Regulatory Perspectives in Developing Therapeutic Proteins with Novel Scaffolds – Translational strategy

AAPS/ASCPT Joint Symposium:
Integrated Translational Strategies for More Efficient Development of Biotherapeutics with Novel Protein Scaffolds

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• Throughout the talk, representative examples of commercial products may be given to illustrate a methodology or approach to problem solving. No commercial endorsement is implied or intended.
Upfront summary of key messages

• Bispecific molecules are new because they interact with more than one target; however, many of the targets are not new.
• Many bispecific molecules are derived based on the successes (or limited success) of existing therapeutic proteins.
• Past experience with therapeutic proteins can be leveraged.
• New issues can be anticipated due to new mechanisms of action.
• Calls for building upon prior knowledge to aim for
  – Understanding of differences between hitting one target vs. two targets,
  – Further exploration of biomarkers in relation to clinical outcomes, and
  – Exploring more complex translational strategy for data integration.
• Clinical pharmacology question-based review (QBR) still applies, i.e., similar considerations in regulatory review.
Overview

• Introduction
  – The general drug development paradigm
  – ‘Old’ novel scaffolds of therapeutic proteins

• Bispecific molecules, what’s new?

• Translational challenges and opportunities
  – Animal → human, clinical PK-PD data integration
  – A case example illustrating the complexity of PD effects

• Last but not least...
  – Bioanalytical assays
  – Immunogenicity impact assessments

• Summary
Drug development paradigm

Drug Dev Phases

Pre-IND

IND

NDA

Preclinical Development

Discovery Research & Preclinical Development

Phase 1 / FIH, MD

Phase 2 / Proof of Concept

Phase 2 / Dose ranging

Phase 3 / Pivotal Trials / Extension safety Trials

Phase 4 / Post-marketing Trials

PK & PD + Clinical Response

Pharmacology (PD)

In vitro

In vivo

PK

Tox & TK

Preclinical Development – safety studies

• Exposure (animal)
• Safety
• Response
• PK-PD Modeling
• Human exposure projection

FIH dose selection

dose selections

Dosing recommendation for labeling

Learn and confirm

Information

Impact

Go/No-Go

Clinical response

Exposure (short term)

Safety

Biomarker PD

PK-PD Modeling (exposure response)

Exposure (longer term)

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Approval milestones for novel therapeutic proteins

• 1982 – recombinant human insulin (Eli Lilly) *
  – Predecessor: 1922 first medical use of insulin extracted from dogs
• 1986 – muromonab, OKT3, a murine mAb (Ortho) – anti-CD3
• 1989 – recombinant human erythropoietin (Amgen)
• 1994 – abciximab, a chimeric mAb (J&J)
• 1998 – palivizumab, a humanized mAb (MedImmune)
• 1998 – etanercept, a Fc-fusion protein (Amgen)
  – Concept from 1984, first description of CD4-Fc fusion protein
• 2000 – gemtuzumab ozogamicin, Mylotarg, an ADC, antibody-drug-conjugate (Pfizer)
• 2002 – adalimumab, a human mAb (Abbott)
• 2014 – blinatumomab, a BiTE, bispecific scFv of murine origin (Amgen)

New novel scaffolds of bispecific molecules:
targeted therapy + “something more” → aim to achieve greater efficacy

Source: Drugs@FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name)
* http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SelectionsFromFDLICurrentSeries/FDAHistory/ucm081964.htm
New novel scaffolds in concept

Kontermann (2012) MAbs
Examples of dual targets for bispecific molecules

<table>
<thead>
<tr>
<th>Cell surface antigens (target cell x effector cell)</th>
<th>Cell surface antigens</th>
<th>Soluble ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>EpCAM x CD3</td>
<td>HER2 x HER3</td>
<td>TNFα x IL-17</td>
</tr>
<tr>
<td>CD19 x CD3</td>
<td>EGFR x HER3</td>
<td>IL-17A x IL-17F</td>
</tr>
<tr>
<td>CEA x CD3</td>
<td>####### x tissue antigen</td>
<td>IL-1α x IL-1β</td>
</tr>
<tr>
<td>CD123 x CD3</td>
<td></td>
<td>IL-4 x IL-13</td>
</tr>
<tr>
<td>CD20 x CD3</td>
<td></td>
<td>Ang-2 x VEGF-A</td>
</tr>
</tbody>
</table>

Mechanism of action

- Redirecting effector cells to target cells (e.g., cancer cells)
- Simultaneous removal of soluble ligands
- Binding to dual antigens on target cells
- Targeted delivery to tissues with a specific antigen
Dual targets for bispecific molecules

Simultaneous removal of two pro-inflammatory cytokines (IL-4 x IL-13)

Oh (2010) Eur Respir Rev

IL-13Rα2 – a negative regulator
Dual targets for bispecific molecules

Bring effector cells close to tumor cells
(\text{CD19} \times \text{CD3})

