Application of Quantitative Systems Pharmacology in Early Clinical Development for Immuno-Oncology Drug Combinations

2019 Multi-Scale Modeling Consortium Meeting
Brian J. Schmidt, PhD
March 6th, 2019
Agenda

• Introduction to mechanistic modeling vis a vis QSP
  – QSP at BMS
  – General considerations for developing and applying models

• QSP application workflows (very high level)

• I-O QSP model application examples
  – Drug x
QSP at BMS

• 8 Dedicated QSP modelers in the Quantitative Clinical Pharmacology group

• Substantial & continual investment in platform development and approaches

Oncology & Immuno-Oncology
  ◆ 3 I-O Platforms
  ◆ Antibody-Drug Conjugate Platform
  ◆ Physiologically-Based Tumor Receptor Occupancy

Cardiovascular Disease
  ◆ Heart Failure
  ◆ Thrombosis

Additional Platform Resources
  ◆ Diabetes/Metabolic Diseases

Immunoscience
  ◆ Rheumatoid Arthritis
  ◆ Immunogenicity
  ◆ Crohn’s Disease
  ◆ Ulcerative Colitis
  ◆ Psoriatic Arthritis
  ◆ Systemic Lupus Erythematosus

Fibrosis
  ◆ Nonalcoholic Steatohepatitis
  ◆ Pulmonary Fibrosis
“Quantitative analysis of the dynamic interactions between drug(s) and a biological system that aims to understand the behavior of the system as a whole, as opposed to the behavior of its individual constituents” (van der Graaf & Benson 2011, J Pharm Sci)
**QSP model introduction (1)**

- Mechanistically link target modulation to disease outcome
- Pathway modeling informed by quantitative measurements:
  - In vitro measures (in-house, literature)
  - Mini-models to extract pathway parameters
- Multiple clinical datasets for modeled assets:
  - Lesion response
  - Gene expression
  - IHC
- Model scales vary
  - Narrowly focused (single asset with well-defined, narrow biology)
  - In-between: asset-level combinations
    - Focus on prioritized biomarkers
    - Stage development
    - Can work towards bigger platforms
  - Disease-scale platform
  - Larger biomarker panels
QSP model introduction (2)

- System focus: provide predictions and analyses before trial data are available for a new intervention/therapy
  - Calibrate model for related therapies
  - Lesion responses, for example on nivolumab
  - Evaluate model performance from withheld data
  - Stronger extrapolation principal if data available for therapies that perturb related pathways

- Challenges and risk mitigation
  - Many parameters
    - Mini-models for parameter extraction from experiments
    - Train on outcomes
    - Only accept solutions that agree with observed clinical outcomes
  - Availability of data
    - Initially focus on tumor types where the best data are available and accessible
    - Clearly communicate where additional pathway or outcome training & validation data will be beneficial

Patient measures (output)
- Molecular readouts
- Drug and mediator concentrations
- Cellular readouts
- Cell counts
- Activation
- Tissue damage and function

Parameters (input)
- Molecular
- Affinity
- Half-life
- Transport or partitioning
- Signaling
- PK
- Cellular
  - Life cycle differentiation
  - Motility and secretion
  - Effects of mediators and interaction
  - Tissue and organ-level responses

Initial conditions (input)
- Concentrations
- Cell populations
- Tissue state

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Methods: virtual patient cohort (1)

- Alternate model parameterizations are sampled (biomarker diversity)
- Multiple interventions (therapies) are simulated for each virtual patient

\[
\frac{dx_i}{dt} = f_i(x_i, x_j, \ldots, x_n) \\
\frac{dx_j}{dt} = f_j(x_i, x_j, \ldots, x_n) \\
\vdots \\
\frac{dx_n}{dt} = f_n(x_i, x_j, \ldots, x_n)
\]

Simulate multiple interventions for each VP
Methods: virtual patient cohort (2)

- Alternate model parameterizations are sampled (biomarker diversity)
- Multiple interventions (therapies) are simulated for each virtual patient
- Biomarker and response data are used to:
  - Guide reasonable parameter bounds
  - Set acceptance criteria on simulated outcomes
  - Plausible VPs must pass numerous acceptance criteria from data

**Virtual patients (Parameterization)**

\[
\frac{dx_1}{dt} = f(x_1, x_2, \ldots, x_n)
\]

\[
\frac{dx_2}{dt} = f(x_1, x_2, \ldots, x_n)
\]

\[
\vdots
\]

\[
\frac{dx_n}{dt} = f(x_1, x_2, \ldots, x_n)
\]

**Tests:** Are outputs in observed ranges for all interventions?

- CD8 < x%
- Treg < y%
- ...
Methods: virtual population

- Simulations also need to match observed statistics
- Often accomplished with “prevalence weight” to create a virtual population
  - Simultaneous fit
    - Multiple biomarkers and response for each therapy
    - Multiple therapies
  - Uses multiple statistical tests and dependent on data to match
    - Summary statistics
    - Distributions
    - Bins
    - Multivariable
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I-O platform 1: initial development to support dose expansions & ongoing trials for drug x

• Questions
  – What is the anticipated dose response of drug x in anti-PD-1 progressed MEL?
  – What is the role of biomarkers in the response?

