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

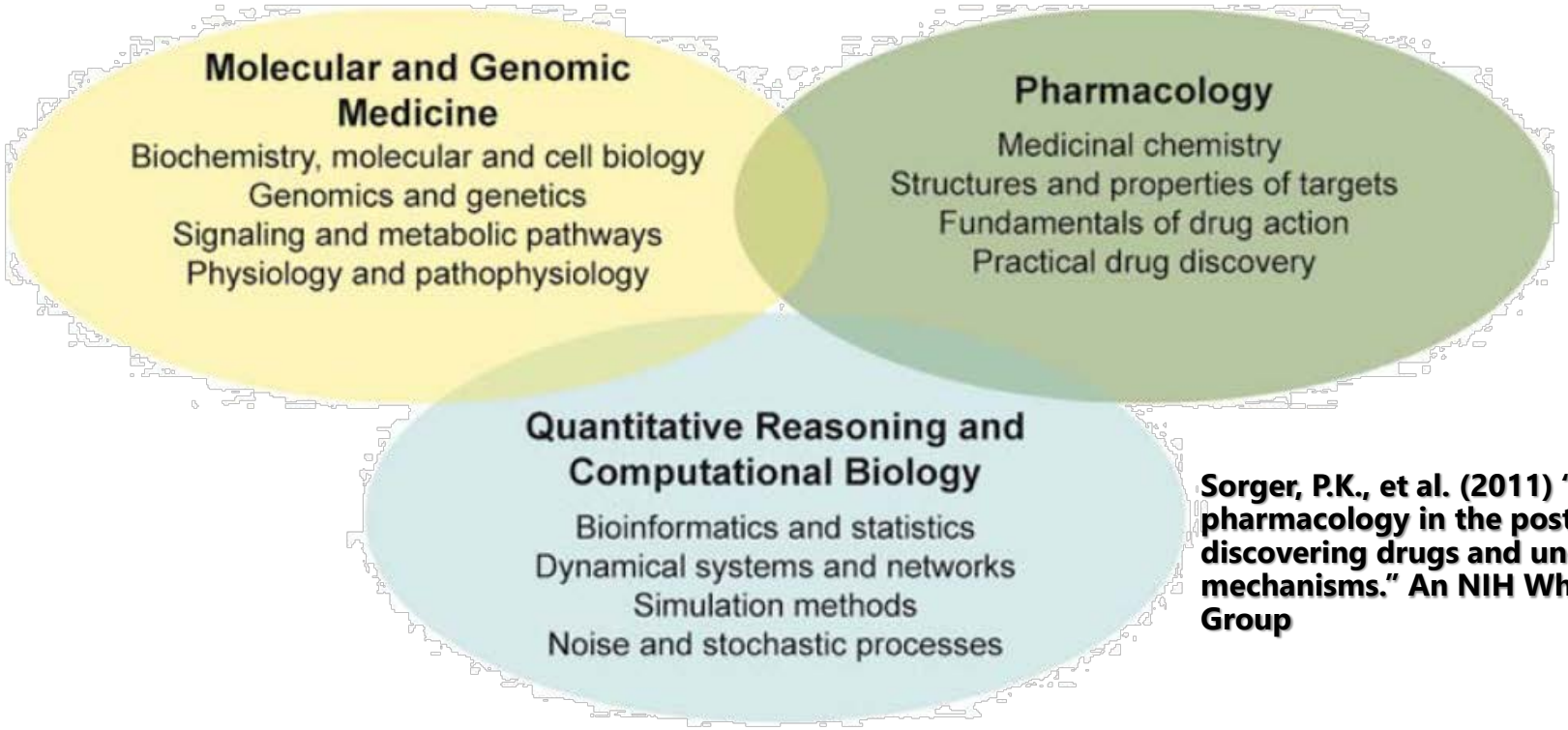
Immunoscience

- Rheumatoid Arthritis
- Immunogenicity
- Crohn's Disease
- Ulcerative Colitis
- Psoriatic Arthritis
- Systemic Lupus Erythematosus

