FDA Perspectives on Combination Therapy of Cancer

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Overview

- Office of Cellular, Tissue, and Gene Therapies, CBER
  - Organization
  - Regulated products
- Office of Oncology Drug Product, CDER
  - Organization
  - Regulated products
- Definition of Combination Products
- Collaboration between CBER and CDER for oncology products
- Points to consider for product and pharm/tox issues

Office of Cellular, Tissue, and Gene Therapies

Celia M.Witten, Ph.D, M.D., Director
Stephanie Simek, Ph.D. Acting Deputy Director

Division of Cellular and Gene Therapies
Raj Puri, Ph.D., M.D., Director
Kimberly Benton, Ph.D., Acting Deputy Director

Division of Human Tissue Products
Ruth Solomon, M.D., Director

Division of Clinical Evaluation and Pharmacology/Toxicology
Ashok Batra, M.D.

Division of Cellular and Gene Therapies (DCGT)

Raj Puri, Ph.D., M.D., Director

Kimberly Benton, Ph.D., Acting Deputy Director

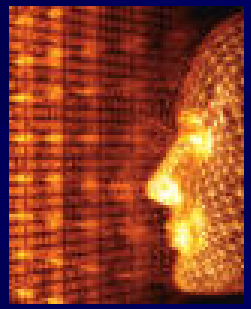
Gene Therapies Branch
Daniel Takefman, Ph.D.,
Acting Chief

Gene Transfer and Immunogenicity Branch
Eda Bloom, Ph.D., Chief

Cell Therapies Branch
Keith Wonnacott, Ph.D.,
Acting Chief

Tumor Vaccines and Biotechnology Branch
Raj Puri, Ph.D., M.D., Acting Chief

Cellular and Tissue Therapy Branch
Steve Bauer, Ph.D., Acting Chief

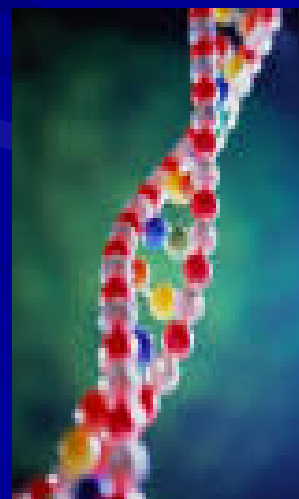


Vision for CBER

INNOVATIVE TECHNOLOGY ADVANCING PUBLIC HEALTH

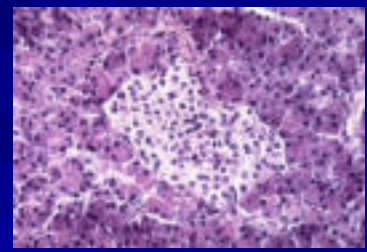
- Protect and improve public and individual health in the US and, where feasible, globally
- Facilitate the development, approval and access to safe and effective products and promising new technologies
- Strengthen CBER as a preeminent regulatory organization for biologics

