

FDA Perspective on the Preclinical Development of Cancer Vaccines

Richard D. McFarland Ph.D., M.D.
Medical Officer

CBER/OCTGT/DCEPT
mcfarlandr@cber.fda.gov

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Safety is Always Primary

FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.

IND Regulations [21 CFR 312.22 (a)]

Safety of a Biological Product is Relative

“The relative freedom from harmful effects of the recipient when a product is prudently administered, taking into consideration the characteristics of the product in the relationship to the condition of the recipient at the time; thus the property of safety is relative.”

21 CFR, Subchapter F

FDA Review is Product-based

- Parallels prudent product development
- Dependent on characteristics of specific product
- Preclinical studies designed to support use of specific products
- Clinical trial design supported by manufacturing, preclinical data
- Supported by science, framed by regulations

Classes of Tumor Vaccines Currently in Development

- Conventional Antigen-based vaccines (Ag)
 - Purified Ag
 - Synthetic peptides
 - Conjugated Ag
 - Tumor cell lysates
- Cell-based vaccines
 - Manipulated tumor cells
 - Activated peripheral blood or BM-derived lymphocytes
 - DCs or other APCs [modified (*i.e.* cell fusion)]
 - Gene-modified tumor cells
 - Cells engineered to express cytokines, growth factors, or tumor Ags

Classes of Tumor Vaccines Currently in Development

- Gene Therapy-based vaccines
 - Plasmid
 - Human tropic viruses (adenovirus)
 - Retroviral based vaccine vectors
 - Non-human tropic based vaccine vectors (fowlpox)
 - Bacterial based vectors (*Listeria sp.*)

Potential Modifying Factors

- Adjuvants
- Immunomodulation
- Concomitant Conventional Chemotherapy
- Formulation (liposomes)
- Route of Administration
 - Site
 - Delivery Device

Phase 1 Preclinical Expectations

- Scientific basis for conducting clinical trial
 - Feasibility/establishment of rationale
 - Establish pharmacologically effective dose(s)
 - Optimize ROA/dosing regimen
 - Rationale for species/model selection for further tests
- Recommend initial safe dose & dose escalation scheme in humans
 - Identification of potential target tissue(s) of toxicity/activity
 - Identification of parameters to monitor clinically
 - Identification of patient eligibility criteria

Phase 1 Preclinical Expectations

Proof of concept and sufficient toxicity data

- Final product (Vaccine and adjuvant, etc)
- Each component separately
 - Vaccine
 - Adjuvant or immunomodulating agent
 - Liposome components
 - Concomitant conventional chemotherapies

Potential Sources of Data to Support Initiation of Clinical Trials

- Preclinical studies specifically designed to support a clinical trial
- Other potential sources
 - Existing animal studies designed to answer other questions
 - *In vitro* studies
 - Clinical trials using the “same” product

Using Published Animal or Human Studies as Sole Support for Initiation of Clinical Trials

- Often they were **not designed to answer a toxicologic** question, and therefore, adequate toxicology endpoints may not have been incorporated into the design
- Published reports **must provide sufficient information for independent review**

Flexible Animal Study Designs

- Proof of concept “activity” studies in animal model(s) of disease
- Toxicology/biodistribution studies in healthy animals (traditional approach)
- Hybrid pharmacology-toxicology study design in animal model(s) of disease
 - Activity endpoints
 - Tissue localization
 - Toxicology endpoints

Proof of Concept (Activity) Models

- From FDA's perspective, the specific choice of the activity model(s) is less important than the underlying rationale for therapy in humans supporting the choice.
- This generally involves understanding the therapy's putative mechanism of action and demonstrating "proof-of-efficacy" in an appropriate preclinical model.

Examples of Proof-of-Concept Models

- Tumor cell survival (cell lines and clonogenic assays)
- Human tumor xenograft murine models
- Metastasis models
- Transgenic and knockout murine models
- Carcinogen-induced tumor models
- Transplantable syngeneic rodent tumors

Bioactivity Endpoints of Potential Relevance to Tumor Vaccine Development

- MHC-peptide tetramer assays (Ag-specific T subsets)
- ELISPOT to assess T cell subset #'s, cytokine profiles (γ IFN production)
- Antibody titers (humoral response)
- Quantitative RT-PCR assays
- TCR dysfunction (α -CD3 stimulation of T cells, TCR ζ chain expression)
- Limiting dilution assays (Ag-specific CD8, ^{51}Cr release, thymidine incorporation)
- Cytokine flow cytometry

Bioactivity Endpoints

- FDA cannot comment as to which immunoassays represent the best measures of 'immune function' or correlation with survival; as these data are not yet available.
- The decision to choose one immune response parameter over another as the appropriate surrogate endpoint has more to do with the scientific question(s) being asked than correlation with a relevant clinical endpoint in a given malignancy.