Fibrosis

- Nonalcoholic Steatohepatitis
- Pulmonary Fibrosis

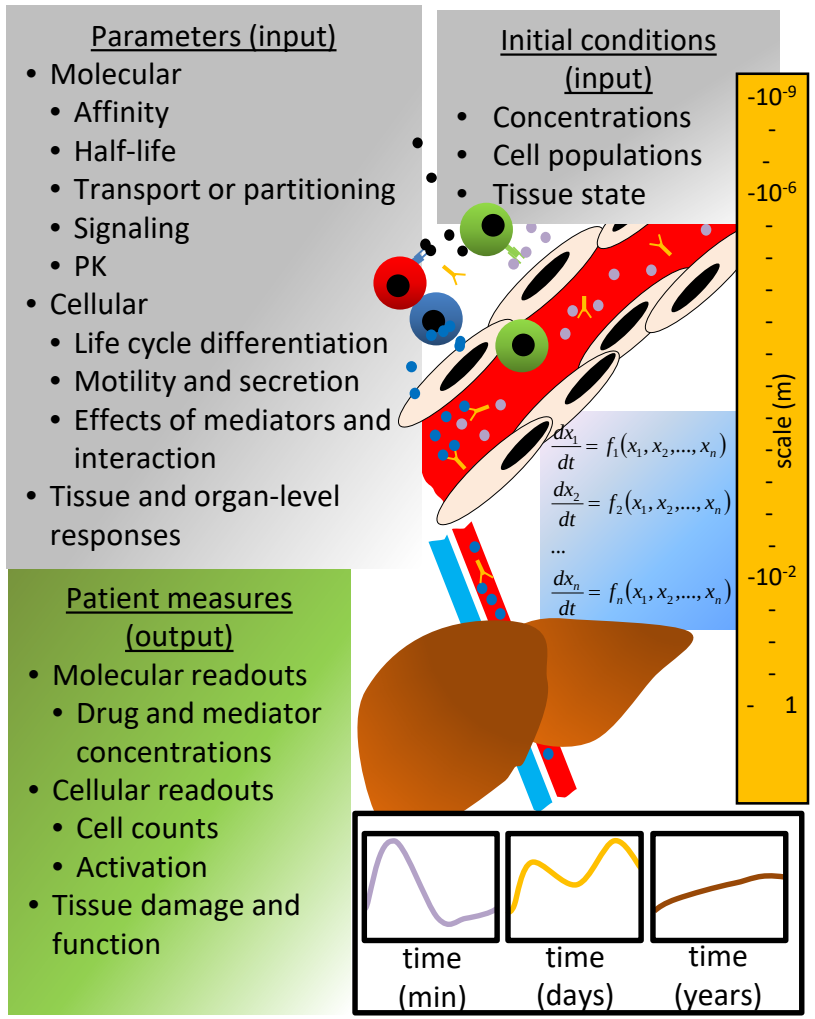
Quantitative Systems Pharmacology (QSP)



Sorger, P.K., et al. (2011) "Quantitative and systems pharmacology in the post-genomic era: new approaches to discovering drugs and understanding therapeutic mechanisms." An NIH White Paper by the QSP Workshop Group

"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)

