Cell and Gene Therapy Products for Cancer Treatment

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Oncology Biologics Development Primer

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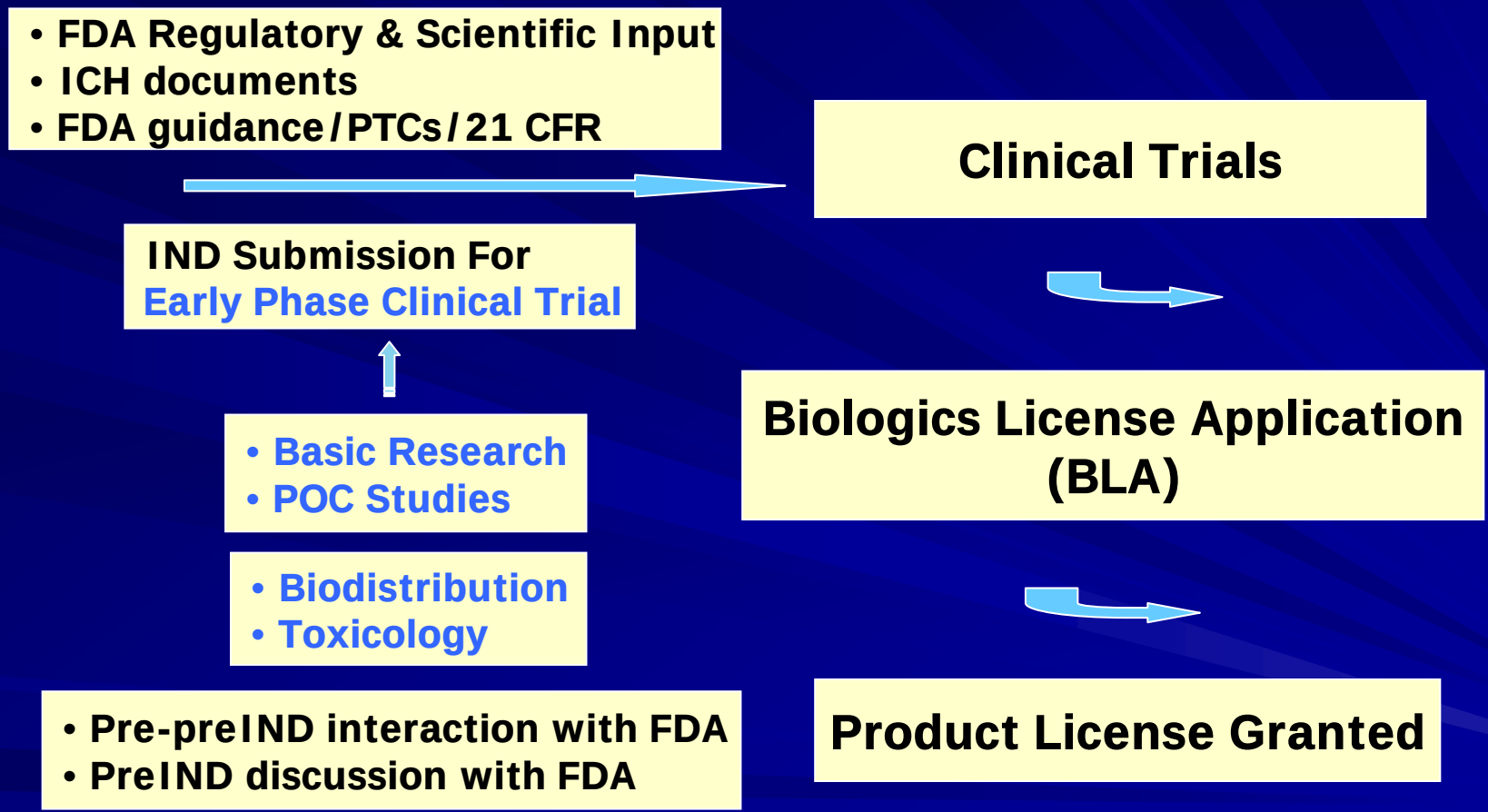
Safety is Always Primary



