Site of Action Models: A Systems Modeling approach to quantifying pharmacology

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Outline

• Introduction and Definitions
  – The basic tenets of pharmacology (3 Pillars)
  – Systems Pharmacology and PK-PD

• System Pharmacology Example 1: TL1a

• PK-PD example: DAGR
What are the 3 pillars?

**PILLAR 1: PHARMACOKINETICS**

**OBJECTIVE**
- Can we get the therapeutic to the target in sufficient concentrations?
- If necessary can we maintain these concentrations at the target?

Utilize parameters such as CL, V and F to project and predict steady state blood or target levels of the therapeutic.
PILLAR 2: PHARMACO-BINDING

OBJECTIVE
- Will the therapeutic bind to the target?
- How strong should the binding be?

\[ K_D = \frac{[D][T]}{[DT]} \]

Optimal KD (Assuming Linear PK)

Use the \( K_D \) value to estimate if the therapeutic has the ‘right’ affinity for the target. If not, optimize the \( K_D \).

PILLAR 3: PHARMACODYNAMICS

OBJECTIVE
- What happens after the drug binds to the target? What is the pharmacological change (biomarker)?
- Can the change be measured? How long does it take to see the effect? How long does it last?

Use the IC50 (EC50) estimates to calculate the dose required to engage the target for an appropriate time in the dosing interval.
What is Systems Pharmacology?

Modeling which explicitly distinguishes between drug and system determinants of a given pharmacological response.

- Baseline effects
- Diurnal variability
- Turnover of target
- Target homeostasis
- Target Mediated Drug Disposition

EXAMPLE 1

- TL1a
  Crohn’s Disease
The Anti-TL1A program

- TL1A = TNF Ligand related molecule 1A (exists in trimeric form. MW ~ 63 kD)
- TL1A and its receptor DR3 are implicated in Crohn’s disease
- A soluble decoy receptor DcR3 seems to help by sequestering TL1A
- TL1A exists in soluble or membrane bound (endothelial cells) form
- An Anti-TL1A antibody should be therapeutically beneficial

The Unknowns about TL1A in Crohn’s

- What is the concentration of TL1A in plasma of Crohn’s disease patients?
- What is the concentration of TL1A in the gut interstitium of Crohn’s disease patients?
- What is the turnover rate of TL1A in the diseased tissue?
- What is the equilibrium between the interstitial and plasma spaces for TL1A?
- What are the proportions of the soluble vs. membrane bound TL1A?
- How much of DcR3 exists and binds to TL1A?
The Unknowns about TL1A in Crohn’s

- What is the concentration of TL1A in plasma of Crohn’s disease patients? (~ 5 pM measured by LC-MS: PDM Biomarkers group)
- What is the concentration of TL1A in the gut interstitium of Crohn’s disease patients? (~ 25 pM assumed based on hTL1A mRNA expression levels reported in the literature)
- What is the turnover rate of TL1A in the diseased tissue? (t\(_{1/2}\) = 60 minutes. Extrapolated from hTL1A dosed to mice and PK parameters calculated)
- What is the equilibrium between the interstitial and plasma spaces for TL1A? (Unknown; calculated such that TL1A concentrations in plasma and interstitium are in equilibrium)
- What are the proportions of the soluble vs. membrane bound TL1A? (Unknown; Not included in the model)
- How much of DcR3 exists and binds to TL1A? (Not clear; since DcR3 is non-signalling, it is ignored in the model. In any case it would help by removing TL1A)

The Unknowns about the Anti-TL1A antibody

- What is the human PK of the antibody? (allometrically scaled from monkey PK)
- What is the SC bioavailability of the antibody? (assumed as 60%; agrees with published literature values)
- What is the distribution of the antibody into the gut interstitium? (~ 10% of plasma levels; from the literature; measured using radiolabeled IgG antibodies)

- What would be the ideal K\(_d\) required to sequester > 80% of TL1A (assuming >80% of TL1A removal is required for efficacy)?
"Site-of-Action" Model

Human Plasma – 3.5 L
Human Gut Interstitium – 0.177 L

TARGET

TL1A TL1A

+ TL1A TL1A

\[ \text{T}_{\text{L1A}} + \text{T}_{\text{L1A}} \rightleftharpoons \text{T}_{\text{L1A}} \text{T}_{\text{L1A}} \]

\[ k_{\text{on}} \quad k_{\text{off}} \]

Gut TL1A = 25 pM

Plasma TL1A = 5 pM

Multiple Dosing Prediction: SC Q2W

Dose → 1 mpk

Plasma TL1A = 5 pM

Dose → 2 mpk

Dose → 3 mpk

Anti-TL1A
Kd:
1 nM
500 pM
200 pM
100 pM

Target TL1A

100 pM

200 pM

500 pM

1 nM

Gut TL1A = 25 pM

Time (hr)
Affinity maturation of the three lead antibodies

$K_0$ of current lead antibodies: 2-4 nM
Goal (based on modeling): <200 pM

EXAMPLE 2

- Anti IL-17
  Psoriasis
IL-17 Suppression by Ixekizumab (Eli Lilly) and Secukinumab (Novartis)

