product in a combination product?
  - Not necessarily. Factors include novelty of products, existence of prior clinical data from similar products, results of pre-clinical studies

Common Questions: Incentives

- Programs of Fast Track, Orphan Status (with possibility of qualifying for development grants), Pediatric Exclusivity, Priority Review and Accelerated Approval can all apply using the relevant criteria

Collaboration between CBER, CDER and CDRH for oncology products

- Organized by Office of Oncology Drug Product (CDER)
- Monday morning meeting to discuss cross-FDA oncology related activities
- Discussion of inter-center review issues
- Monthly Executive Briefing on oncology activities
- Joint workshops and participation in interaction with stakeholders such as interaction with iSBTc, CVC, AACR, ASCO, AAI, International Biological Society (IABs), ASGT, ISCT, and others

Collaboration between CBER, CDER and CDRH for oncology products contd..

- Joint participation in FDA and NCI Inter-Agency oncology Task force (IOTF)
- Joint participation in policy and guidance document development (e.g., tumor specific guidance's on end points)
- Supplementation of expertise to advisory committee discussions [Cell, Tissue and Gene Therapy Advisory committee (CTGTAC), Oncology Drug Advisory Committee (ODAC) and device panels]
- Joint participation in FDA Critical Path Initiative to promote development of oncology products

Guidance Documents Information

- **Guidances can be found at:**
  - **CBER:**
    http://www.fda.gov/cber/guidelines.htm
  - **CDER:**
    http://www.fda.gov/cder/guidance/index.htm
  - **CDRH:**
    http://www.fda.gov/cdrh/guidance.html

Contact Information

ashok.batra@fda.hhs.gov

301-827-2289

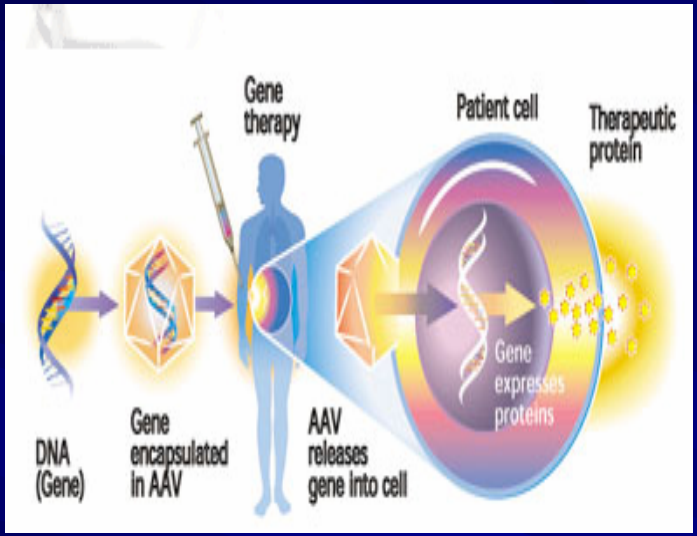
- http://www.fda.gov/cber
- 1-800-835-4709 or 301-827-1800
- matt@cber.fda.gov (manufacturers or regulated industry)
- combination@fda.gov (Office of Combination product)
- **General Information:**

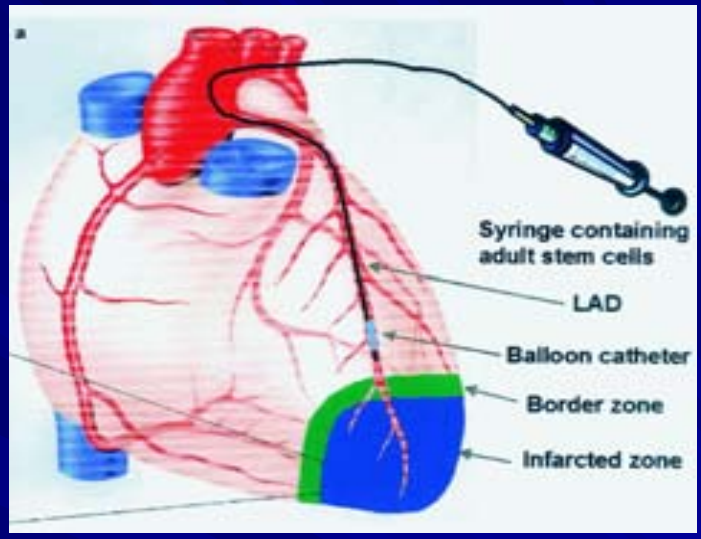
CBER -Office of Communication, Training & Manufacturers Assistance

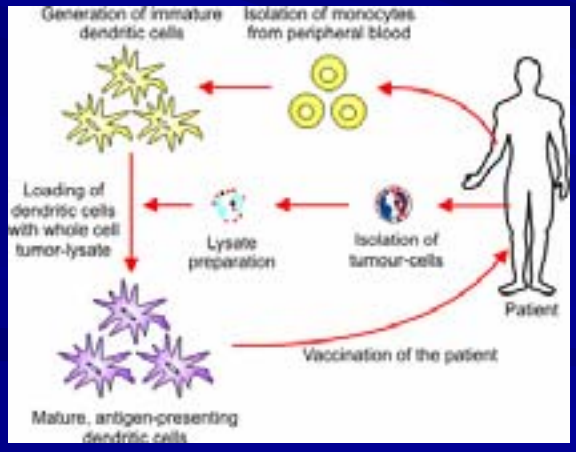
octma@cber.fda.gov (consumers, health care professionals)

OCTGT welcomes your input

Thank You


Gene therapy
Patient cell
Therapeutic protein
DNA (Gene)
Gene encapsulated in AAV
AAV releases gene into cell
Gene expresses proteins


Syringe containing adult stem cells
LAD
Balloon catheter
Border zone
Infarcted zone


Generation of immature dendritic cells
Isolation of monocytes from peripheral blood
Loading of dendritic cells with whole cell tumor-lysate
Lysate preparation
Isolation of tumour-cells
Patient
Vaccination of the patient
Mature, antigen-presenting