Preclinical Development [CDER]: Biological Therapeutics for Cancer Treatment

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iSBTc Oncology Biologics Development Primer
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Disclaimer

- The opinions expressed by Dr. McDougal are his, and do not reflect official policy of the US or FDA.
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Objectives for this Presentation

- Present a FDA/CDER nonclinical reviewer’s perspective
- Provide insight into our approaches for reviewing your IND-enabling, nonclinical safety data
- Introduce/remind you about current guidance for toxicology testing.
CDER/Office of Oncology Drug Products (OODP) Regulates Biologic Cancer Therapies

OODP has 3 divisions:
• Division of Biologic Oncology Products (DBOP)

**DBOP** regulates:
- Monoclonal antibodies
- Recombinant proteins
- Cytokines
- Growth factors
- Enzymes
- Biological immunomodulators
- Other (non-vaccine) therapeutic immunotherapies
- Radiolabeled biologics for therapeutic use
CDER/OODP Regulates Biologic Cancer Therapies

OODP/DBOP
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OODP/DDOP (Division of Drug Oncology Products)
- ‘Traditional’ cytotoxic compounds and ‘small molecules’
- Hormones and metabolic factors
- Synthetic peptides
- Oligonucleotides and siRNA
- Small molecules conjugated to antibodies
Examples of DBOP Regulated Products:

http://www.fda.gov/cder/Offices/OODP/DBOP_products.htm

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*For cancer indications only*
What Do We Need to See in an IND for a New Anti-Cancer Biologic?

Chemistry & Manufacturing Controls (Quality)
Nonclinical (Pharmacology/Toxicology)
Clinical

Nonclinical:
1. Pharmacodynamics (PD)
   - the biology, activity, mechanism of action, potency
2. Pharmacokinetics (PK)
   - Distribution, elimination – AUC, $C_{\text{max}}$, $V_d$, $T_{1/2}$
   - anti-product antibody – formation, clearance
3. Toxicology
   - Testing in relevant animal species
Supporting the First-in-Human (FIH) Study—Nonclinical Reviewer Perspective (1)

- It is helpful if your IND clearly **informs** and **explains** HOW you have demonstrated safety.

- The FDA (nonclinical) Toxicologist may have a different perspective from the Industry Toxicologist if:
  - I’ve already reviewed an IND for this
  - I have access to FDA institutional knowledge
  - I evaluate your contract lab reports differently

- Alternative approaches may be acceptable. Please:
  - Consider requesting a pre-IND meeting to discuss.
  - Justify them in the IND.
Supporting the FIH Study– Nonclinical Reviewer Perspective (2)

- Toxicologist’s job: to verify that the nonclinical data support the safety of the proposed clinical trial.

- Toxicity:
  - Can we predict what the toxicities will be in patients?
  - Are they acceptable for this indication?
  - What is their progression / recovery?
  - Can we monitor clinically for the toxicity?
Supporting the FIH Study– Nonclinical Reviewer Perspective (3)

- Toxicologist’s job: to verify that the nonclinical data support the safety of the proposed clinical trial.

- Appropriateness of:
  - Start dose,
  - Dose escalation scheme,
  - Maximum dose.

- Schedule of dosing,
  - Maximum duration of dosing.

- Exclusion / inclusion criteria,
  - Clinical monitoring,
  - Communication of concerns and risks.
Demonstration of pharmacologic / biologic activity is the first step in the development of ANY new drug or biologic.

Nonclinical does not review for clinical efficacy.

‘Proof of concept’ studies are reviewed to understand the potential risks in context (risk:benefit).

- For biologics, most toxicity is exaggerated pharmacology.
- ‘Are the animal data predictive?’
- ‘What does the animal response mean for patient safety?’
- ‘Is this observation incidental or treatment-related?’

Examples
- Tumor vs normal cell growth inhibition ☞ show that healthy tissues are not targeted?
- In vivo studies of anti-tumor activity in tumor xenograft models ☞ identify the lowest biologically active dose?
Nonclinical Review: Step 1

Preliminary questions:

■ WHO ?
   (the index [patient] population)

■ WHAT ?
   (What is the intended pharmacological action?)

■ HOW  ?
   (the protocol)

■ All the nonclinical data get filtered through these lenses (risk:benefit).
1st question: What data directly predict effects of treatment in patients?  *PD data:*

- **The target**
  - Distribution / expression
  - Mechanism of Action (MOA)
  - Differences in healthy versus cancer

- **How the product interacts with the target**
  - Binding, affinity, specificity
  - Potency
  - Downstream effects
  - Effect of disease on the product
  - Other targets? Low affinity or off-target binding
Nonclinical Review: Step 3

2nd question: Are the animal test species pharmacologically and toxicology relevant? *PD data:*

- **Relevant species:**
  - Does the animal respond to treatment the same way that humans will?
    - Expression / distribution of the target
    - Homology / orthology
    - MOA, downstream effects
    - Binding, affinity, specificity, potency
    - PK

- **Non-relevant species:**
  - May miss some or all of the pharmacologic and toxicologic activities that will occur in humans.
  - Underpredict toxicity ☹ Not useful for dose-setting.
Why are the Pharmacokinetic (PK) Studies Important?

