FDA and Cancer Vaccine Development

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Outline

- FDA Overview
- Cancer Vaccines
  - Types of Cancer Vaccines
  - Clinical Development of Cancer Vaccines
- Basis for Marketing Approval/Endpoints efforts
- Combination Therapies
- FDA Collaboration and Outreach

FDA Organization

- Office of the Commissioner
- CBER (Center for Biologics Evaluation and Research): vaccines, blood and blood products, human tissue/tissue products for transplantation, cells, gene therapy
  - Office of Cellular, Tissue, and Gene Therapies
  - Office of Vaccines Research and Review
  - Office of Blood Research and Review
- CDER (Center for Drug Evaluation and Research): drugs, monoclonal antibodies, cytokines, therapeutic proteins
- CDRH (Center for Devices and Radiological Health): devices for treatment, implants, diagnostic devices
- CVM
- CFSAN
- NCTR

Office of Cellular, Tissue, and Gene Therapy

- Cellular therapies
- Cancer vaccines
- Immunotherapy
- Gene therapies
- Tissue and tissue based products
- Xenotransplantation products
- Devices used for cells/tissues

OCTGT Product Examples

- Cell Therapy Products
  - Progenitor cells, e.g. hematopoietic progenitor cells, stem cells derived from various types of human tissues…
  - Differentiated cells, e.g. islet cells, cartilage cells, dendritic cells, T lymphocytes…
  - Tissue engineered products, e.g. various cell types embedded in a scaffold
  - Xenotransplantation

Product Examples (cont'd)

- Gene Therapy Products
  - Many types of replication deficient viral vectors
  - Plasmid DNA vectors
  - Various types of transgenes delivered by those vectors
  - Replication competent or attenuated viruses for the treatment of various type of cancers via viral lysis of tumor cells
- Therapeutic Vaccines
  - Cancer vaccines
  - Vaccines for the treatment of other diseases such as Alzheimer's disease

Immunotherapy of cancer

- Active: aim to elicit host immune system to mediate tumor destruction.
  - Cancer vaccines
    - Tumor specific
    - Non-Tumor specific
  - Cytokines
- Passive: Tumor destruction by administered agent
  - Antibodies
  - Adoptive T cell therapy

Types of Cancer Vaccines

- Antigen/adjuvant vaccines
- Whole cell cancer vaccines
- Dendritic cell (DC) vaccines
- Viral vectors and DNA vaccines
- Idiotype vaccines

Types of Cancer Vaccines

- Antigen/adjuvant vaccines
  - Specific protein fragments or peptides stimulate the immune system to fight tumor cells.
  - One or more cancer cell antigens are combined with a substance that causes an immune response, known as an adjuvant.

- Whole cell cancer vaccines
  - Autologous or allogeneic whole cell vaccine preparations containing cancer antigens used to stimulate an immune response.

Types of Cancer Vaccines

- Dendritic cell (DC) vaccines
  - Autologous dendritic cells (DCs) are obtained through a leukapheresis.
  - DCs are stimulated with autologous cancer antigens and re-injected into the patient.
  - Once injected, DC vaccines activate the immune system's T cells. Activation by DCs is expected to cause T cells to multiply and attack tumor cells expressing that antigen.

Types of Cancer Vaccines

- Viral vectors and DNA vaccines
  - Nucleic acid sequence of the tumor antigen is used to produce cancer antigen proteins.
  - The DNA containing the gene for a specific cancer antigen is manipulated in the laboratory so that it will be taken up and processed by immune cells called antigen-presenting cells (APCs).
  - The APC cells then display part of the antigen together with another molecule on the cell surface.
  - The hope is that when these antigen-expressing APC cells are injected into a person, the immune system will respond by attacking tumor cells containing the same antigen.
  - Vector-based and DNA vaccines are attractive because they are easier to manufacture than some other vaccines

Types of Cancer Vaccines

- Idiotype vaccines
  - Since antibodies are molecules containing protein and carbohydrate, they can themselves act as antigens and induce an antibody response
  - Antibodies produced by certain cancer cells (i.e., B-cell lymphomas and myelomas), called idiotype antibodies, are unique to each patient and can be used to trigger an immune response in a manner similar to antigen vaccines.