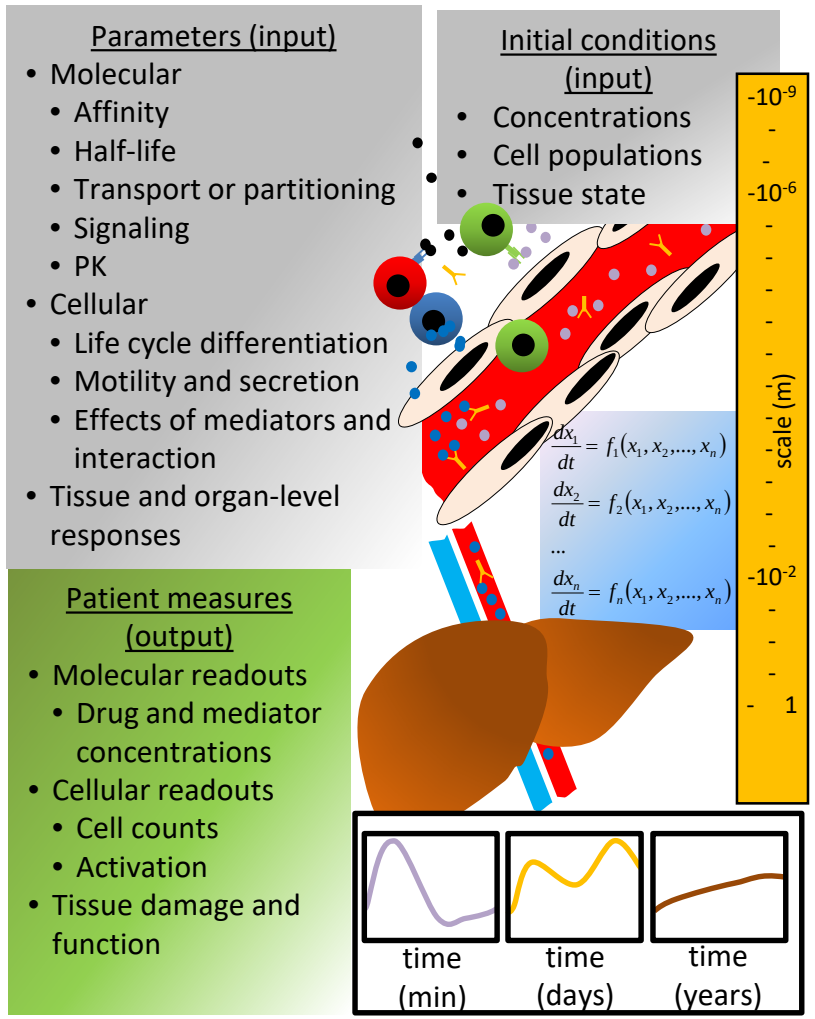
QSP model introduction (1)



***Drug Discov Today (2013)* 18(3-4): 116-127**

- 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)