- PK of a new biologic allows estimation of:
  - Exposure to agent after any given dose
    - Correlation with pharmacologic/therapeutic effect
  - Duration of exposure (half-life)
    - Dosing interval for the clinical study
    - Time to reversal of any biologic or toxic effects
  - Development of anti-product antibodies
    - Both total and neutralizing activity
    - Do they affect clearance of the product?

Each pivotal *in vivo* toxicology study should include PK.
Toxicology Studies for Anti-Cancer Biologics (1) – Study Design

- Usually standard assays in healthy animals.
- For biologics, main groups and recovery groups at all doses.

- Should include a dose that exceeds the therapeutic effect (exaggerated pharmacology)
- Dosing regimen should mimic the clinical trial
  - # of doses, timing of dosing

- Monitor PK & antibody development.
- Incorporate safety pharmacology into tox. studies.
Toxicology Studies for Anti-Cancer Biologics (2) - Duration

- Nonclinical duration should equal at least 1 clinical cycle (plus recovery period).
- For some indications, cancer patients may receive multiple cycles (until progression or SAE).
- Dosing to steady-state is recommended.
  - Ex- For a mAb with $t_{1/2} = 8 – 11$ days, 5 weekly doses to support FIH may be appropriate.
Expecting to see exaggerated pharmacology.
- Looking for toxicities secondary to the main effect.
- Also looking for off-target toxicities.

Is there a no adverse effect level (NOAEL)?
- Critical target tissues/organs/systems
- Severity, reversibility
- Clinically monitorable

Do the observed effects correlate with PK?
- Dose-response
- Reversibility after clearance
- Anti-product antibody effects on PK
Toxicology Studies for Anti-Cancer Biologics: Reviewer Perspective (2)

- For Biologics, NH Primates may be the only relevant model.
- Non-rodent studies are not powered for statistical significance.
  - Look for individual animal responses.
- Working with limited data, regulatory decisions are made based on reasonable assumptions
  - The observed effect *may* be treatment-related.
  - The observed effect *may* indicate unacceptable toxicity.
Toxicology study results and setting the FIH dose

- Pivotal toxicology studies’ route & dosing regimen should mimic proposed clinical use
  - Alternative routes/regimens acceptable in some cases

- Ideal: high-dose was toxic & mid- or low-dose was NOAEL

- FIH dose extrapolated from animal results using adequate safety margins
  - Recognizing that biologics may have a smaller therapeutic index than ‘small molecules’
  - For FIH trials with anti-cancer biologics, goal is to start at a biologically-active dose (MABEL)
Specific Safety Concerns for Biologics?

1. Many biologics are highly selective and specific. Not equally active across species.
2. PK differences between humans and animals, especially for humanized mAbs.
3. Anti-product antibodies may affect / limit in vivo testing.
4. Immunogenic responses (or lack of response) in animals may not predict human responses.
Specific Safety Concerns for mAbs?

In addition to the concerns for all biologics:

- Bind targets in healthy tissues (cross-reactivity).
- Exaggerated pharmacology.
- Slow elimination.
- Slow recovery from toxicity.
Specific Safety Concerns for Cytokines & Growth Factors?

In addition to the concerns for all biologics,

- Species-specificity
- Interactions with host endogenous cascade
- Tumor-promoting potential
- Immunogenicity/antibody production
  - effects on neutralization of endogenous counterpart to test agent
CMC and Nonclinical – Reviewer Perspective

- Product development during preclinical testing phase is acceptable
- Use of non-GMP protein products allowed for nonclinical testing

- Need to know exactly what was tested, and how it differs from the clinical material
- Need demonstration of comparability of the pivotal nonclinical study’s test material with the clinical grade material
Forthcoming Guidance

Coming soon…(?...)

- **Guidance for Industry and Reviewers: Nonclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals**

- Please send comments (when the drafts are published)

ICH S9: Preclinical Guideline on Oncology Therapeutic Development
- Concept paper endorsed 5/2007
Some Further Resources

  - ICH S6: Safety Studies for Biotechnological Products
  - ICH M3: Timing of Pre-clinical Studies in Relation to Clinical Trials
  - ICH S5a: Detection of Toxicity to Reproduction for Medicinal Products

- Points to Consider
  - Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use - 1997
    - www.fda.gov/cber/gdlns/ptc_mab.pdf
  - Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals – 1995
    - www.fda.gov/cber/gdlns/ptc_tga.txt
Thanks!

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Thank you for listening.

Comments and questions solicited.

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