Unique Issues : Cancer Vaccines, Cell and Gene Therapies

- Product manufacturing and characterization, especially autologous products
- Paucity of Predictive pre clinical models of efficacy
- Patients with compromised immune systems may not be good candidates
- Clinical Studies
  - Metabolism does not follow standard pharmacokinetics
  - Patient selection and endpoint definition require careful consideration
  - Distinct product mechanism of action may require different trial considerations especially for early phase studies
    - Optimal biologic dose/maximum tolerated dose
    - Consideration of unique toxicity profiles and monitoring

Product Characterization for Cell and Gene Therapies

- Importance of product characterization
  - To ensure lot to lot consistency, integrity, stability, demonstrate comparability
  - Quality of all product components (e.g., growth factors, cells) should be demonstrated
  - In process & final product testing (e.g., sterility, purity)
  - Sterility, safety, purity, potency of final product
  - Products with multiple active components- identity and potency

Additional Challenges for Cancer Immunotherapy

- Many therapies used in combination with other agents (adjuvants or chemotherapies) or other treatment modalities
- Adjuvant or other agents commonly used in Vaccine therapy:
  - Adjuvants as stand-alone products are not licensed
  - Each specific preventive or therapeutic vaccine/adjuvant formulation is subject to licensure

Early Phase Development of Cancer Therapeutics: Cytotoxic Drugs

- Study objectives
  - Determination of dose range appropriate for future studies and toxicity profile (MTD)
- Considerations:
  - Starting dose based on preclinical tox studies
  - Dose escalation
  - Monitoring for dose limiting toxicity (DLT)
  - Pharmacokinetic & pharmacodynamic data
- Generally conducted in patients with advanced cancer

Early Phase Development of Cancer Vaccines

- Study objective: Identification of a pharmacologically effective dose or optimal biologic dose rather than MTD
- Rationale
  - Biologically active doses may occur well below the MTD
  - May not be feasible to achieve MTD
  - Immunological endpoints

Clinical Development of Cancer Vaccines

Phase 2 studies-tumor vaccines

- Continues exploration of dose, schedule, route of administration
- Exploration of combination approaches (e.g., immunoadjuvants, cytokines, multiple antigens)
- Development of hypotheses to be tested in phase 3

Clinical development of cancer vaccine --- patient population

- Metastatic disease
  - Advantages
    - Shorter and faster enrollment
    - Short evaluation period
    - Small sample size
    - Allows tumor response evaluation
  - Disadvantages
    - Often multiple prior cancer treatment
    - Incompetent immune status (from prior therapies)
    - Inadequate evaluation due to rapid disease progression
- Minimal or no evidence of diseases
  - Advantages
    - Fewer prior therapies
    - Better in immune status (Immunocompetent)
    - Adequate time for evaluation before disease progression
    - May be optimal for the proposed MOA of cancer vaccines
  - Disadvantages
    - Longer trial period
    - Large sample size
    - Trial endpoints may be challenging

Regulations on Drug Approval

- 21 CFR 314.126
  - Determination of **substantial evidence** to support the claims of **effectiveness** for new drugs.
  - Primary basis: **Adequate and well-controlled investigations**

- 21 CFR 314.126
  - Acceptable safety

- 21 CFR 201
  - Product label
    - Defines an appropriate patient population
    - Provides adequate information to enable safe and effective use

Two Types of Approvals

- Regular (Full) approval or
- Accelerated Approval
- Basis for the approval type: the criteria (endpoints) in determining the effectiveness

Regular (full) Approval

- Direct clinical benefits
  - Prolongation of overall survival (live longer)
  - Improvement of symptoms (live better)
  - Favorable effect on established surrogate
  - Composite endpoints

Accelerated Approval

- 21 CFR 314.510 for drugs (subpart H)
- 21 CFR 691.41 for biologics (subpart E)
- The product
  - Treats serious or life-threatening illnesses
  - Provides meaningful therapeutic benefit to patients over existing treatments
  - Is tested in adequate and well-controlled clinical trials
  - Has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity
  - Fulfils post-marketing commitment to verify and describe its clinical benefit

Licensing ("pivotal") studies for Cancer Therapeutics

Similarities between Tumor Vaccines and Drugs

- Need to be internally controlled (randomized)
- Similar objectives: improved survival, disease-free survival, or time to progression
- Evaluated in context of available therapy and standard of care
- Regulatory consistency (CBER/CDER)
- Statistical considerations – primary analysis of Intent to Treat (ITT) population

Licensing ("pivotal") studies for Cancer Therapeutics

Differences between Cancer Vaccines and Drugs

- Minimal residual disease patients may be more likely to benefit from vaccine
- Blinding may be more feasible
- Anti-tumor activity may occur without to tumor shrinkage
- Treatment effects may be delayed

Licensing ("pivotal") studies for Cancer Therapeutics

Phase 3 Studies - Efficacy standards

- "Substantial evidence" of net clinical benefit or of an effect on a surrogate reasonably likely to predict clinical benefit
- "Adequate and well-controlled clinical trials"