***Drug Discov Today (2013)* 18(3-4): 116-127**

- 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

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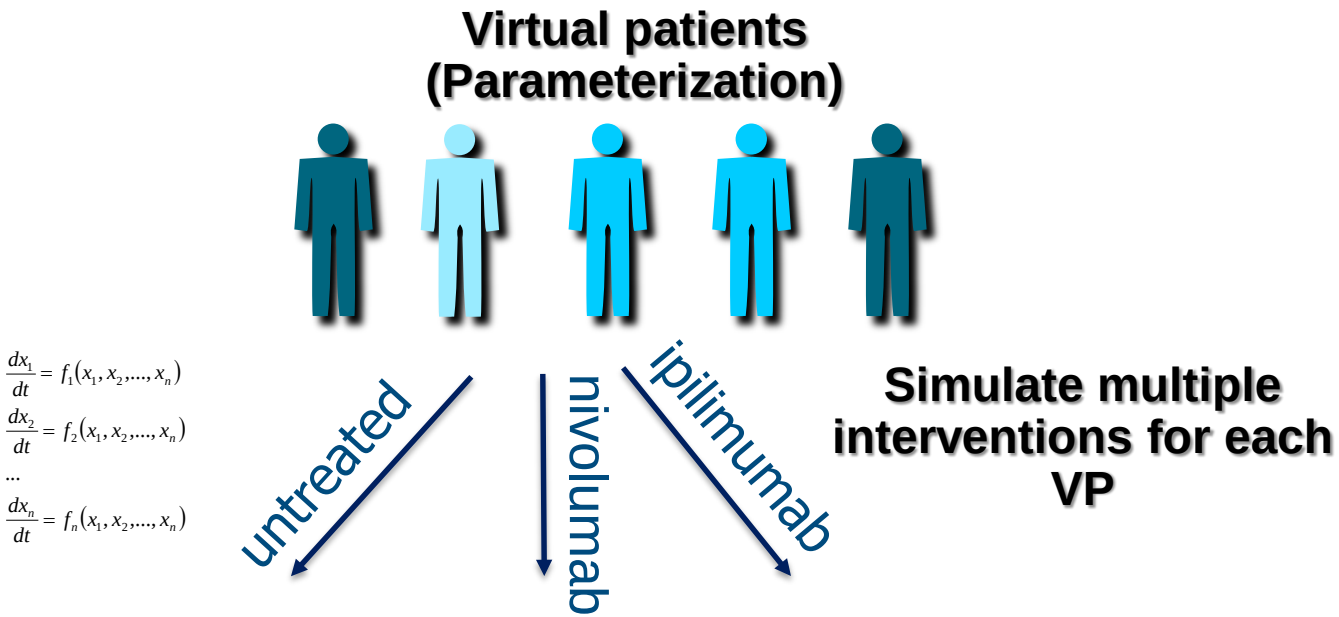
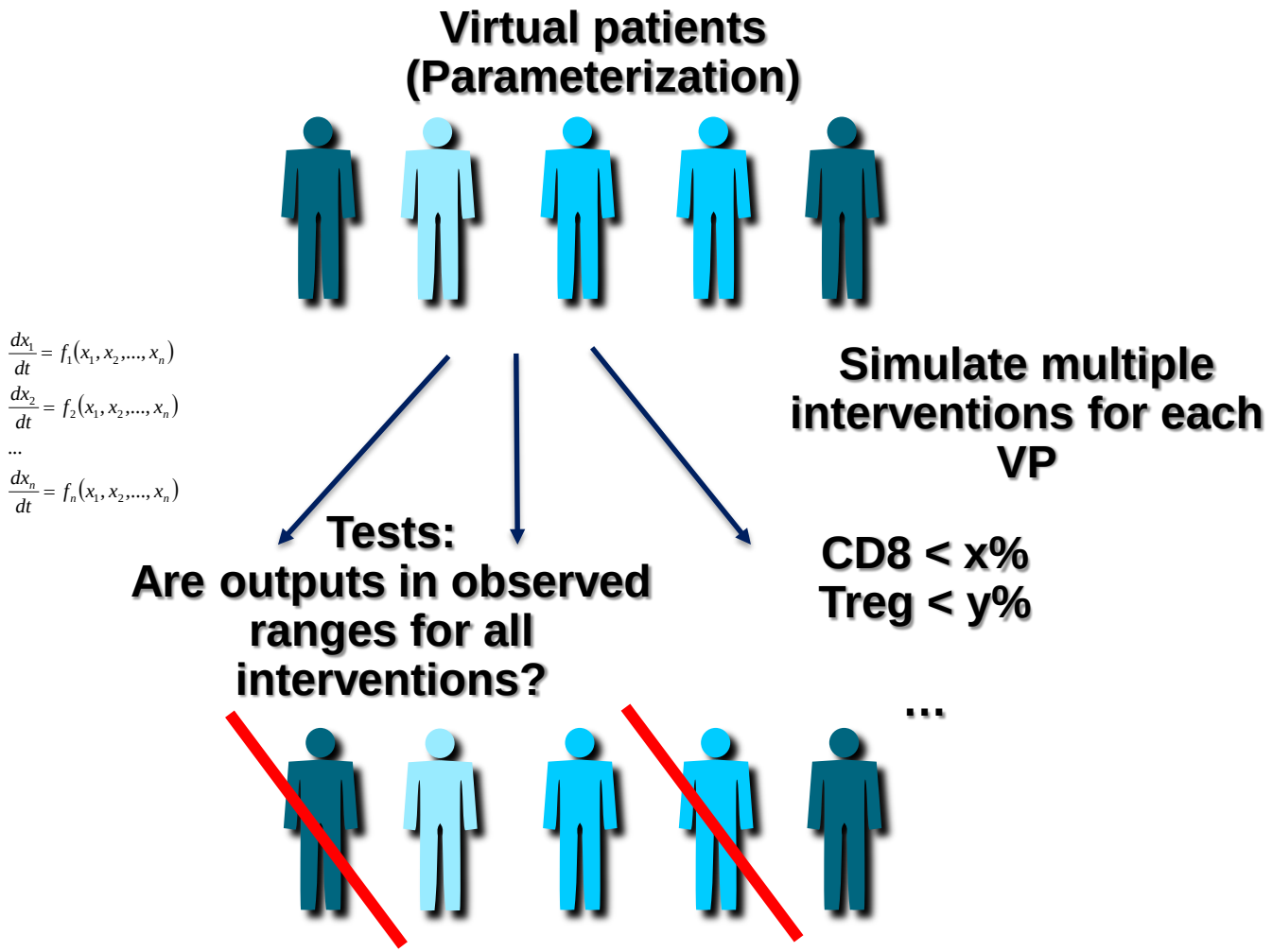
Methods: virtual patient cohort (1)



