Biomarkers in Development of Cell Therapies

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May 24, 2010
Products Regulated by OCTGT/CBER/FDA

I) CELLULAR THERAPIES
• Somatic cell therapy (CT)
  – Progenitor cells (Adult-, fetal-, embryonic-derived stem cells)
  – Peripheral- & cord blood-derived progenitor cells
  – Differentiated cells (islet cells, cartilage cells, etc.)
• Xenotransplantation
• Tissue engineering/combination products

II) OTHER THERAPIES
• Gene therapy (GT)
  – Replication-deficient viral vectors (retrovirus, adenovirus, AAV, vaccinia/fowlpox, HSV, lentivirus, viral particles; bacterial vectors, etc.)
  – Replication-competent viral vectors
  – Plasmid DNA vectors
• Viral therapy (VT)
  – Oncolytic viruses
• Immunotherapy (IT)
  – Tumor vaccines
  – Other therapeutic vaccines
Potential For Cell Therapies:

- Repair
- Replace
- Restore
- Regenerate

S Bauer (CBER/OCTGT)
Development of Biotherapeutic Agents

• FDA Regulatory & Scientific Input
• ICH documents
• FDA guidances/21 CFR

IND Submission

• Basic Research
• POC Studies
• Toxicology/Safety

Pre- and even pre-pre-IND discussions with FDA/CBER; OCTGT has an active Pre-IND program.

Clinical Trials

Biologics License Application

Product License Granted

Phase 4

Biomarkers can be highly informative at any stage of development
What is a biomarker?

• “A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”¹

• The Pharmacogenomics Guidance defines a valid biomarker as “a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.”²

• This validity is closely linked to context----how it is used, what we think we can do with it. The process of qualification of biomarkers at FDA is discussed in detail by Goodsaid and Frueh. ³

• Examples of valid markers: US FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

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¹ Biomarkers Definitions Working Group Clin Pharm Ther 69:89-95, 2001
Biomarker definitions and examples

For the purpose of the present discussion of cellular products, a biomarker can be considered as an objectively and reliably measured entity that might be used in order to:

- promote the acquisition of safety and efficacy data during product development, especially during early-phase trials
- help reduce risks and increase efficacy both pre- and post-marketing
- help in long-term safety monitoring post-marketing
What can a biomarker be used for?

- Biomarkers can yield a wealth of useful information in relatively short time---in many instances, well before data from surrogates or clinical outcomes can become available. Among the many potential uses of biomarkers in development of cell therapies:

  - rapid way to determine pharmacodynamic action of a drug or other product *in vivo* or *in vitro*
  - to characterize complex products, such as cells
  - to help elucidate mechanism of action of a drug or biologic
  - to facilitate dose selection during early-phase clinical trials
  - to serve as a means of tracking of cells following administration into experimental animal models or humans
  - to determine or predict a safety signal in a target population
  - to enrich trial population to select for patients likeliest to respond to the therapy or least likely to experience an AE related to the therapy
  - to aid in phase 4 studies in larger populations than enrolled during phase 1-3
Well-established example of successful use of biomarkers in development of osteoporosis drugs

- Serum and urinary biochemical markers of bone resorption (e.g., NTx, CTx) and formation (osteocalcin, BSAP, P1CP) can be used to demonstrate PD activity of a drug.

- Both resorption and formation rates are elevated following estrogen withdrawal (menopause).

- An anti-resorptive drug (e.g., a bisphosphonate) lowers both, and they move in the same direction because they are physiologically linked.

- An anabolic bone agent (e.g. teriparatide) can *elevate* both formation and resorption rates.

- Net effect on bone mineral content depends on formation-resorption balance, independent of whether both rise or both fall. Depending on the drug, a positive balance can occur, independent of directionality, leading to an increase in BMD, which may result in decreased fracture rate.

- **CONTEXT IS IMPORTANT**
Use of bone turnover markers in osteoporosis drug development

- These serum and urine biomarkers can be used for fairly rapid determination of drug PD, but are not surrogates for clinical outcomes. Used frequently to aid in dose determination in phase 2. **Time frame 1-3 months. Relatively small number of patients (50-150).**

- Bone mineral density scans determine whether there is net increase or decrease in BMD. **Time frame about 6-12 months; usually involving a few hundred patients.** BMD change is not always a reliable surrogate for fracture reduction—depends on disease. **CONTEXT IS IMPORTANT.**

- Fracture risk reduction: This is the key clinical outcome for phase 3 pivotal trials. **Time frame 2-3 years. May require a few thousand subjects.**
What a biomarker is not

• A biomarker is not a clinical outcome.

• A biomarker is not a surrogate for a clinical outcome unless it has demonstrated its ability “to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence.”

• A biomarker is not valid until it passes defined examination and is generally accepted. Qualification depends on establishment of performance, linkage to physiological/toxicological/etc. event, and also depends on context.

• A biomarker is not designed only to speed product development. Biomarkers should be able to improve safety/efficacy profiles at every stage in development.

1 op cit Clin Pharm Ther 2001
One clinical trial design to validate a biomarker

Example: the Marker Validation for Erlotinib in Lung Cancer (MARVEL) trial (NCI).

All subjects tested for tumor biomarker (+ or -)

Marker + or Control

Marker - or Control

in this case, biomarker = EGFR
tx= erlotinib
control = pemetrexed, which works by a different mech.
How might biomarkers help in development of cell therapy products? Some examples of particular interest and importance:

• **Product characterization**: Individual cells are extremely complex, and cellular products are heterogeneous. Biomarkers may help in determination of safety and efficacy parameters of cells (gene expression, proteomics, metabolomics, specific immunological markers, etc.) (Qualification if used for these purposes --- e.g., to make safety determinations---is a review issue.)