Basis for Marketing Approval

- Replicable demonstration of efficacy with acceptable safety in adequate and well-controlled trials
- Ability to write a product label that:
  - defines an appropriate patient population for treatment
  - provides adequate information to enable safe and effective use of the drug

Oncology Endpoints Efforts

- Workshops
  - discussion of endpoints in different stages of disease
  - involve academia, industry, patient advocacy
- Oncology Drugs Advisory Committee
  - Meetings focused on specific Diseases
  - Follow-up on issues raised at workshop
- FDA Guidance: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Endpoint Challenges for Cancer Immunotherapies

- Potential delayed onset of activity
- Generally no expectation of effect on tumor volume
- Difficulty in assessment of progression

Cancer vaccines in Combination Therapies

- Cancer vaccines (Ag, adjuvants, cytokines, or co stimulatory molecules- Multiple agents).
- Device
- Biologic therapies
- Chemotherapeutic agents
- Radiation

Combining Cancer Vaccines with Other Agents

General challenges:

- Clinical development programs designed to
  - Establish that each component is *required to achieve the intended use, indication, or effect*
  - Generate sufficient data to write adequate directions for use (patient population, dose/schedule, risks)
  - Conducted with product in which each component adequately characterized (GMP)

Combining Cancer Vaccines with Other Agents

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

Combining Cancer Vaccines with Other Agents

Non-Clinical Challenges

- Establishing a safe starting dose/dose escalation for first-in-human studies
  - Standard assessments differ by product (drug/device/biologic)
  - Integrating information from each product
  - Identifying toxicities novel to the combination

Combining Cancer Vaccines with Other Agents

Clinical Challenges

- Contribution of each agent in definitive trials may require multi-arm, parallel design trials; trial design analysis plan must be pre-specified
- Overall strength of evidence is considered; non-clinical data may provide compelling evidence of contribution to effect if it can be “bridged” to clinical outcomes

Facilitating 21st Century Medical Product Development: Collaboration with NCI

- Interagency Oncology Task Force (IOTF)
  - Facilitates interagency collaboration
  - Supports FDA/NCI joint fellowship training program
    - NCI supported training in cancer-related scientific research and regulatory review
    - http://iotftraining.nci.nih.gov/index.html
- Joint workshops
  - Examples to follow
- Biomarker development
- Scientific collaboration
  - Inter Agency Agreements (IAG)

Joint FDA/NCI Workshops

- Bringing Therapeutic Cancer Vaccines and Immunotherapy Through Development to Licensure
  - February 8-9, 2007
    https://cms.palladianpartners.com/cms/1156354418/home.htm

- Accelerating Anticancer Agent Development and Validation Workshop
  - June 20-22, 2007

- RAID Investigator Workshop 'Working with FDA: Biological Products and Clinical Development'
  - May 14, 2007

FDA/NCI Co-Sponsored Workshop on Cancer Vaccines and Immunotherapy

- February 8-9, 2007
- Participation from AACR, AAI, CVC, IABs, iSBTc, BDA, Paul Ehrlich-Institute
- Agenda available
  - https://cms.palladianpartners.com/cms/1156354418/materials/agenda.htm
- Videocast available
  - http://videocast.nih.gov

- Content of workshop
  - Unique regulatory aspects of developing cancer vaccines and immunotherapies
    - Early and late phase clinical trial design
    - Preclinical testing
    - Manufacturing controls
- Outcomes of the workshop
  - Greater dialogue among participants on the opportunities and challenges for these products
  - Better understanding of guidance that is needed from FDA to facilitate development of these products

Working with FDA: Biological Products and Clinical Development

RAID Investigator Workshop 'Working with FDA: Biological Products and Clinical Development'

- Training workshop developed in collaboration between FDA and NCI (RAID)
  - May 14, 2007
  - http://web.ncifcrf.gov/research/brb/workshops/cd/index.html
- Provided an introduction to what is needed to start clinical trials
  - Practical
  - Regulatory
  - Scientific

Immunotherapy Agent Workshop

- July 12, 2007
- Identified immunotherapy agents with high potential for use in treating cancer
- web.ncifcrf.gov/research/brb/workshops/NCI%20Immunotherapy%20Workshop%207-12-07.pdf

Immunotherapy Agent Workshop (cont'd)

- NCI website solicited suggestions for potential agents from cancer therapy community
  - Agents with substantial immunologic or physiologic activity
  - Not adequately tested in cancer patients

Immunotherapy Agent Workshop (cont'd)

- 124 potential agents of interest identified and considered
  - Potential for use in cancer therapy
  - Multiple, independent clinical investigator need
  - More than one clinical setting (different tumor types or as part of therapy regimen)
  - Not broadly available for clinical trials
  - Not commercially available
- 20 agent list developed in rank order

