Regulatory and Scientific Considerations for Potency Testing and Immune Monitoring

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"Immuno-Oncology Biomarkers 2010 and Beyond: Perspectives from the iSBTc Biomarker Task Force"

Date: September 30, 2010
Time: 10:00 AM to 12:00 PM
Location: NIH Masur Auditorium

Presenter Disclosure Information

Raj K. Puri, M.D., Ph.D.

The following relationships exist related to this presentation:

No Relationships to Disclose

Regulation of Cancer Therapeutics in the US

- Office of Oncology Drug Products, CDER
  - Drugs (small molecules)
  - Biologics, including
    - Monoclonal Antibodies
    - Therapeutic Proteins
    - Cytokines
- *Office of Cellular, Tissue and Gene Therapy, CBER*
  - Cell therapies
  - Gene Therapies
  - Cancer vaccines and Immunotherapy

Cancer Vaccines and Immunotherapy Products

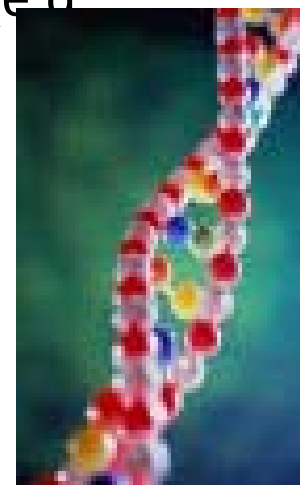
- Cells
  - E.g., dendritic cells, activated T lymphocytes (TIL, NK, LAK), B cells, monocytes, cancer cells chemically modified or unmodified
- Tumor cell lysates
- Proteins, peptides
  - Mixed with adjuvants
- Idiotypic and anti-idiotypic antibodies

Gene Therapy and Gene Modified Cancer Vaccines and Immunotherapy Products

- **Vectors Expressing Transgenes**
  - Plasmid DNA vectors
  - Replication defective viral vectors
  - Attenuated bacterial vectors

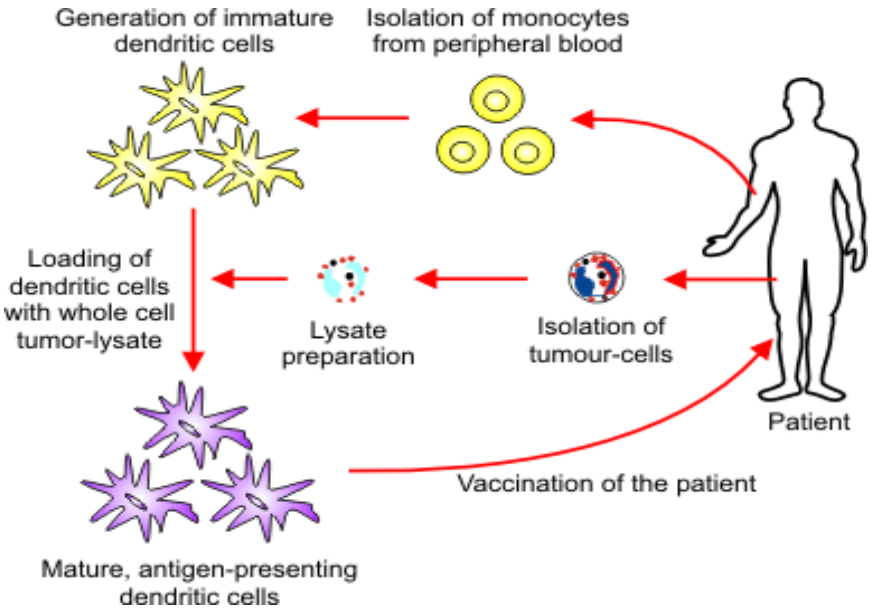
- **Gene Modified Tumor vaccines**
  - *Ex vivo* gene modified cells ..
  - Non-viral and viral vectors expressing immunogenic molecules (e.g. TAA, TCR ligands, co-stimulatory molecules..)

- **Gene Modified PBMCs and T cells**
  - Peripheral blood mononuclear cells (PBMCs) or purified T cells expressing chimeric T cell receptor...



Cancer Therapy Products may be Combined with other Biological Agents or Adjuvants

- Dendritic cells pulsed with tumor antigens, peptides, 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)



Successful Product Development

- Demonstrate product to be safe, pure, stable, potent and effective
- Full product characterization
- Demonstration of manufacturing and product consistency
  - Control of manufacturing process
  - Ensure continued production of quality products
  - Adherence to cGMP regulations

Characterization for Product Release 21 CFR 610

- Sterility
- Safety
- Purity
- Identity
- **Potency**

Potency Regulations

- **21 CFR 600.3 (s):**

The word potency is interpreted to mean the specific ability or capacity of the product...to effect a given result.

- **21 CFR 610.10:**

Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency...

