Clinical Trial Design, Approval Process and Trial Conduct

Topic: Special Considerations in Gene Transfer:
Surrogate Endpoints

Michael Kalos, Ph.D.
University of Pennsylvania School of Medicine

May 18, 2010
Clinical Trials Training Course
ASGT Annual Meeting
Washington, DC
Overview of session

- Surrogate Endpoints: Definitions and applications
- Surrogate Endpoints and Biomarkers
- Biomarkers in Gene Transfer/Cell Therapy Trials
- Some insights and thoughts on the clinical development of Surrogate endpoints
**Surrogate endpoints: setting the framework**

- The overriding objective (i.e. clinical endpoint) in the development of new therapeutics is to develop agents that cure or significantly impact disease.

- The ability to measure success through evaluation of the clinical endpoints is often compromised
  - Times to progression very long
  - Direct measurements on target are inadequate
  - Particularly for early stage trials, demonstration of clear efficacy is not possible

- Surrogate endpoints are biological parameters (i.e. biomarkers), derived from the analysis of the patient/patient material, whose detection is absolutely linked with the desired clinical endpoint

- Accordingly, appropriately developed surrogate endpoints can serve as complements/surrogates to clinical endpoints
Biomarkers

- Biomarkers are defined as any biochemical feature that can measure the effects of treatment on patients or on the progress of disease.
- Biomarkers can measure:
  - Impact on disease: tumor size, circulating tumor cells, selection for antigen escape variants, tumor derived factors (PSA, CA125)
  - Delivery of therapeutic entity (DTH, inflammation, etc.)
  - Effect of treatment on patient biology
- Appropriately designed Biomarker studies:
  - Allow for early insights into Proof of Mechanism (POM) and proof of Concept (POC), and insights about Minimum Anticipated Biological Effect Level (MABEL)
  - Can critically guide subsequent trial design
  - Can lead to the identification and development of surrogate endpoints
Biomarkers Drive The Translational Research Engine

The cycle of Re-search

- Research and Development
  - Biological Effects in models
    - Correlative studies
    - Surrogate endpoints?
  - Biological effects in patients-
    - Product, systemic/disease effects
  - Patient specimens
- Clinical Trials
- Potency/identity-characterization
- cGMP Manufacturing
**Biomarkers in cell therapy/gene transfer clinical trials**

In the context of cell therapy/gene transfer trials, the definition of biomarkers can be extended to include a description of biochemical and functional features of the cell product that are i. **important for product bioactivity**, and ii. **related to the gene transfer event**

- **Persistence/homing of gene-modified infused cells**
  - Flow cytometry, Q-PCR

- **Surface phenotype/function of infused cells**
  - Flow cytometry, ELISA

- **Expression and functionality of transferred gene**
  - Flow cytometry, gene-specific functional assays
The biomarker dilemma

Our ability to define and implement appropriate biomarker discovery/evaluation studies is compromised by our lack of a comprehensive understanding of how the therapeutic agents are impacting patients.

It is important to:

- Design biomarker studies that are as broadly comprehensive as possible.
- Ensure that specimens (serum/plasma, tissue, PBMC, tumor) are appropriately processed and archived for future evaluation.
- Perform biomarker studies at a high level of quality.
Consensus report released May 12, 2010 by Institute of Medicine (Health Arm of the National Academy of Sciences)

Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease

- In this report, the IOM recommends that the FDA adopt a consistent scientific framework for biomarker evaluation in order to achieve a rigorous and transparent process. The biomarker evaluation framework should consist of three steps:
  - Analytical validation to ensure biomarker tests are reliable, reproducible, and adequately sensitive and specific
  - Qualification to ensure the biomarker is associated with the clinical outcome of concern
  - Utilization analysis to determine that the biomarker is appropriate for the proposed use
Principles of quality

• Biomarker studies guide the development of candidate therapeutics from the earliest stages of development all the way through late stage clinical studies and the establishment of surrogate endpoints.

• Accordingly, in biomarker studies, assays need to:
  – Measure what they claim to measure
  – Be quantitative and reproducible
  – Produce results that are statistically meaningful

In other words, assays need to be scientifically sound

Validated or qualified assays
**Assay Validation vs. Assay Qualification**

**Assay Qualification:** Establishes that an assay will provide meaningful data under the specific conditions used

- No pre-determined performance specifications
- No set guidelines for qualifying assay
- Used to determine method performance capabilities (such as validation parameters)

**Assay Validation:** Establishes the conditions (specifications) to assure that the assay is working appropriately every time it is run

- Specifications established *prior* to validation
- Specifications *must be met* at every run
- Method can fail validation; if it does needs to be investigated and cause assigned
Assay validation overview

1. Define assay: What will it measure and how will it be measured

2. Define how each of the validation parameters will be evaluated with statistical significance
   - Specificity
   - Accuracy
   - Precision (inter- and intra-assay)
   - Calibration/standard curve (upper and lower limits of quantification)
   - Detection limit
   - Robustness

3. Validation process
   - Pre-validation stage
     - Perform exploratory and optimization experiments
   - Establish and define assay specifications
     - Compile pre-validation report
     - Compose validation plan that includes specification and acceptance criteria
   - Perform validation studies- need to meet specification values
   - Compile validation report, complete SOP and worksheets
How do you validate biological assays?

Establish in a statistically significant manner:

- Specificity
- Accuracy
- Precision (inter- and intra-assay)
- Calibration/standard curve (upper and lower limits of quantification)
- Detection limit
- Robustness

- Biological assays very difficult to validate due to inherent variability
  - Stochastic events
  - Temporal differences in samples intra-patient
  - Genetic variability inter-patient

- Absolutely need expert statistical support
- Require rigorous SOP and excellent technical skills
Summary/Conclusions

• Biomarkers drive the translational and clinical research paradigm