How system pharmacology can facilitate clinical drug development in oncology

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Overview

- Introduction to Quantitative Systems Pharmacology
- Case study 1: CD3-bispecifics
- Case study 2: EP4 – PD1 IO combination therapy
- Case study 3: Optimizing dosing regimen
"High cost and attrition of drug development require novel approaches to improve efficiency"
Immuno Oncology (IO) Problem Statement

• IO one of the most promising areas of drug development
  o However, currently only a minority of patients are benefiting

• Combination therapy is required but challenging
  o Cannot explore all possible combinations in all cancer types experimentally via “trial and error”
  o Biology complex and difficult to translate
  o Multiple types of modalities
  o Several recent clinical failures

~4000 IO drugs/therapies in development
>5000 Active trials

Nature Reviews Drug Discovery 27th September 2019
https://www.nature.com/articles/d41573-019-00167-9
IO combinations: needle in a haystack?

Incyte wipes out late-phase epacadostat program after pivotal failure of Keytruda combination

by Nick Paul Taylor | May 1, 2018 9:23am

Immunotherapy 2018 Review: From the Nobel Prize to Clinical Trial Failures

by Federica Parisi PhD, December 20, 2018 at 04:00 PM | Tags

Another big setback as Tecentriq combo fails phase III trial

28-11-2017

Germany’s Merck KGaA (MRK.DE) and US pharma giant Pfizer (NYSE: PFE) have suffered a setback with their immuno-oncology (IO) combo Bavencio (avelumab).

Opdivo/Yervoy combo for melanoma fails in key patient population

November 20, 2019 10:50 AM EST | Jason Mast | R&D

Bristol-Myers Squibb’s efforts to expand their checkpoint inhibitor combination have run into another recalcitrant cancer.
What is Quantitative Systems Pharmacology (QSP)?

- **Network/pathway models**
- **PBPK models**
- **(Semi)mechanistic PK/PD models**
- **Heuristic models**

**Systems biology**

**System pharmacology**

**Pharmacometrics**

**Model complexity**
- Determined by low-level organization
- Model selection rarely performed

**Middle-out:** what we know
- Model complexity determined by existing information
- Model selection based on function

**Bottom-up:** reductionism

**Model complexity**
- Determined by high-level organization
- Model selection based on statistics

**Top-down:** intact system
EMA encourages the development and use of complementary mechanistic models in translational drug research, such as the present example. Guidance on novel technologies can be obtained from EMA under the form of a qualification advice or a qualification opinion (Qualification of novel methodologies for medicine development: http://www.ema.europa.eu/ema/index.jsp?curl=pages/ regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0. Accessed 8 June 2018). Their inclusion in future guidelines will be further considered in line with increasing scientific knowledge.
Typical questions for QSP

• In a given biological pathway, what is the best target and modality for pharmacological intervention to treat disease X?
• How can we improve the therapeutic effectiveness of an existing drug through combination therapy?
• Can we predict the effect of a drug in a special population?
• Can we individualise dosing regimen based on patient characteristics:
• Can we predict human response (dose) to a novel mechanism based on preclinical data?
• Which biomarkers do we require to answer the above questions?
Overview

• Introduction to Quantitative Systems Pharmacology

• Case study 1: CD3-bispecifics

• Case study 2: EP4 – PD1 IO combination therapy

• Case study 3: Optimizing dosing regimen
Efficacy (and on-target toxicity) is driven by formation of a trimolecular complex (trimer) between drug, T-cell and tumor cell, not PK *per se*.

The concentration response relationship is bell-shaped:

- A well described phenomenon for ternary complexes. Confirmed for CD3 bispecifics.
- A function of CD3 and tumor antigen expression, Effector/Target ratio and drug affinity.