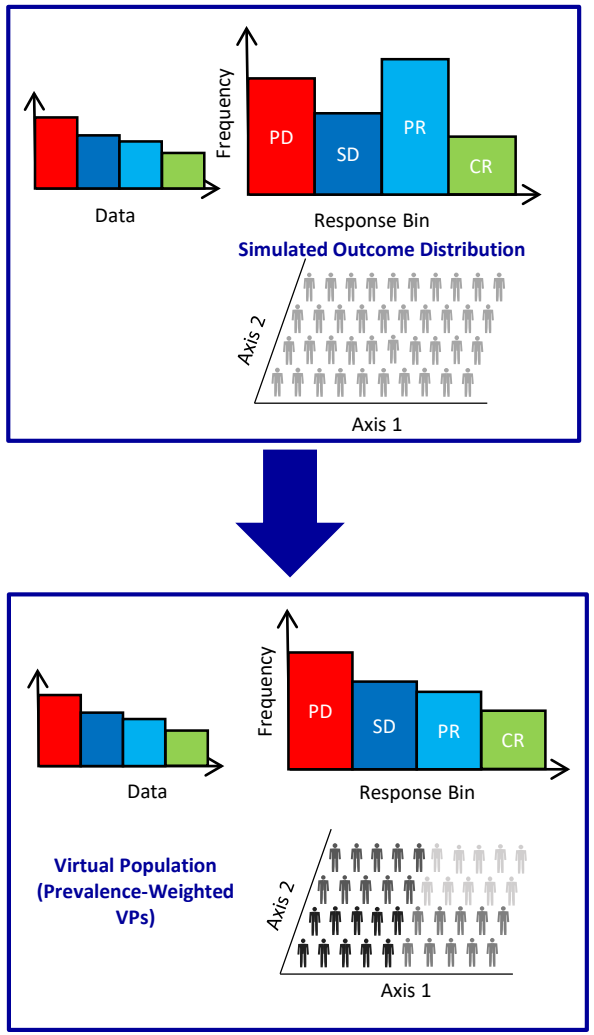
- Alternate model parameterizations are sampled (biomarker diversity)
- Multiple interventions (therapies) are simulated for each virtual patient

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

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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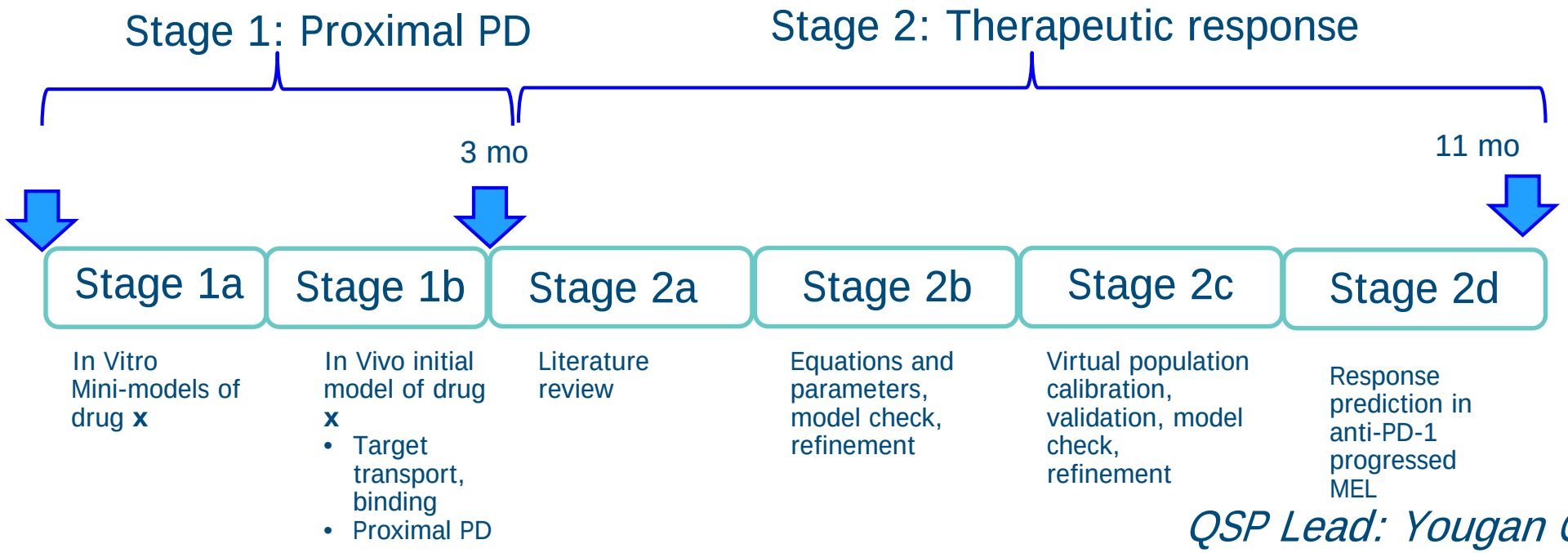
I-O platform 1: initial development to support dose expansions & ongoing trials for drug x

