Therapeutic Cancer Vaccines

- Goal for all therapeutic cancer vaccines:
  - To enhance the natural immune response so that it becomes an effective therapy
- Approaches being investigated in clinical studies:
  - Whole tumor cells
  - Tumor cell lysates
  - Proteins
  - Peptides
  - DNA

Potency Assays for Cell-based Therapeutic Cancer Vaccines

- Challenges
  - Develop a potency assay before the results of Phase 3 are known
  - Antigenic correlates of efficacy are tentative before Phase 3 results are known, and the correlates may not be known even after Phase 3
- A framework for measuring potency during clinical development can be based on experience with other biological products, especially infectious disease vaccines

Definitions of Potency

- ICH
  "the measure of **biological activity**, using a suitably **quantitative** biological assay, based on the attribute of the product that is **linked to the relevant biological properties**."
- WHO
  - Adopted ICH in November 2003
  - WHO Comment: "Potency tests measure **biological activity** of a vaccine, but do **not necessarily reflect the mechanism of protection** in human."

Potency Assays

- Purposes of a potency assay
  - Ensure that a given batch has at least a pre-defined minimum level of potential biological activity that will give an expected result (e.g. an antibody response)
  - Demonstrate batch-to-batch consistency by a method that in some way depends on and reflects biological activity.
- Measurement of potential biological activity is usually direct, but it may be indirect
- *Ideally*, the measured biological activity correlates with efficacy

Potency Assays for Infectious Disease Vaccines

- Ideally, a potency assay applies to all products in a given class:
  - Diphtheria toxoids
  - Live poliovirus vaccines
- 1 or more Ags are required for biological activity by inducing a clinically beneficial immune response (Ab, CMI, or both)
- If IR correlates with efficacy, then
  - *In vitro* tests can be use to measure antigen content
  - *In vivo* tests have been used to measure
    - Ab production
    - Protection against challenge

Potency Assays for Live Vaccines Against Infectious Diseases

- Potency usually is based on titration of the infective dose in cell cultures and usually includes a reference preparation linked to a WHO International Standard
- The amount of infectious units required is based on the results of clinical trials where dose and IR is correlated with efficacy
- Minimum level of infectious units is established
- Upper limit may be indicated in some cases
- Acceptability range is broad: +/- 0.5 $\log_{10}$

Potency Assays for Killed Vaccines Against Infectious Diseases

- Potency usually is based on the quantitative measure of the content of 1 or more selected Ags
  - D antigen for inactivated poliovirus vaccines
  - HA for inactivated influenza vaccines
- Acceptability range is broad: +/- 0.5 $\log_{10}$
- Direct link between IR and efficacy is not always possible
  - Whole cell pertusis
  - Anthrax

Potency Assays for Non-Vaccine Therapeutic Biological Products

- **Carticel**
  autologous cultured chondrocytes approved for the repair of damaged cartilage
  - Cell viability >80%
  - Potency: number of live cells
- **Interferon-alpha**
  approved to treat Stage III melanoma and other cancers
  - Potency: antiviral activity (not directly related to therapeutic activity)
    - Demonstrates biological activity
    - Can be used to assess manufacturing consistency

Criteria for an Acceptable Potency Assay for Cell-based Therapeutic Cancer Vaccines

- Assumption:
  The induction of a protective IR is the most probable mechanism to account for efficacy.
- Results of any potency assay must answer 2 questions
  - Is the amount of one or more selected Ags sufficient to induce a clinically meaningful IR?
    - Based on clinical studies, this confirms that enough Ag is present to result in a therapeutic IR
  - Is the amount of one or more selected Ags in the vaccine consistent from batch-to-batch?
    - Target level +/- 0.5 $\log_{10}$
    - Also select other Ags, if necessary, for which the amount of Ag expression is sensitive to manufacturing conditions – even if those Ags are unrelated to efficacy

Potency Assay Considerations for Cell-based Therapeutic Cancer Vaccines

- Quantitative measurement of 1 or more cellular Ags (surface or internal)
  - Must be related to biological activity or effect
  - Ab formation in humans provides a link to biological effect
- Is a bioassay also necessary?
  - During clinical development, direct correlates of clinical protection have not yet been established

Possible Outcomes of Efficacy in Phase 3 Studies of Cell-based Therapeutic Cancer Vaccines

1. IR to 1 or more selected Ags correlates with efficacy
   - Ideal situation
   - Potency can be based on one or more of the Ags
2. IR to 1 or more selected Ags is demonstrated, but there is no correlation with efficacy
   - IR is complex and may involve both the cellular & humoral arms to an unknown combination of Ags
3. IR to selected Ags is poor, but clinical efficacy is established
   - Quantitative Ag expression is probably unacceptable
   - A bioassay provides an alternative measure of potency, and should be developed in parallel as a backup

An Acceptable Potency Assay for Cell-based Therapeutic Cancer Vaccines

- Number of viable cells that express selected Ags that correlate with efficacy
- Quantitative measure of expression of the selected Ags
- Consistent with:
  - ICH & WHO definitions of potency
  - Approach used for infectious disease vaccines and an analogous product (Carticel)

An Acceptable Potency Assay for Cell-based Therapeutic Cancer Vaccines When There Is No Correlation With Efficacy

- Viable cell count
- Bioassay

Possible Bioassays for Cell-based Therapeutic Cancer Vaccines

- Animal challenge (*in vivo* protection)
  - No current model exists
  - Validation issues
  - May not reflect the human IR
- Animal Ab production to selected Ags
  - May not reflect the human IR
    - Reaction to different epitopes on an Ag
    - Transgenic animals may be useful

Possible Bioassays for Cell-based Therapeutic Cancer Vaccines

- Vaccine cell lysis by human CTLs cell lines to selected Ags
  - Availability of the CTL lines
  - Standardization of assay
  - Validation of the assay
  - Clones are reactive to only a single epitope
- Production of a cytokine marker in a mixed-lymphocyte culture
  - T-cell response to multiple Ags
  - Cells obtained from humans or animals who received the vaccine
  - Cytokine release measured after co-culture

Final Selection of a Potency Assay for Cell-based Therapeutic Cancer Vaccines When a Correlation With Efficacy Is Established

- Routine lot release
  - Viable cell count
  - Quantitative Ag expression
- Comparability (manufacturing changes)
  - Viable cell count
  - Quantitative Ag expression
  - Bioassay