Our research activities are critical to the success of each element



Products Regulated by CBER

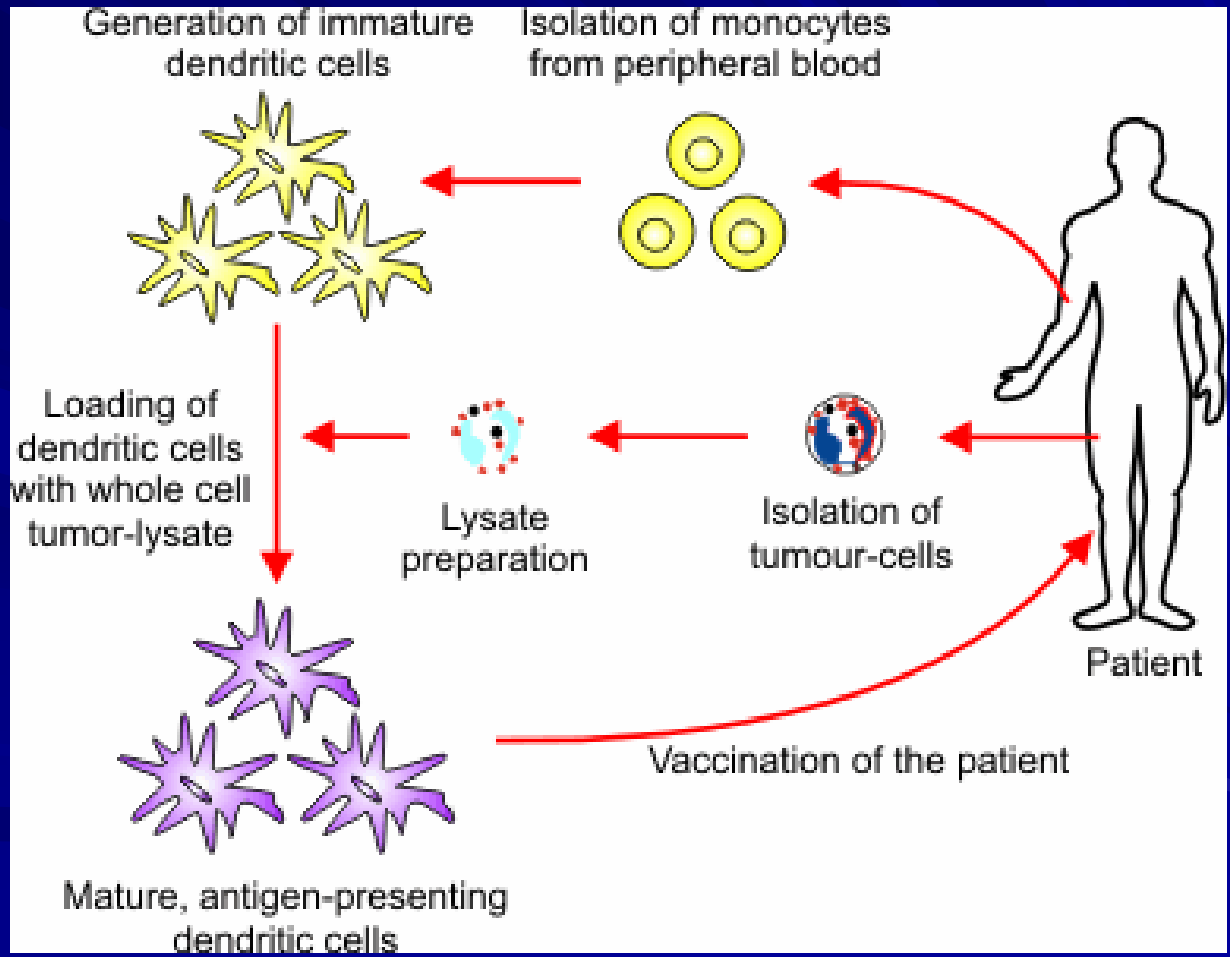
- Blood, blood components and derivatives
- Vaccines (preventive and therapeutic)
- Allergenics



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

Tumor Vaccines and Cancer Immunotherapy Evaluated by OCTGT

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



Office of Oncology Drug Products

Richard Pazdur, M.D., Director
Karen Weiss, M.D. Deputy Director
David Ross, M.D., Ph.D., Associate Director for Regulatory Science

Division of Drug Oncology Drug Products
Robert Justice, M.D. , Director

Division of Medical Imaging and Hematology Products
George G. Mills, M.D., Director

Division of Biologic Oncology
Patricia Keegan, M.D., Director

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 therapeutic 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.

Combination Products
21 CFR 3.2(e) Product Jurisdiction

- Comprised of two or more regulated components
  - Drug/device
  - Biologic/device
  - Drug/biologic
  - Drug/biologic/device
- NOT biologic-biologic combinations (including CBER-CDER)

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); or
  - 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.

Common Themes

- Components under different regulatory authorities
- Specifically intended for use together

Example 1

- 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 2

- 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

Not Combination Products

- 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)

FDA Review Framework 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]

Collaboration between CBER, CDER and CDRH for oncology products

- Organized by Office of Oncology Drug Product
- 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, 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 guidances 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

Key points to consider for Product Characterization

- Importance of product characterization
  - All product components as well as final product to be characterized and tested
  - In process & final product testing
  - To ensure lot - to lot consistency, integrity, stability, demonstrate comparability
  - Potency and identity tests for individual components and final product

Key Points to Consider 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

Additional Detailed Discussion Provided by

- **Regulatory perspectives** presented by:
  - Steven Hirschfield, M.D., Medical Officer, Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT), OCTGT, CBER
- **Breakout Session 3: "Regulatory Issues and Development of Combinations" participated by:**
  - Ashok Batra, M.D., F.A.C.S., Director, DCEPT, OCTGT,CBER
  - David Ross, M.D., Ph.D., Associate Director for Regulatory Science, Office of Oncology Drug Product, Office of New Drug, CDER

Contact Information

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General Information:

CBER -Office of Communication, Training & Manufacturers Assistance

- http://www.fda.gov/cber
- 1-800-835-4709 or 301-827-1800
- matt@cber.fda.gov (manufacturers or regulated industry)
- octma@cber.fda.gov (consumers, health care professionals)
- CDER Office of Training and Communication
- CDRH Office of Communication, Training, Education and Radiation Programs
- combination@fda.gov (Office of Combination product)

Thank you

- We are in the midst of explosive new advances in targeted therapy, immunotherapy, cancer vaccines and other areas of medical research leading to development of safe and effective new cancer medicines for the 21st century.
- New technologies need expert, innovative & interactive science, new models, standards and assays.
- We see a positive future with exciting science and great opportunity for everyone.