- 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



QSP Lead: Yougan Cheng

Overview of I-O platform 1

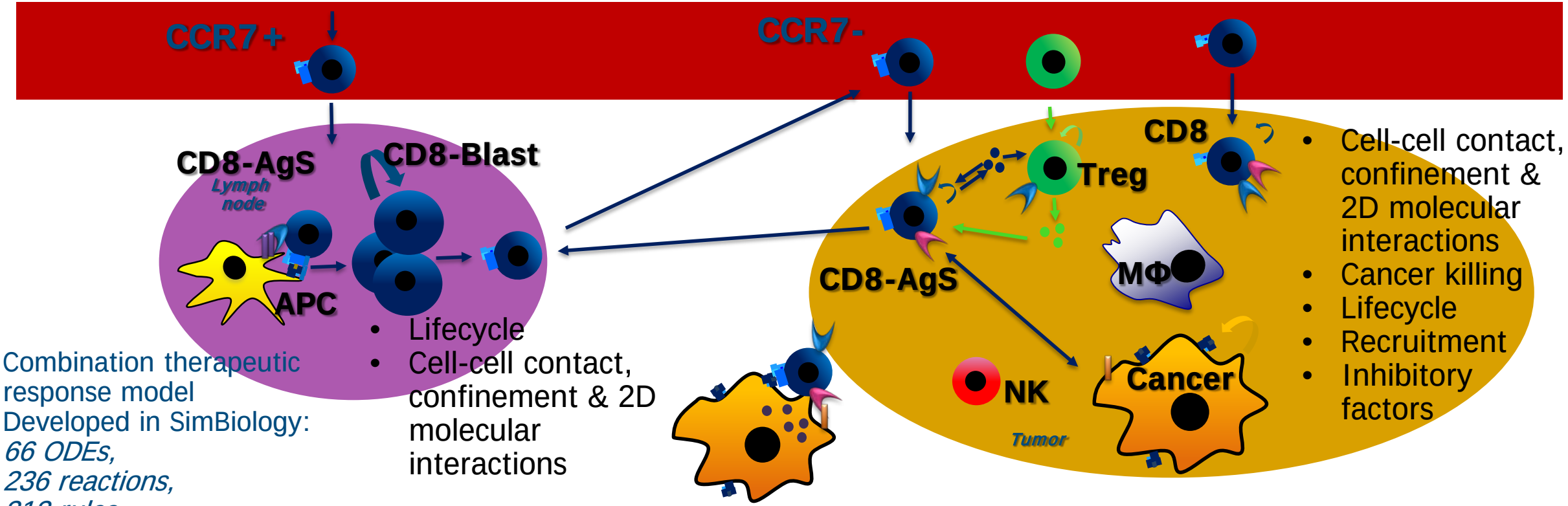
Mini-model(s) parameterize key asset pathways from in vitro data

