

# ***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***

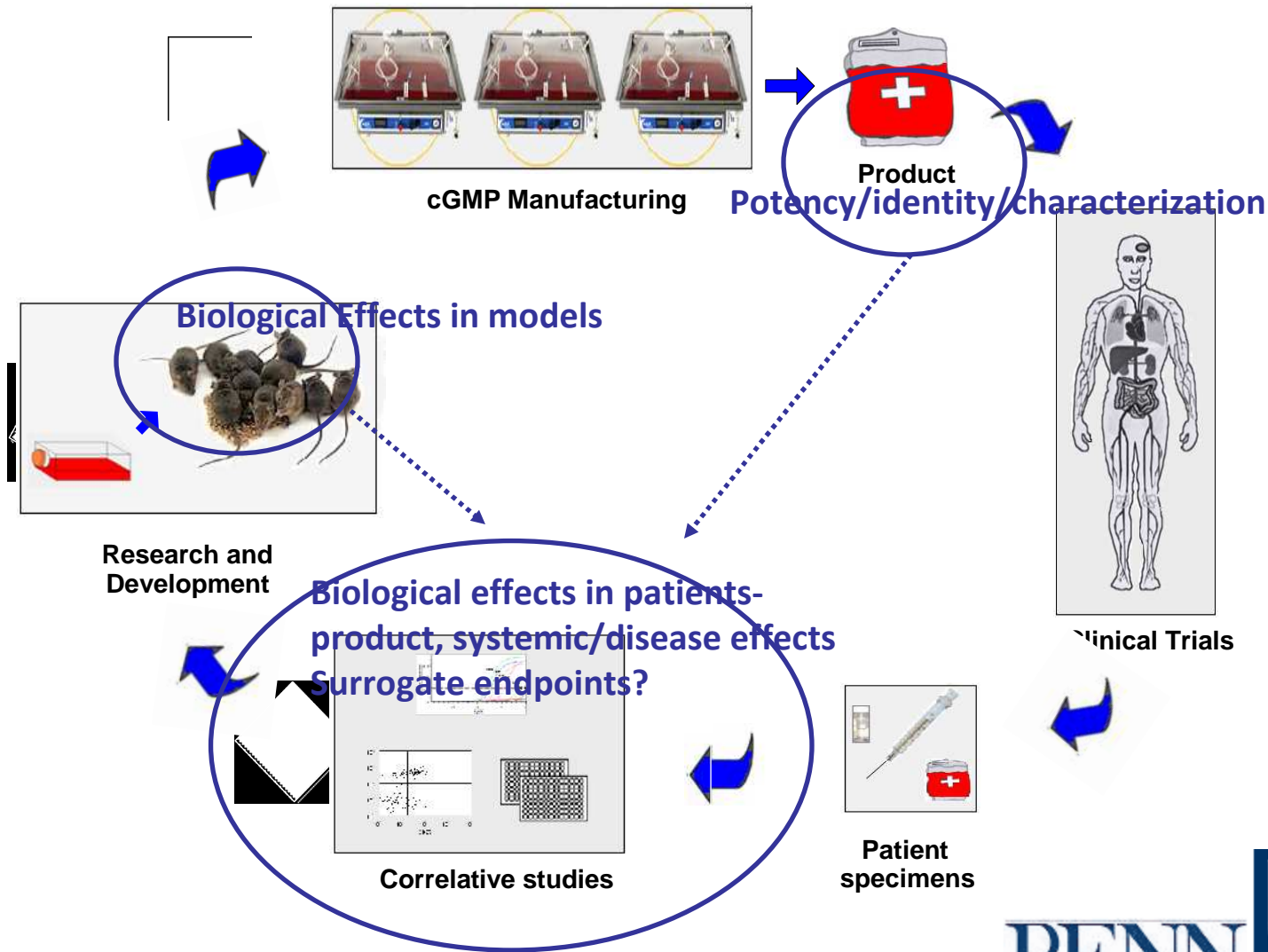
- The overriding objective (i.e. clinical endpoint) in the development of new therapeutics is to develop agents that cure or significantly impact disease.
- The ability to measure success through evaluation of the clinical endpoints is often compromised
  - Times to progression very long
  - Direct measurements 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



## ***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 re-search paradigm