**Parameters**

**PK:**
- **CL** = 0.254 (L/day)
- **Q** = 0.660 (L/day)
- **V1** = 3.3 (L)
- **V2** = 2.9 (L)

**Physiology:**
- **Vskin_int** = 0.800 (L)
- **mAbskin_mAbp** = 0.3 (L)
- **Q_skin** = 0.200 (L/day)
- **Target:**
  - **Q_ab** = 0.500 (L/day)
  - **Tp_0** = 1.5e-005 (nM)
  - **Tskin_0** = 2.8e-004 (nM)
  - **Thalf** = 15.0 (min)
  - **KD** = 5.0e-003 (nM)
  - **koff** = 18.0e-002 (L/day)

**Target:**
- **CL** = 0.18 (L/day)
- **Q** = 0.660 (L/day)
- **V1** = 3.5 (L)
- **V2** = 3.0 (L)

**Physiology:**
- **Vskin_int** = 0.800 (L)
- **mAbskin_mAbp** = 0.3 (L)
- **Q_skin** = 0.200 (L/day)

**Target:**
- **Q_ab** = 0.500 (L/day)
- **Tp_0** = 1.5e-005 (nM)
- **Tskin_0** = 2.8e-004 (nM)
- **Thalf** = 15.0 (min)
- **KD** = 0.090 (nM)
- **koff** = 5.49 (L/day)

Ixekizumab and Secukinumab in Psoriasis

![Graph showing the comparison of Ixekizumab and Secukinumab in Psoriasis](image)

- **PASI = 2.9**
- **PASI = 2.3**
- **PASI = 2.0**
- **PASI = 4.5**
- **PASI = 3.0**
- **PASI = 18.2**
Details of Secukinumab experiments (Novartis)

Partition Ratio (Skin:Serum) of Secukinumab

Drop in Serum Conc due to increased BWt of Psoriasis patients

\[ \frac{\text{Skin}}{\text{Serum}} = 23\% \]

\[ \frac{\text{Skin}}{\text{Serum}} = 35\% \]
IL17-A levels in Psoriatic Skin

**IL-17A, but Not IL-17F, is Significantly Higher in Psoriasis Lesional Skin Compared With Non-lesional Skin or Skin of Healthy Volunteers.**

- **Baseline IL-17A in Skin of Psoriasis Subjects and Healthy Volunteers (Mean ± SD):**
  - Psoriasis: 92% higher
  - Non-lesional skin: 99% higher

In skin (dermal ISF), baseline IL-17A levels were significantly higher in lesional vs. non-lesional skin of psoriasis subjects (adjusted geometric mean 9.8 vs. 0.6 pg/mL, P < 0.001). In healthy volunteers’ skin, all baseline IL-17A levels in dermal ISF were below the LLOQ (0.095 pg/mL).

In circulation (serum), baseline IL-17A levels were significantly higher in psoriasis subjects vs. healthy volunteers (adjusted geometric mean 0.53 vs. 0.20 pg/mL [P < 0.05]; figure not shown). Post-dose free IL-17A could not be measured due to presence of secukinumab.

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**Recreating the Secukinumab PK data**

Novartis trial data superimposed with SOA predictions

- **Plasma Concentration (nM) vs. Time (days):**
  - 300 mg SC Single Dose
  - Novartis Microperfusion Study
  - Healthy
  - Novartis Microperfusion Study Psoriasis

- **Key Data Points:**
  - 244 nM - 71 nM
  - 142 nM - 31 nM
EXAMPLE 3

• iRAK 4

Inhibiting iRAK-4 in inflammatory cells will have an anti-inflammatory effect
Deconstructing the pathway

Model Equations
**Initial Conditions**

- **Monocytes** = $1 \times 10^6$ cells/mL blood
- **LPS** = 1 nM
- **TLR4** = 1000 nM per $1 \times 10^6$ monocytes/mL
- **pIRAK4** = 0 nM
- **IRAK-M** = 0 nM
- **ERK** = 1 nM
- **pERK** = 0 nM
- **TNFα** = 0 nM

**Parameters**
- **LPS half-life** = 20 minutes
- **IRAK4 half-life** = 8 hours
- **ERK half-life** = 8 hours
- **IRAK-M half-life** = 8 hours
- **TNFα half-life** = 30 minutes

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**Simulated and measured responses to LPS as bolus and infusion**

- **LPS**
- **IRAK4**
- **IRAK-M**
- **TNFα**

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Simulated human responses to LPS bolus with an IRAK-4 oral inhibitor

Simulated and measured response versus exposure curves
Conclusions

• Systems Pharmacology and PK-PD modeling are powerful tools to study and approximate the complexities of a biological/pharmacological system

• Early deployment of these tools can significantly reduce costs by eliminating programs that have a poorly predicted efficacy

• Discovery and development activities can be streamlined and accelerated

• GO/NO GO decisions can be made effectively and objectively, rather than “Let’s try it out and see what happens”

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