• **Determination of pharmacodynamic action** of the cellular product during both preclinical development and clinical trials. Especially helpful if determination of clinical outcomes requires long observation periods and mode of administration is complex.
Biomarkers in cellular product development (cont.)

- Non-invasive means of tracking of cells after administration, especially during clinical trials.

- Where do cells go? How well do they function? How long do they survive?
  - Important issue for numerous cell products: islets, cells for cardiac repair, cells for CNS diseases, etc.
  - Development of imaging modalities for tracking of cellular products is one area of active investigation. $^{18}$F (PET), $^{111}$In (γ), Fe nanoparticles (MRI), other modalities under investigation.
Current examples: one easy problem and two not-so-easy problems in need of biomarker solutions

**Allogeneic islet transplantation in T1D:** What are early indicators of cell survival and function? Of PD action?

Solution: There are multiple well-characterized and objectively-measured analytes in blood. C-peptide levels (fasting and after challenge), which are extremely low at baseline in T1D patients, are secreted by the transplanted islets and reflect functional mass of the graft.

Fasting and post-prandial blood glucose levels, HbA1c, reduced insulin requirements are also used to measure PD action of islet product.

Rapid disappearance of severe hypoglycemia denotes an early and important direct clinical benefit.
not-so-easy problems: islets and cartilage

- Allogeneic islet transplantation: What explains the extreme range of success and failure? A few patients fail following 1-3 transplants within a year. Most recipients have substantial islet function and clinical benefit for 2-3 years. Some are completely or nearly insulin-independent for >5 years after the last transplant, even after a single transplant.

  - What genomic and biochemical properties of islets (and recipients) predict success or failure?

  - Problem is of utmost importance, especially given short supply of islets.
Autologous cartilage implantation: How can we predict clinical efficacy from product characterization when clinical efficacy is defined as pain/function superiority in a 2-3-year clinical trial and product characterization is expressed in biochemical/genomic terms?

- Link biochemical/genomic markers to animal models and then to clinical outcomes?

- Addressing these problems requires further basic science research plus lots of outcomes data from long clinical trials.

- Establishment of sufficiently large databases may require pre-competitive collaboration.
Role of FDA in accelerating development of biomarkers

- Development of biomarkers is an important part of Critical Path Initiative
- FDA is taking a pro-active role: Intensive research (laboratory, clinical, epidemiological) occurs in all FDA centers (CDER, CBER, CDRH, CFSAN, CVM, NCTR)
- Our office (OCTGT/CBER) is involved in several initiatives:
  - CBER Genomics and Proteomics Review Group (CGPRG)
  - Biomarkers consortium and other external agencies
    - e.g., recent workshops on islet imaging and development of biomarkers for β-cell mass and function
- Internal working groups (cell therapies, gene therapies, cartilage) host seminars and sponsor other activities aimed at development of biomarkers
CBER Genomics and Proteomics Review Group: Ongoing Activities

- **Collaboration within the FDA:**
  - Main mission: integrating –omics technologies into regulatory review
  - Inter Center Consultation on policy development and review of regulatory files
  - Interdisciplinary Pharmacogenomics Review Group
  - Guidance document development
  - Inter Center and Inter Agency Research Collaborations

Courtesy Dr. Raj Puri
Complex, novel medicines require complex, novel approaches for FDA evaluation

- Use of Genomics technology leading to:
  - Better characterization of cell and gene therapy and tissue engineered products
  - More consistent manufacturing processes e.g., comparability of cell substrates
  - Rapid and thorough evaluation of adventitious agents
  - Genetic stability of vaccines
  - Better assessment of safety and efficacy

Courtesy Dr. Raj Puri
Goal: To identify specific gene and protein signals (biomarkers) from medical products and link the signals to product quality (identity, purity and potency), yield of final product, and patient outcomes.
Identifying Biomarkers and Their Correlation with Safety and Efficacy in Preclinical Animal Models

Mesenchymal Stem Cell Characterization

Biomarkers

Goal:
Correlate candidate biomarkers with \textit{in vivo} outcomes

\textit{In vivo} Model of Critical Hind Limb Ischemia

Principal Investigators: Michael Alterman, Steve Bauer, Deb Hursh, Brent McCright, Malcolm Moos, Raj Puri
Several members of CBER/OCTGT participate in collaborative research activities conducted by the Biomarkers Consortium
Example: Adiponectin Project. Goal: to explore the utility of adiponectin as a predictive biomarker of glycemic control in T2D patients treated with PPAR agonists.

Blinded data from pre-existing clinical trials pooled (~2000 pts)

Analysis
NIDDK
Results
Review
Biomarkers
Consortium
Project Team

Analysis
Quintiles

GSK
Lilly
Merck
Roche

Publications: ADA (June 2009); Clinical Pharmacology and Therapeutics, June 2009, May 2010

Statistical analysis of pooled, blinded data demonstrated relationship between adiponectin and glucose reduction in response to PPAR agonists.
Refs. for adiponectin project conducted by members of the Metabolic Disorders Steering Committee of the Biomarkers Consortium

• Report of the study itself:

• Description of lessons learned in conducting this type of study:
Conclusions

• The development of valid biomarkers will certainly accelerate development of FDA-regulated products and enhance safety monitoring as well.

• Biomarker development is a high-priority enterprise within FDA and among FDA and multiple stakeholders.

• For cell products, the development of biomarkers offers special opportunities and challenges.

• Linkage of biomarkers to pharm/tox and clinical outcomes may require analyses of multiple, large databases.

• Engagement in pre-competitive data sharing and analysis has been shown to be feasible and should be considered.

• In design of specific protocols, sponsors/investigators are encouraged to discuss use of biomarkers with the FDA review division.
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