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

Dose Extrapolation

- 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

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

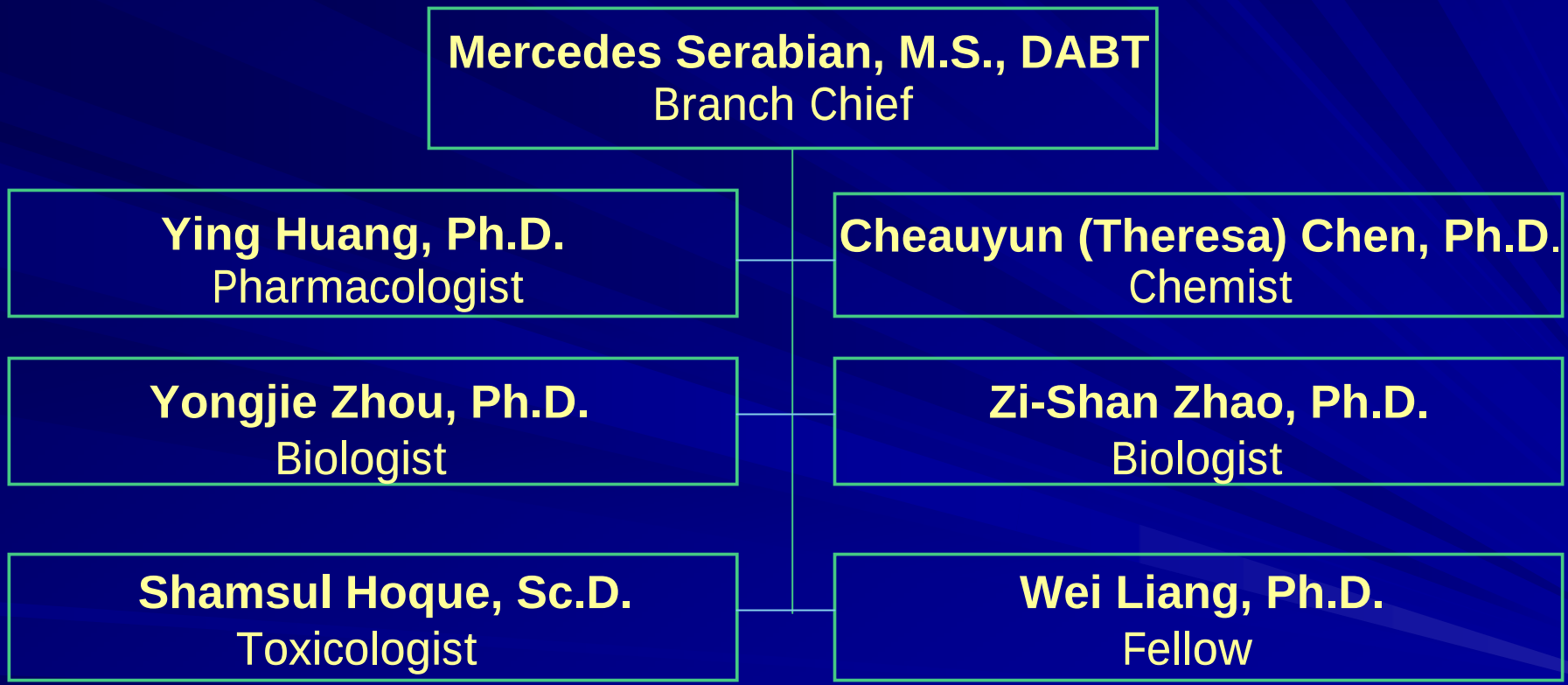
Sources of Toxicology/BD Data

- 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 DCEPT/OCTGT



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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
- Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (1998) 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