Overcome tumor resistance w/ dual targeting
(\text{HER2} \times \text{HER3})


Vu (2012) Front Oncol
Some mAbs can engage effector cells - as part of the mechanisms of action

Weiner et al. (2010) Nature Review Immunology
Bispecific molecules, what’s new?  
- relative to ‘old’ novel scaffolds of therapeutic proteins

• They are new because they interact with more than one target; however, many of the targets are not new.
• They have new mechanisms of action.  
  – in some cases, enhanced delivery to target tissues
• They aim for the same ultimate clinical outcomes, e.g.,  
  – kill cancer cells, tumor regression, survival,  
  – suppress inflammation, reduce signs & symptoms, disease remission
• Their benefit-risk considerations are also disease-dependent.
• They have same ultimate goal for the development programs.  
  – give the right drug, to the right patient, at the right dose and the right time
Pre-IND focuses on FIH dose selection

Drug Dev Phases

- Discovery Research & Preclinical Development
- Phase 1 / FIH, MD
- Phase 2 / Proof of Concept
- Phase 2 / Dose ranging
- Phase 3 / Pivotal Trials / Extension safety Trials
- Phase 4 / Post-marketing Trials

Preclinical Development – safety studies

Studies

- Pharmacology (PD)
  - In vitro
  - In vivo
- PK
- Tox & TK

PK & PD + Clinical Response

Information

- Exposure (animal)
- Safety
- Response
- PK-PD Modeling
- Human exposure projection

Impact

- Go/No-Go

Learn and confirm

FIH dose selection

dose selections

Dosing recommendation for labeling

• Clinical response
• Exposure (longer term)

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Common translational challenges

• Human PK-PD projection can be challenging; for instance, if targets are specific to humans.
  – Surrogate molecules are needed for preclinical studies.
  – Relevance of animal data to humans may be unclear (both toxicity and PK)
• MABEL determination can be challenging.
  – Relevance of animal PD data to effects in humans may be unclear.
  – May need to consider a multitude of in vitro and in vivo data.
• Anticipation of cytokine release syndrome may be needed.
  – Examples*: catumaxomab, blinatumomomab, MEDI-565, ... etc.
• A conservative approach to selecting doses for FIH study may be warranted.

During clinical development — focuses on data integration to support dose selections

Drug Dev Phases

- Preclinical Development
- Discovery Research & Preclinical Development

Phases

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Learn and confirm

FiH dose selection

Dose selections

Harmonized, phase-appropriate data

Clinical response

Dosing recommendation for labeling

Supplements

BLA

NDA

Pre-IND

IND

BLA Supplements

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Past experience can be leveraged (PK modeling)

Gao et al (2014) JPP
Past experience can be leveraged (PK modeling)

- Translating plasma concentration to tissue/cellular concentration
  - Tissue-targeted delivery
  - Intracellular target site

Krippendorff et al. (2009) JPP
Past experience can be leveraged (PK-PD modeling)

Salphati (2010) Drug Metab Dispos
Dayneka et al. (1993) JPB
PK-PD data integration challenges
- to support dose ranging and dose selection

• In principle, use of PD endpoints is more efficient for dose-ranging and exploration of E-R relationship.
• New mechanisms of action may require new tools (assays, markers, models, analyses ...).
• Major challenge may be in finding suitable PD markers.
  – Biochemical/PD markers may be many.
  – Relevance to clinical outcomes may or may not be established.
  – PD marker levels in target tissues vs. in plasma.
• If no suitable PD markers are identified, may need to rely on clinical efficacy endpoints; a suboptimal situation.
• Nonetheless, foundational knowledge from existing products against each of the individual targets would be useful for development programs of bispecific molecules.
Example of PK-PD integration challenges
- Example: blinatumomab (approved Dec. 2014)

- New mechanisms of action: anti-CD19 x anti-CD3
- Engages effector T cells and cancer cells (B cells)
- Leading to numerous PD effects, among them
  - T cell activation $\rightarrow$ lyse B cells $\rightarrow$ B cell depletion
  - One activated T cell can lyse multiple target B cells
  - T cell expansion $\rightarrow$ change of EC50 over time
  - Effector/target cell ratio changes over time
- PD markers
  - T cells (activation, redistribution, and expansion),
  - B cell (depletion),
  - cytokines (rise and fall, cycle-dependent magnitude)

- Overall PD effects are complex

Nagorsen, et al. (2012) Pharmacol Ther; Drugs@FDA, Clinical pharmacology review of BLA
Example of PK-PD integration challenges
- blinatumomab case example (cont’d)

- Cytokine release (dose-dependent & cycle-dependent)
  - mitigated by glucocorticoids pre-medication
- Safety profile differed with infusion durations
  - Infusion for hours vs. weeks (better)
- CNS events seems to be dependent on the ratio of B/T cells (low → worse)
  - Reversible and mitigated by double-step dosing in cycle 1
- Exposure-response (E-R) relationship for B cell depletion has limitations because baseline B cell counts may be a confounding factor in clinical study.
  - Considerable variability across individuals in target B cell levels

- The pharmacodynamic complexity may need innovative approaches for data integration; e.g., systems pharmacology approach, multiple models to address different questions.

