USING BIOMARKERS
FOR
EARLY PHASE DOSE SELECTION
WITH
PROTEIN ANTAGONIST DRUGS

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TALK FRAMEWORK

- Setting the stage: introductions and definitions
- PK and binding as major early markers
- Biological activity as validation for binding
- Walk-through example
- Regulatory implications
THERAPEUTIC PROTEINS


• **Antagonists** (e.g. antibodies, soluble receptors) - block native protein interactions by binding to target protein(s)
  – Examples – anti-TNF, anti-VEGF, anti-BLyS/APRIL

• **Agonists** (e.g. cytokines, growth factors) - stimulate cell surface receptors
  – Examples – erythropoietin, rhGH, G-CSF, IL-2

• **Targeting agents** (e.g. antibodies, immunotoxins) – target specific cell surface antigens or deliver therapeutic agents
  – Examples – anti-CD20
EXAMPLES:
BLYS/APRIL antagonist (atacicept)

- B cell differentiation
- B cell survival
- Antibody production
- Ig class switch
THE RESPONSE CASCADE


Fig. 1. Schematic representation of the concept of a “cascading” PK/PD model for prediction of in vivo drug effects on the basis of intermediary biomarker responses.

PHASE 1 DATA

HOW TO USE THIS INFORMATION FOR DOSAGE REGIMEN DESIGN IN PHASE 2/3?
Atacicept exposure–response cascade (RA)

FREE DRUG
FREE TARGET COMPLEX

DOSE & Freq.

BLyS/APRIL Inhibition

IgX FACS

MoA Biomarkers

Diseased Biomarkers

Disease related activity

Clinical activity

Clinical efficacy

Binding & Inhibition

Biological activity

IgX RF ACPA

ESR, CRP JOINT CNTS

ACRXX% DAS28

Clinical Markers

Clinical Endpoints
THERAPEUTIC PROTEINS

- Large molecules, slow PK and PD
- Specific binding to targets dominant (by engineering)
- Target load often:
  - Significant (in molar concentration terms)
  - Distributed across various tissues
  - Constantly renewed by endogenous production of targets
  - Endogenous production may be boosted by depletion
- Nonspecific binding sometimes negligible (!!! check)
- No P450 metabolism, but Ab’s to drug possible
- Protein drug metabolism often capacity limited
PK & TARGET BINDING: MAJOR EARLY MARKERS

• **Free drug PK is expected to be nonlinear**
  – Unless nonlinearity is overwhelmed
  – Or unless total drug is measured
  – PK Assays are critical

• **Dosing should be targeted at the saturation**
  – Below saturation – sub-therapeutic regimen
  – Above saturation – waste of drug and/or potential over-inhibition
  – Saturation – both in blood and tissues
  – Saturation is a dynamic process – at all times
PK & BINDING

BINDING EQUILIBRIUM:

• Binding affinity
• Drug & ligand concentrations
  – Systemically
  – In tissues
• Dosing schedule
• Endogenous ligand production
  – Systemically
  – In tissues
PK, BINDING & DOSING

OBJECTIVE:

• Adequate binding
  – Process in time
  – At Sites of Action
  – Not necessarily complete binding of ligand

• Markers of PK/binding
  – Free drug
  – Total drug
  – Complex concentration
  – Free ligand concentration

• Means to achieve goal:
  – Type of dosing regimen
  – Dosing levels
  – Dosing frequency
  – Mode of administration
ACCUMULATION OF COMPLEX

BLyS Concentration after Rituximab in RA


BLyS accumulation rate in serum: \(~0.08\) ng/mL/day
DESIGN SO FAR:

• Type of dosage: Loading - Maintenance
  – Eliminate initial target ligand load
  – Boost the redistribution of target ligand
  – Compensate endogenous ligand production

• Dose levels and dosing frequency ???

• Mode of administration: ???
RECEPTOR MEDIATED PK


Free Atacicept

![Graph showing free atacicept levels over time for different doses.]

Atacicept/BLyS Complex

![Graph showing atacicept/BLyS complex levels over time for different doses.]

- 2.1 mg
- 70 mg
- 210 mg
- 630 mg
QUIZ: DOSING FREQUENCY?

Terminal Halflife: 20-30 days
QUIZ: DOSING FREQUENCY?

30-40% incomplete inhibition

Next dose?
Biological activity tracks target ligand binding

More frequent dosing at smaller doses yields better effect

Biological Activity

Drug-Ligand Complex

- 18 mg/kg IV
- 4x3 mg/kg SC
- 4x1 mg/kg SC
DESIGN SO FAR:

• Biological activity tracks binding

• Type of dosage: Loading - Maintenance
  – Eliminate initial ligand load
  – Boost the redistribution of ligand
  – Compensate endogenous ligand production

• Dose levels and dosing frequency
  – More frequent smaller doses yield higher biological activity compared to less frequent higher doses
  – Single dose saturation – between 75 and 210 mg
  – Dosing interval to maximize inhibition – 7 – 14 days
  – What doses / dosing intervals???

• Mode of administration: ???
S.C. ADMINISTRATION of PROTEIN DRUGS

- Uptake by lymphatic system
- Poorly quantified
- Dependent on MW
- Lymphatic & blood circulation closely interwined
- Consider kinetic vs dynamic rates
- Lymph can be SoA
COMPARING S.C. & I.V. ADMINISTRATION

S.c. Atacicept systemic bioavailability is ~ 35 - 40% …

… but biological activity is the same …

Free atacicept [ng/mL]

Time [days]

IgM [% of Baseline]

Time [days]
COMPARING S.C. & I.V. ADMINISTRATION

... because target binding is the same!
DESIGN SO FAR:

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  – What doses / dosing intervals???

• Mode of administration: SC
TIME TO BECOME QUANTITATIVE...

ATACICEPT Pop PK/PD MODEL

Simulations: Dose saturation of effect

Varying doses, same dosing frequency (QW)

Going beyond 150 mg for QW not justified
• Biological activity tracks binding

• **Type of dosage: Loading - Maintenance**
  – Eliminate initial ligand load
  – Boost the redistribution of ligand
  – Compensate endogenous ligand production

• **Dose levels and dosing frequency**
  – More frequent smaller doses yield higher biological activity compared to less frequent higher doses
  – Single dose saturation – between 75 and 210 mg
  – Dosing interval to maximize inhibition – 7 – 14 days
  – Dosing frequency – once weekly (QW)
  – Dose levels for Phase 2/3 study: 25, 75 and 150 mg

• **Mode of administration: SC**
Merck KGaA, ZymoGenetics start Phase II/III Lupus trial

By Steve Goldstein
Last update: 3:53 a.m. EST Dec. 13, 2007

LONDON (MarketWatch) -- Germany's Merck KGaA (DE:659990) and its partner ZymoGenetics, Inc. (ZGEN) have initiated a Phase II/III clinical trial of atacicept in lupus nephritis, a severe form of systemic lupus erythematosus. The kidneys are affected in at least 30% of the estimated 1.5 million people suffering from SLE worldwide. This study will evaluate the efficacy and safety of atacicept for the treatment of patients with active lupus nephritis. The trial is being conducted under a Special Protocol Assessment agreement with the U.S. Food and Drug Administration and is intended to support worldwide applications for marketing authorization. Merck KGaA is unrelated to the American drugmaker of the same name.
CONCLUSIONS

• PK and target binding are major early biomarkers for protein antagonists

• Saturation of binding can be used for early phase dosage regimen design

• Population PK/PD modeling helps quantify saturation

• Mechanistic validation should be implemented as much as possible