Asset proximal pathway model

Model checks, alternate parameterizations

Therapeutic response model

Model checks, Alternate VPs, Statistical calibration



- Lifecycle
- Cell-cell contact, confinement & 2D molecular interactions

- 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

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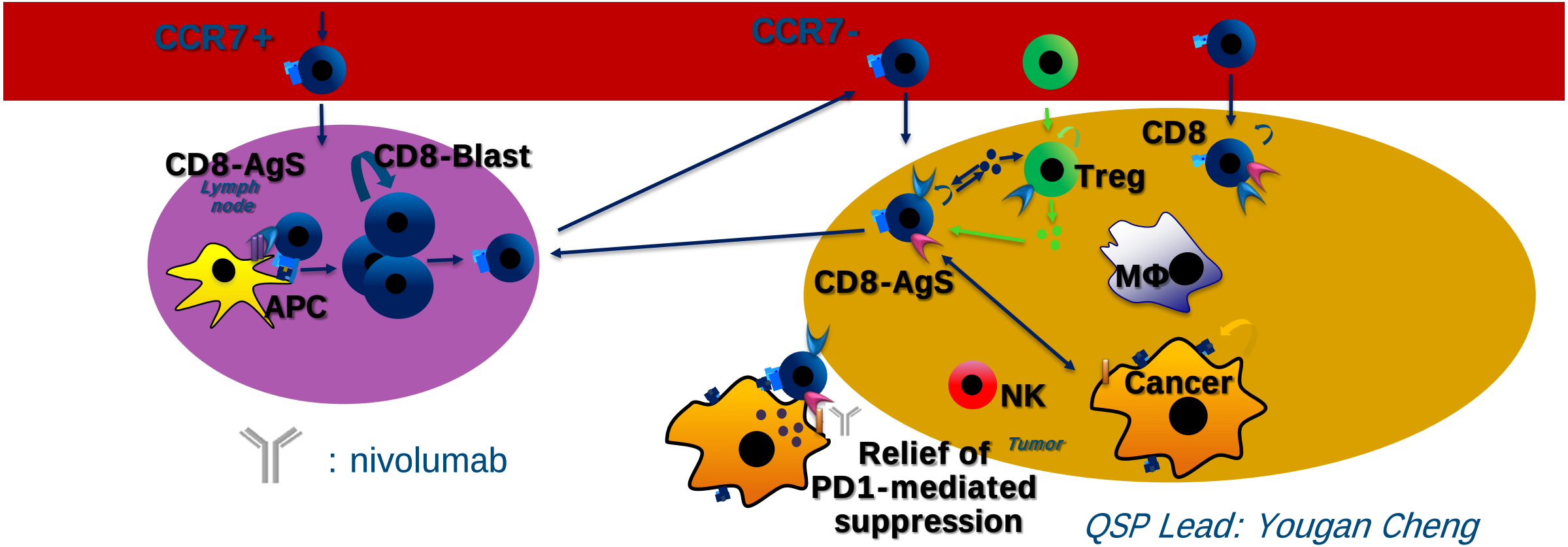

QSP Lead: Yougan Cheng

Implemented ipilimumab mechanism

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

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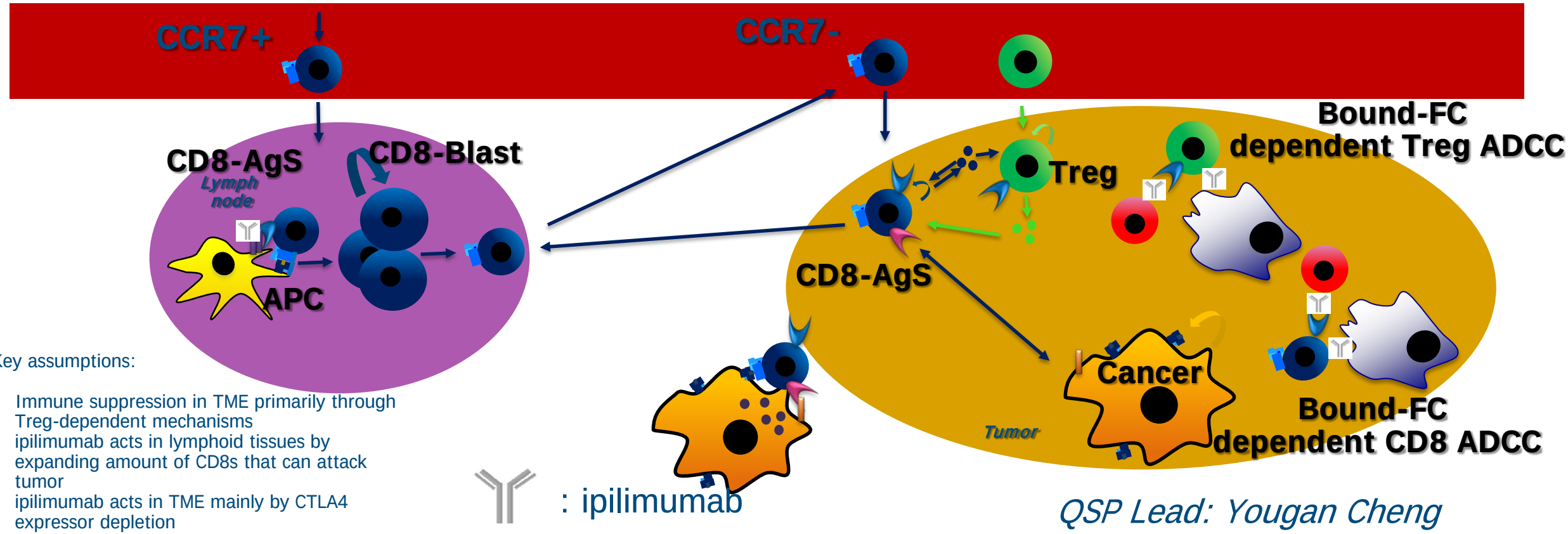


