Cell and Gene Therapy Products for Cancer Treatment

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International Society for Biological Therapy of Cancer (iSBTc)
Oncology Biologics Development Primer

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Safety is Always Primary

- FDA Regulatory & Scientific Input
- ICH documents
- FDA guidance/ PTCs/ 21 CFR

IND Submission For Early Phase Clinical Trial

- Basic Research
- POC Studies
- Biodistribution
- Toxicology

Clinical Trials

Biologics License Application (BLA)

Pre-prel ND interaction with FDA
Prel ND discussion with FDA

Product License Granted

Discovery Phase / Safety Assessment
CBER/OCTGT-Regulated Products for Cancer Treatment

- Gene therapy (GT) products
  - Many types of replication deficient viral vectors
  - Plasmid DNA vectors
  - Various types of transgenes delivered by those vectors
OCTGT Products (cont’d)

- Viral therapy (VT) products
  - Oncolytic viruses (OVs) - replication competent or attenuated viruses, e.g. adenoviruses, vaccinia, herpes simplex viruses, Newcastle disease virus (NDV)....
  - OVs can be either naturally occurring or genetically modified viruses, to achieve tumor-specific targeting and ‘bystander’ tumor cell killing, etc.

- OV expressing transgene
  - properties of GT and VT are considered
OCTGT Products (cont’d)

- Immunotherapy (IT) products:
  - Tumor vaccines
    - Gene-based non-viral and viral vectors expressing immunogenic molecules (e.g. TAA, TCR ligands, co-stimulatory factors)
    - Ex vivo modified immunologic cells, e.g. APCs, T & B cells, inactivated tumor cells, ….

- Cellular products
  - NK cells, TIL, ….
  - Peripheral- & cord blood- derived progenitor cells, e.g. cells w/ CD34+, CD8+, ALDH^br, ….
Potential Safety Concerns for GT & VT Products

- Phenotype/activation state of target cell(s)
- Type of vector/virus, mode of introduction
- Vector/virus biodistribution to non-target cells
- Level of viral replication and persistence in non-target tissues
- Inappropriate immune activation
- Potential for insertional mutagenesis and/or oncogenicity
- Transgene related concerns
Potential Safety Concerns for IT Products

- Immunogenicity to xenogeneic/allogeneic cells
- Uncontrolled cell proliferation or tumorigenicity
- Host response (physiologic, anatomic, etc.)
- For gene-based tumor vaccines, similar concern as for GT products
Preclinical Expectations for Early Phase Clinical Trials

- Scientific basis for conducting clinical trial
  - Feasibility/establishment of rationale
  - “Proof-of-concept” [POC]
  - Establish pharmacologically effective dose(s)
  - Optimize ROA/dosing regimen
  - Provide rationale for species/model selection for further tests
Preclinical Expectations (cont’d)

- Recommend initial safe dose & dose escalation scheme in humans
  - Potential target tissue(s) of toxicity/activity
  - Parameters to monitor clinically
  - Eligible patient population
Preclinical Evaluation – GT, VT & IT Agents vs. ‘Traditional’ Biologics

- Similar general requirements for safety
  - Pharmacologic profiles
  - Proof-of-concept
  - Dose-response relationship
  - Toxicology profile
Preclinical Evaluation – GT, IT and VT Agents

BUT… the approach by which safety data are obtained will differ:

GT, VT, IT (gene-based) ….. IT, Cell Products

- Biodistribution of vector/virus
- Kinetics of gene expression
- Immunogenicity to allogeneic cells
- Uncontrolled cell proliferation following ex vivo modifications
Pharm/Tox Studies

- Pharmacology/POC studies
  - Relevance of animal species/models
  - Dose levels/regimen at which the desired biological activity can be observed via the proposed ROA
- Toxicology (T) studies in a biologically relevant species of healthy and/or tumor-bearing model
- Hybrid pharmacology-toxicology study design
  - POC + T – Obtain toxicology endpoints in a tumor-bearing model
Selection of biologically relevant animal species/model

- The use of NHPs is not required
- The use of multiple species (e.g. a rodent and a non-rodent) is not required
- But scientific justification must be provided for the selection of the animal species/model
- When to consider the use of species-specific agents, e.g. autologous cells, homologous transgenes?
Toxicology Study Design

- Appropriate controls
- Mimic clinical scenario as closely as possible, e.g. product, formulation, ROA, dosing regimen
- Reasonable group size to provide adequate interpretation of the data
- Sufficient duration to allow for appearance of any toxicities... and the potential for resolution of toxicities
- Selection of multiple dose levels, determination of No-Observed-Adverse-Effect-Level (NOAEL)
Toxicology Study Design (cont’d)

Standard Toxicology Endpoints

- Mortality
- Clinical observations, body weights, etc.
- Hematology and coagulation
- Serum chemistry
- Gross pathology
  - Scheduled and unscheduled deaths
- Microscopic pathology
  - Scheduled and unscheduled deaths
  - Examine both target and non-target tissues
- Specific immunohistochemistry staining
The objective is to recommend a starting clinical dose level and dose escalation scheme that are safe and biologically plausible.

Dose extrapolation between animals and humans based on:
- POC data – minimally active dose level
- Safety data from animal studies (e.g. toxicology, vector BD) - NOAEL

Calculation of clinical dose levels based on
- Fixed dose level (e.g., absolute dose)
- Body weight
- Organ mass (volume/weight)
Vector/Virus Biodistribution (BD) Studies for GT & VT Products

- Use the same species as for the toxicology study
- Use the maximum dose administered in the toxicology study
- Use the same ROA as for the toxicology study
- Biodistribution profile in both target and non-target tissues, including the blood
- Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events

[www.fda.gov/cber/gdlns/gtclin.pdf](www.fda.gov/cber/gdlns/gtclin.pdf)
BD Studies
- Specific Considerations

- Novel GT & VT products: the BD data need to be completed prior to initiation of clinical trials to assess kinetic profile & persistence of vector/virus

- GT vectors similar to those previously used in humans:
  - Safety database in humans with a similar ROA
  - BD data in animals by cross-reference to other INDs
  - Conduct of BD study in parallel with early phase clinical trials

- BD data using the clinical material are needed for license application
Sources of Toxicology/BD Data

Toxicology data in support of a clinical trial can come from:

- GLP-compliant toxicology studies
- Well-controlled studies conducted in-house
- Published data in peer-reviewed journals
- Cross-reference to similar products in previously submitted MF/INDs
Early Communication

**Pre-pre-IND interactions**
- Non-binding, informal scientific discussions between Pharm/Tox in OCTGT/CBER and sponsor

**Pre-IND meetings**
- Submit a pre-IND package to include:
  - Product development/characterization – Chemistry, Manufacturing and Controls (CMC)
  - Summary of preclinical information – Pharmacology, *in vitro* and/or *in vivo*; Toxicology study protocol/plan
  - Proposed clinical protocol outline
- Schedule a pre-IND teleconference
Pharmacology/Toxicology Staff
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Selected Guidance Documents

- Reference for the Regulatory Process for the Office of Cellular, Tissue and Gene Therapies (OCTGT)
  www.fda.gov/cber/genadmin/octgtprocess.htm
- Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological products
  www.fda.gov/cder/guidance/1397fnl.pdf
  www.fda.gov/cber/gdlns/somgene.pdf
- The ICH S6 document: Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals
  www.fda.gov/cder/guidance/1859fnl.pdf
- Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events
  www.fda.gov/cber/gdlns/gtclin.pdf