Preclinical Toxicology Assessment

- For tumor vaccines often traditional animal models for toxicity evaluation often yield limited information, especially where human-specific Ags are being targeted.
- No one animal model can address all concerns or fulfill all necessary criteria to mimic humans.
- In such situations (e.g. autologous DC vaccines, human HLA-specific therapies), information about the antigen, construct, etc. involved and its tissue distribution and expression in humans is very important (e.g. mRNA expression, tissue crossreactivity studies where mAb against the Ag have been tested, genomic database searches).

Tissue Cross-Reactivity Studies

- Should be performed prior to human exposure for novel antigens with potential for expression in normal tissues.
- Tissue binding should be determined using appropriate immunohistochemical procedures.
- A range of human tissues should be tested.
- Analogous study in primary pre-clinical toxicity species may help substantiate species relevance of the animal model.

Choice of Animal Species for Toxicity Testing Should be Based on Expression and Homology of the Targeted Antigen

- Animal models expressing the targeted Ag or epitope of interest, when available, are more likely to reveal the effects of Ag “sinks” or tissues with unexpected Ag expression on biodistribution tissue localization and/or toxicity.
- Critically important for assessing risk of autoimmunity.
 - (+) signals in *in vitro* testing: incorporate relevant safety monitoring into preclinical, clinical studies.
 - (labs: ANA, RF, CH50, physical exam monitoring: cytopenias, arthalgias, rash).

Animal Models: GT Vector-based Vaccines

- May need to evaluate tissue biodistribution and persistence; especially in germ-line tissues.
 - When aberrant or unexpected localization is observed, studies should be conducted to determine whether the gene is expressed, and whether its presence is associated with pathologic changes.
- May need assessment of replication competent virus
- Potential for an overly robust inflammatory response to viral, bacterial vectors (e.g. adenovirus).
- Evaluation for adventitious viruses.
- May require long-term animal studies.

Transgenic Animal Models: Pros and Cons

Pros:

- May express the human protein of interest and/or may express the appropriate human HLA molecule (e.g. HLA-A2.1) necessary for immune responsiveness.
- With 'conditional transgenics' can activate a gene in a cell-specific manner.
- Easier to handle than non-human primates

Transgenic Animal Models: Pros and Cons

Cons:

- Transgenics appear to respond to most, but not **all** human HLA-restricted epitopes to which humans respond.
- Genetic drift and non-uniformity can be a problem.
- Significant inter-experiment variability in response magnitude has been described.

Animal Models: Which Are Best ?

Depends on the question asked:

- For solid tumor malignancies: solid tumor xenograft models may mimic human disease more than tumor cell lines administered to animals.
- Animal model may not express the relevant human receptor or protein, hence might need to rely on a transgenic model or evaluate the effect of therapy on the animal homologue of the human protein.

Role of Genomics, Proteomics in Tumor Vaccine Development: The Pros

- Believed useful in drug discovery/identification of targets, understanding disease pathways and a new therapy's mechanism of action.
- In principle, can monitor complete biochemical pathways rather than single biomarkers.
- Identification of “bridging biomarkers” to monitor key damage responses in lab animal models and humans.
- Identification of polymorphisms that may modify sensitivity to disease or treatments.
- Potential to reduce animal use in vaccine development (3Rs)

Role of Genomics, Proteomics in Tumor Vaccine Development: Cons

- Non-quantitative and of unknown predictive value.
- Need to establish the relationship of chosen microarray endpoints with accepted preclinical and/or clinical endpoints and will need to validate these.
- In order to be clinically useful, patterns of correlation will need to exist, that are reproducible (heretofore a problem with array platforms).

Early Communication (“pre-pre-IND”)

- Non-binding, informal scientific discussion between FDA and sponsor
 - Via telecons
 - Via scientific meetings/workshops
 - Via outreach presentations (*i.e.*, this meeting)
- Provide pre-read materials to FDA
- Discuss specific issue (s) of interest
- A two-way communication to allow for information exchange

Pre-IND Meeting

- Submit a pre-IND package to include:
- Product development/characterization
 - Chemistry, Manufacturing and Controls (CMC)
- Summary of device information
 - Bench and/or *in vivo*
- Summary of preclinical information
 - Pharmacology/Toxicology - *in vitro* and/or *in vivo*
- Proposed clinical protocol



Concluding Remarks



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- The animal model and extent of primary data required for any particular product should be science-based, but framed by regulatory requirements to protect the safety of human subjects in all phases of clinical investigations.
- The decision to allow a therapy to go forward into a phase 1 trial involves a risk:benefit assessment of safety concerns vs. the likely clinical response based on supportive preclinical & clinical data (similar products).

Contact Information

- Richard McFarland Ph.D., M.D.
- E-mail- mcfarlandr@cber.fda.gov
- Voice- 01-301-827-5102
- Fax- 01-301-827-9796

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike, Woodmont I, HFM-760
Rockville, Maryland 20852 USA