CD3 bispecific molecules behave like functional agonists and are exceptionally potent. Difficult to design clinical trials to ensure safety/efficacy:

- Clinical trials with CD3 bispecific molecules taking too long
- Can be multiple rounds of sub-efficacious doses
- Some CD3 bispecific molecules are failing in the clinic
Dose prediction/MABEL for CD3 bispecifics

Method 1: PK driven approach
Match predicted drug $C_{\text{max}}$ or $C_{\text{ave}}$ to EC$_{20}$ in relevant assay

*Easily understood by all, accepted by regulatory agencies → but not technically correct as driven by drug concentration rather than trimer concentration.*

Method 2: Receptor occupancy approach
- Select the dose which results in 10-20% receptor occupancy at $C_{\text{max}}$.
- **Not recommended (Saber et al. 2017).** Why?
  - Two targets- which do you choose? CD3 will (usually) always be lower than TAA as there are 100-200K CD3/T-cell.
  - Immune agonists: RO for efficacy is often variable and lower than 10%

Method 3: QSP modeling approach
- Match in vivo trimer concentration in tumor to the estimated EC$_{20}$ of trimer concentration from QSP model, which causes 20% tumor cell killing in vitro.
- **Normalizes for differences between in vitro experiments and clinic including cell numbers, expression levels, shed target, E:T ratio. Accounts for trimer formation driving efficacy and toxicity.**
CD3 bispecific antibody (PF-06671008) targeting P-cadherin on solid tumors based on Dual Affinity Re-Targeting (DART®) scaffold with human IgG1 Fc domain

P-cadherin:
- Cell surface protein involved in $\text{Ca}^{2+}$-dependent cell-cell adhesion.
- Upregulated in breast, gastric, endometrial, colorectal and pancreatic cancers.
- Low expression in normal tissues.
- Variable across species
CD3 bispecifics QSP Model

- # circulating T-cells
- T-cell expansion/contraction
- Binding affinities for CD3 and P-cad

CD3 expression on TILs
- Pcad expression on tumor cells
- # tumor cells
- # TILs
- Internalization rate

Levels of shed target
Translating to **Human**

**Predicted human PK**

**Predicted human tumor trimer concentrations**
Sensitivity analysis

- Expression
- Tumor trimer concentration
- Dose

E:T = effector: target cell ratio

- E:T
- Tumor trimer concentration
- Dose

P-cadherin expression and tumor immune status (E:T) are sensitive parameters, likely to be variable across patients.
Conclusions

QSP model provides translational framework for quantitative decision for CD3 bispecific drug discovery and development:

• Characterizes PKPD relationship across mouse xenograft models

• Integrates in vitro and in vivo data

• Translates preclinical data to human dose and clinical efficacy

• Identifies important biomarkers / parameters driving efficacy

• Aids design of CD3 bispecific constructs with optimal properties
Why spoil a good biology story with pharmacology?

NEWS AND VIEWS · 18 NOVEMBER 2019

Trispecific antibodies offer a third way forward for anticancer immunotherapy
Case study 2: IO combination therapy

Mazzarella et al., European Journal of Cancer 117 (2019) 14e31
Case study 2: EP4 – PD1 IO combination therapy

EP₄ blockage increases differentiation of monocytes into M1 type macrophages and dendritic cells

QSP Objectives

- **Dose selection**: FIH from preclinical
- **Combination discovery**: EP4 + PD1
- **Generation of hypotheses** guiding further preclinical experiments
Combination discovery and dose selection necessitate quantitative dynamic model covering wide biological scope including all stages of Cancer Immunity Cycle.
Knowledge integration for QSP model development

- Cancer-immune system biology
- TCGA data: TME – fractions of cell-types
- Cell/cytokine baseline

Basic immune system biology

TCGA data/TSNA database: TMB and neoantigens

Landscape of literature based cancer-immune cycle models

Omics data – TME fraction

Unified biological process map

Clinical studies

Exome sequencing data: TMB and neoantigen

Validation published clinical studies

Statistical analysis
From biology literature to mechanistic model

- PubMed: Literature
- Influence graph
- Mind map
- Simulator
- Biological Process Map
QSP Model

- ODE model with 56 state variables, 88 rate laws, 138 parameters
- 161 literature references
- 27 Eisai pre-clinical datasets on CT-26 syngeneic tumor growth inhibition (TGI), CT-26 tumor infiltration by CD8+ T-cells and monocytes, blood cell counts, intratumor and plasma PGE2 levels.