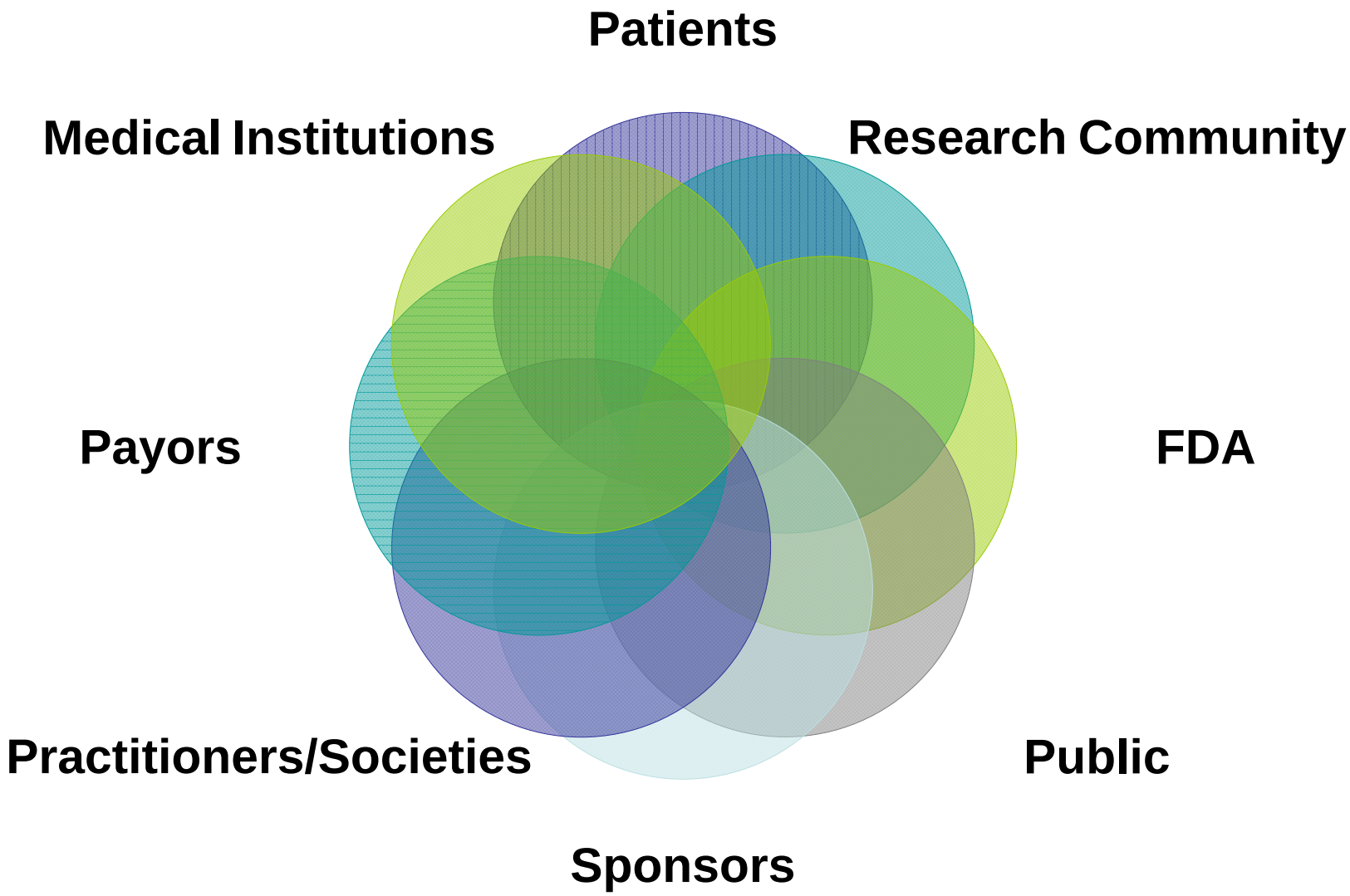
Collaboration Opportunities to Improve Cancer Therapies: Biomarkers

- FDA, NCI, and CMS Collaboration
  - Oncology Biomarker Qualification Initiative (OCBI) http://www.fda.gov/bbs/topics/news/2006/NEW01316.html

- The Biomarkers Consortium
  - Joint venture FNIH-NIH-FDA-Academia-Industry
    www.biomarkerconsortium.org

Advancing Medical Science

– As a public-private research partnership of the Foundation for the National Institutes of Health (FNIH), The Biomarkers Consortium endeavors to discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics. Biomarkers are molecular, biological, or physical characteristics that indicate a specific, underlying physiologic state to identify risk for disease, to make a diagnosis, and to guide treatment.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