• Multi-step approach
  
  Stage 1: Proximal PD
  - 3 mo

  Stage 1a
  - In Vitro Mini-models of drug x

  Stage 1b
  - In Vivo initial model of drug x
    - Target transport, binding
    - Proximal PD

  Stage 2: Therapeutic response
  - 11 mo

  Stage 2a
  - Literature review

  Stage 2b
  - Equations and parameters, model check, refinement

  Stage 2c
  - Virtual population calibration, validation, model check, refinement

  Stage 2d
  - Response prediction in anti-PD-1 progressed MEL

QSP Lead: Yougan Cheng
Overview of I-O platform 1

Mini-model(s) parameterize key asset pathways from in vitro data

Asset proximal pathway model

Model checks, alternate parameterizations

Therapeutic response model

Model checks, Alternate VPs, Statistical calibration

CCR7+

CCR7-

CD8-AgS
Lymph node

CD8-Blast

CD8-AgS

CD8

CD8

NK

Cancer

APC

Tumor

Treg

MΦ

• Cell-cell contact, confinement & 2D molecular interactions
• Cancer killing
• Lifecycle
• Recruitment
• Inhibitory factors

Combination therapeutic response model
Developed in SimBiology:
66 ODEs,
236 reactions,
212 rules

QSP Lead: Yougan Cheng
Implemented nivolumab mechanism

- Mini-model(s) parameterize key asset pathways from in vitro data
- Asset proximal pathway model
- Model checks, alternate parameterizations
- Therapeutic response model
- Model checks, Alternate VPs, Statistical calibration

**Diagram:**
- CCR7+
- CCR7-
- CD8-AgS
- CD8-Blast
- APC

**Cell Types:**
- Lymph node
- Tumor
- Treg
- CD8
- MΦ
- NK
- Cancer

**Relief of:**
- PD1-mediated suppression

**QSP Lead:** Yougan Cheng

**WHO ARE YOU WORKING FOR?**

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**Bristol-Myers Squibb**
Implemented ipilimumab mechanism

Asset proximal pathway model

Mini-model(s) parameterize key asset pathways from in vitro data

Model checks, alternate parameterizations

Therapeutic response model

Model checks, Alternate VPs, Statistical calibration

Key assumptions:

• Immune suppression in TME primarily through Treg-dependent mechanisms
• ipilimumab acts in lymphoid tissues by expanding amount of CD8s that can attack tumor
• ipilimumab acts in TME mainly by CTLA4 expressor depletion

CCR7+ CCR7-

CD8-AgS CD8-Blast

CD8-AgS

APC

 APC-dependent Treg ADCC

Tumor

Bound-FC dependent CD8 ADCC

QSP Lead: Yougan Cheng

WHO ARE YOU WORKING FOR?

Bristol-Myers Squibb
Algorithmic VPop development

Is the incorporated physiologically feasible mechanistic variability able to explain the observed biomarker/response diversity?

Run on 64 core server using QSPToolbox:

https://github.com/BMSQSP/QSPToolbox

“expandVPopEffN.m”


QSP Lead: Yougan Cheng
Response calibration

• Focus on 3 month time point (first lesion scans; minimize dropouts)
• Calibrate to all patients where we have data at 3 months
• Calibrate to on-treatment VPs

The VPop is fitted against various biomarker **bins, mn/sd and distributions** (a total of **51 simultaneous fits**). The **composite goodness of fit (range: 0-1)** of these 51 simultaneous fits is **0.71**. Typically, a VPop is considered accepted if the composite goodness of fit is **greater than 0.05**.
VPop captures clinical distributions

Cumulative distribution functions (CDFs) shown

- Data
- VPop

QSP Lead: Yougan Cheng
Nivolumab: simulated lesion response and PDL1

VPop (weighted VPs)

90% percentile (shaded area) and median (blue solid line) in Vpop
Red line represents the 90% percentile in the data

Day 56, relative SLD (fraction)

Day 84, relative SLD (fraction)

All VPs (2651 VPs)

Day 0, PDL1 expression

Day 28, PDL1 expression

QSP Lead: Yougan Cheng
Model validation: BLIND PREDICTION of nivolumab & ipilimumab combo therapy

Vpop 90% percentile (shaded area) and median (blue solid line) in VPop

Day 84, relative SLD (fraction)

Relative SLD (fraction)

All VPs

Sampled using 200 virtual trials of 200 VPs each

QSP Lead: Yougan Cheng
Model validation: BLIND PREDICTION of ipilimumab after progression on nivolumab

- Ipilimumab efficacy after progression on anti-PD1 therapy in melanoma:
  - 0.13 (N=97) Long V, et al. Pigment Cell melanoma Res 2017

- “In summary, although there are no prospective trials to assess the efficacy of ipilimumab in patients with metastatic melanoma whose disease progressed during frontline treatment with an anti–PD-1 agent, we can surmise that approximately 10% to 20% of patients will achieve a response to second-line ipilimumab.” -Svetomir Markovic and Richard W. Joseph

QSP Lead: Yougan Cheng
Model impact for drug x (so far)

- Proximal PD model predicted some clinical immunological activity at a very low starting dose for drug x early in development, subsequently confirmed.

- Current model impacts with development team:
  - Model predicts drug x has a biphasic dose response in anti-PD-1 progressed MEL, so far qualitatively observed in a broader dose escalation cohort but small N.
  - Model has been used to provide guidance on unexpected relationship observed between cell type y and lesion response.
  - Model has been used to provide guidance on the impact of dose fractionation on cell type y and lesion response.

- CURRENT CHALLENGES
  - Note calibrating tumor-type specific responses.
  - Have small N and multiple tumor types in early clinical development.
New programs: stepwise addition of new MOAs

- Each model iteration associated with a new clinical asset
- Additional data for clinical calibration (deconvolution)
- Adding new pathways one-at-a-time and verifying fit to data and predictions still good
- gMDSC/mMDSC, M1/M2 macrophage polarization, NK life cycle, DC maturation, soluble mediators; Th subsets
Calibration of even more tumor endpoint distributions

- Truer CR classification and CR/PD censoring, here out to 6 months
- Using RNA-seq to calibrate cell markers or net protein production where it makes sense

BOR for ipilimumab and nivolumab
Up to 6 months so far
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