Approaches for Potency Measurements

- **Direct Measurement of Biological Activity**
  - *In vitro or in vivo biological assay methods (bioassay)*
- **Indirect Measurement of Biological Activity (Surrogate Assay)**
  - *Non-bioassay, analytical assay methods that are correlated to biological activity*
- **Multiple Assays (Assay Matrix)**
  - *Combination of assays (biological or analytical) where the combined results, constitute an acceptable potency assay*

Assay Attributes

- **Potency Assays**
  - Indicate biological activity (s) specific/relevant to the product
  - Measure activity of all components deemed necessary for activity
  - Provide quantitative readout
  - Indicate product stability
  - Results available for lot release
  - Meet predefined acceptance and/or rejection criteria
  - Required prior to initiation of Phase 3 and validated during Phase 3 trial.

Challenges: Assay Development

- Limited material to test
  - Lots are often patient-specific, limited doses
- Limited time to test
  - Many products administered within hours of harvest
    - Storage/holding may effect viability, potency, etc.
- Lot-to-lot variability (inherent variability in starting cells or tissue)
- Unknown/complex mechanism of action (i.e. relevant biological activity)
- Limited availability of reference standards

Potency Assay Development Approaches

- Need to identify **functional** biomarkers
  - e.g. Correlate with in vitro differentiation
  - e.g. Detect functional cells in complex mixture
- Develop genomic or proteomic techniques to identify functional biomarkers
- Unique biochemical markers and secreted proteins
- Flow cytometric assessment of cell phenotype for purity may link to identity and/or potency

Example: Cellular Immunotherapy Product

- **Tumor Infiltrating Lymphocytes (TIL) and DCs**
- Potential Potency Assay Matrix:
  - Viable cell number
  - Tumor specific cytotoxicity and/or cytokine release
  - Surrogate biomarker – phenotype expression, factor release – correlate with function (functional biomarker)
  - Biological activity - antigen presentation

Importance of Product Characterization

- Many cancer vaccine manufacturers are performing minimal characterization assays
  - Reason: Assay development is difficult, time-consuming, and expensive
  - Problem: Limits knowledge of your product and may hamper development in the long-term
- Solution: find a better balance
  - Determine product parameters that:
    - Demonstrate product quality and stability
    - Can be used in comparability studies
    - Affect clinical efficacy

Immune Monitoring

- Advantage of Immunological monitoring
  - Support proof of concept
  - Achieve a better understanding of immunological mechanisms
    - T cell responses (Th1/Th2/Th17)
    - Modulation of T Regulatory cells etc
  - Suggestive of activity (PSA, CA-125, etc.)
- An immune response may be identified as a correlate of clinical benefit, harm, or lack of benefit or harm

Challenges and Approaches: Immune Monitoring

- Challenges in Immune Monitoring:
  - Which Immune response to consider?
  - Where and when to measure?
- Better product knowledge critical
- Preclinical and early clinical studies may be valuable
- Consider Assay-therapeutic co-development if a specific antigen or target is required for eligibility
  - Anticipate assay development requirements
  - May need CDRH input, IDE

Immune Response Monitoring

- Monitoring of immune response may play a significant role in both early and late phase of development of a cancer vaccine
- Early trials: decision making process for further development of the cancer vaccine, selection of optimal dose and regimen
- Late trials: may correlate with clinical efficacy parameters, however....

Immune Response Monitoring

- Immune response elicitation frequently involves a multistep process to mediate effect and therefore may not be expected to provide useful surrogates for efficacy
- Multiple monitoring assays may be needed to detect and confirm the physiological response and increase the validity of the tests
- Assays should be reasonably validated at the time of the initiation of late phase trials
- Pre-specification of Assay parameters prior to initiation of late phase clinical trials: Assays conditions, positive and negative test results, statistical analysis methods for test results

FDA Guidance: Potency and immune monitoring

Draft Guidance for Industry Potency Tests for Cellular and Gene Therapy Products (released Oct. 2008):

http://www.fda.gov/cber/gdlns/testcellgene.htm

Draft Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines (released Sept. 2009)

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM182826.pdf

Summary

- Potency assays and immune monitoring data are extremely important for successful development of cancer vaccines and immunotherapy products

- Immune response data may provide potential correlate(s) to analytical assay(s) suitable for lot release assay

- A product with specific characteristics determined by analytical tests when results into specific immune response(s) in hosts may serve as a “functional biomarker”

Acknowledgement

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  - Denise Gavin
  - Peter Bross
- Potency Guidance Working Group
- Cancer Vaccines Guidance Working Group

Regulatory Information

- References for the Regulatory Process for the Office of Cellular, Tissue, and Gene Therapies (OCTGT) http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm
- OCTGT Regulatory Questions
  - Dr. Patrick Riggins (Branch Chief RPM)
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- General CBER Issues

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