Tumor – tumor size; Tc, Treg, Th17 – CD8, Treg and Th17 T-cells, M1, M2 – M1 and M2 Macrophages, IDC – immature dendritic cells, APC – antigen presenting cells, mMDSC, gMDSC - monocytic and granulocytic myeloid-derived suppressor cells, SCs – the sum of all suppressor cells, PGE2 – Prostaglandin E2, E7046 – amount of E7046, EP4 – EP4 receptor; L, R – anti-PD1 and PD1; _b, _ln, _c are tags of specie names in blood, lymph nodes and cytoplasm.
Simulation of CT26 tumour in BALB/c mouse

- TGI for CT26 tumour
- CD8 cells in tumour
- Immature Dendritic Cells in Tumour
- monocytic myeloid derived suppressor cells

**TGI for CT26 tumour**

- Vehicle
- E7046 150 mg/kg
- Simulation (Vehicle)
- Simulation (E7046 150 mg/kg)

**CD8 cells in tumour**

- Vehicle
- E7046 150 mg/kg
- Simulation (Vehicle)
- Simulation (E7046 150 mg/kg)

**Immature Dendritic Cells in Tumour**

- Vehicle
- E7046 150 mg/kg
- Simulation (Vehicle)
- Simulation (E7046 150 mg/kg)

**mMDSC in blood**

- Vehicle
- E7046 150 mg/kg
- Simulation (Vehicle)
- Simulation (E7046 150 mg/kg)
Prediction of dose response in pre-clinical tumours

- The model correctly predicts responder / non-responder status in 3 out of 4 pre-clinical tumours.
- The model achieves good quantitative predictions of tumour growth inhibition by different doses of E7046.
Two mechanisms are investigated. A) Mechanism 1 assumes additive effect of E7046 and anti-PD1. Simulation under this assumption correctly predicts that combination increases efficacy but exaggerates the effect. B) Mechanism 2 assumes additional cross-talk between PGE2 and PD1 checkpoint pathways leading to indirect inhibition of anti-PD1 effect by E7046. This mechanism better describes experimental data.
Mechanism 2 is corroborated by clinical data

The clinical data of Wang et al., 2018 were published after model predictions were made.


Activation of PGE2/EP2 and PGE2/EP4 signalling pathways positively regulate the level of PD-1 in infiltrating CD8+ T cells in patients with lung cancer

Jinhong Wang,1 Li Zhang,2 Dong Kang,3 Deguang Yang,4 and Ying Tang5

In agreement with our hypothesis, PD1 and EP4 intracellular pathway do interact. Treatment with EP4 antagonist decreases PD1 expression thus lowering anti-PD1 efficacy. This explains less than additive effect of anti-PD1 / E7046 combination.
~60 Individuals from 7 companies (biologists, clinical pharmacologists, clinicians, modellers, regulatory, software,…

The Consortium aims to develop an industry-standard QSP IO model coupled to a robust IT platform, through which combinations of different cancer therapies, different dose regimens and biomarkers in a virtual patient population can be tested, and guide decision making in drug development.
Case study 3: Optimizing dosing regimen

Oscillatory stress stimulation uncovers an Achilles’ heel of the yeast MAPK signaling network

Amir Mitchell,1,2 Ping Wei,1,3+ Wendell A. Lim1,2,4

Science 350 (6266), 1379-1383. DOI: 10.1126/science.aab0892 originally published online November 19, 2015
Optimization of Cancer Treatment in the Frequency Domain

Pascal Schulthess, Visi Rottschäfer, James W. T. Yates, and Piet H. van der Graaf

Cell-cycle specific

Metronomic

Acquired resistance

Etoposide

Temozolomide

Elimination rate

Gefitinib

Therapeutic window

- yes
- yes & optimal
- no
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Optimizing dosing regimen
• Pascal Schulthess
• James Yates / Astra Zeneca
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