Bioanalytical assays for drug concentrations

• **Keystones to clinical pharmacology program**
  – A continuum through all phases of research & development

• **Are the measured concentrations useful for E-R correlation?**

• Does the assay measure active moiety with bispecific functionality intact?

• Does the assay pick up moieties that are not functional because of binding with antidrug antibodies (ADA)?

• Are there matrix interferences?

• What’s the impact if the assay method is changed midway in the development program?
Bioanalytical assays for drug concentrations
- Observations in 20+ case examples of bispecific molecules

• Many products use two reagents each for a domain (anti-A x anti-B).
• Some Fc-containing products use a reagent binding to Fc domain.
• Some use bioassays, e.g., blinatumomab.
• Some use multiple assays in early studies to verify the stability of product in circulation, then select a single assay format to move forward.
• Matrix interference appears common, strategy to address it includes changing assay reagents, acid dissociation, ... etc.
• Assays may be modified over time.

Commentary
- (1) assays with acid dissociation → measure total concentration → need to evaluate suitability for PK-PD analysis
- (2) assays changed → consider bridging strategy to facilitate data integration
Assessing the impact of immunogenicity

- **Immunogenicity assessment is important because anti-drug antibodies (ADA) can impact PK, PD, efficacy, and safety.**

- Are assays sensitive and tolerant to drug concentrations in study samples?
- Do ADA have neutralizing capability and affect the intended functions?
- What part of the bispecific molecule do ADA bind to?
- Is there a potential for cross-reactivity to endogenous proteins?
- More details can be found on published literature, industry whitepapers, and guidance documents.

Status of immunogenicity reporting

- Survey of US prescribing information (up to February 2015)

### Reporting status of immunogenicity data components (reported vs. not reported)

<table>
<thead>
<tr>
<th>Component</th>
<th>Reported</th>
<th>Not Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA incidence</td>
<td>108/121 (89%)</td>
<td>NR</td>
</tr>
<tr>
<td>Neutralizing Activity</td>
<td>73/121 (60%)</td>
<td>NR</td>
</tr>
<tr>
<td>Impact on PK</td>
<td>31/121 (26%)</td>
<td>NR</td>
</tr>
<tr>
<td>Impact on Efficacy</td>
<td>59/121 (49%)</td>
<td>NR</td>
</tr>
<tr>
<td>Impact on Safety</td>
<td>73/121 (60%)</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported; ADA: binding, anti-drug antibodies; PK: pharmacokinetics

Wang et al. Manuscript submitted
High concordance rate for ADA impact on PK and efficacy

Impact on PK

Impact on Efficacy

Reported Impact on PK + Efficacy

Concordance PK + Efficacy

Concordance definition:
• ADA+ → higher clearance (lower exposure) & reduced efficacy
• ADA+ → no effect on clearance & no effect on efficacy

The high concordance rate suggests a high potential for PK data to be an early marker of immunogenicity impact on efficacy → Beneficial to plan for coinciding PK and ADA assessment

Wang et al. Manuscript submitted
An example of literature support - PK can be an early marker for ADA impact on efficacy

- ADA+ has higher dropout / lower response rate (starting from ~Week 25).
- ADA+ has lower trough concentrations (starting from ~Week 12).

**Figure 4.** Dropout Due to Treatment Failure

ADA: anti-drug antibody

**Figure 2.** Median Concentrations Over Time

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Without ADA</th>
<th>ADA titer 13–100 AU/mL</th>
<th>ADA titer &gt;100 AU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>0</td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
</table>

No. at risk

- ADA-: 196, 151, 135, 118
- ADA+: 76, 59, 43, 29

Bartelds *et al.* 2011 JAMA
In summary...

• Many bispecific molecules are derived from existing protein therapeutics.

• New issues rise due to new mechanisms of action.
  – Similar experience with single-target products.

• Stay on course – leverage past experiences with mAbs, Fabs, fusion proteins, etc.,
  – Use MABEL / NOAEL approach for FIH dose selection
  – Deploy bioanalytical assays useful for PK-PD correlation and exposure-response (E-R) exploration.
  – Utilize PD markers, if available, for E-R analyses, dose ranging, dose selection.
  – Evaluate immunogenicity impact on PK, PD, efficacy, and safety.
In summary...

• Build upon prior knowledge
  - Better understand differences between hitting one target vs. two targets.
  - Improve understanding along the mechanistic pathways.
  - Invest in evaluating biomarkers and aim to explore relationship to clinical outcomes.
  - Explore innovative approach, e.g., systems pharmacology, as a translational strategy for products with complex mechanism of action (MOA).

• Characterize ADME to inform dosing in general population and specific populations.
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