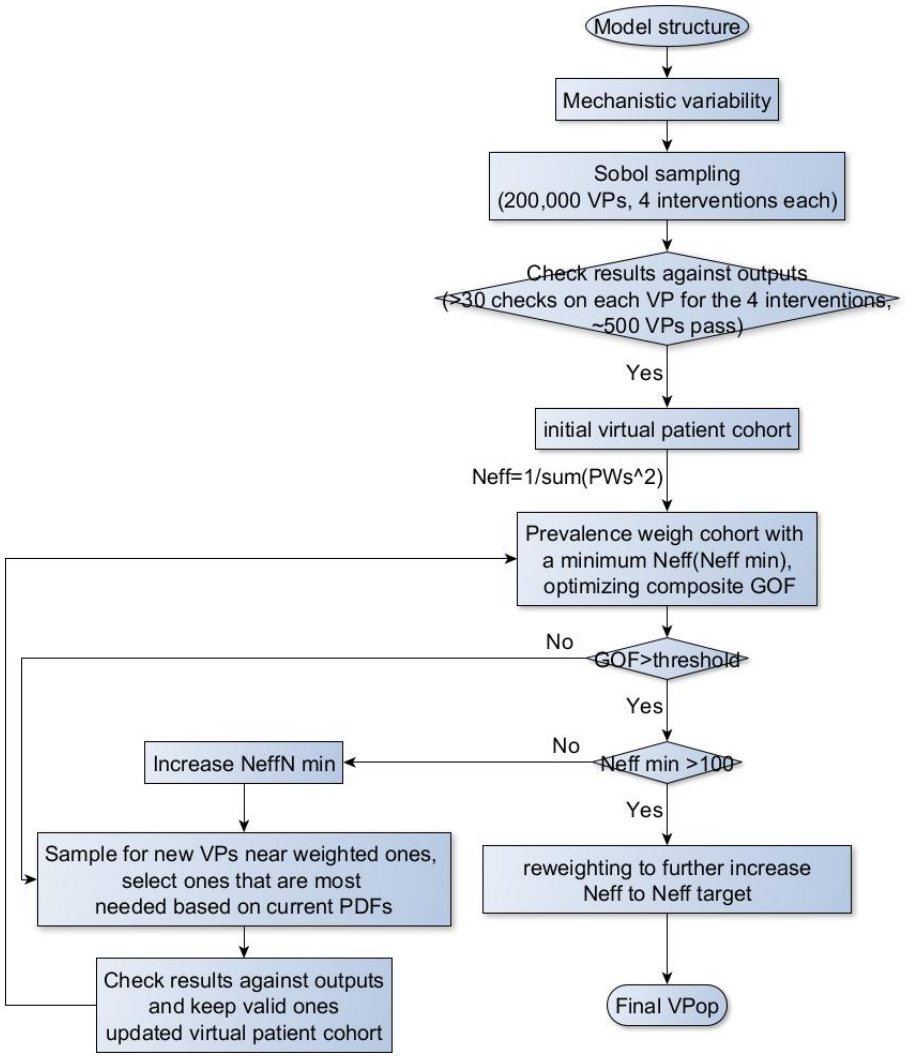
Key assumptions:

- 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

: ipilimumab

QSP Lead: Yougan Cheng

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"

Cheng Y, et al. (2017) QSP Toolbox: Computational Implementation of Integrated Workflow Components for Deploying Multi-Scale Mechanistic Models. AAPS J 19(4), 1002-1016.

QSP Lead: Yougan Cheng

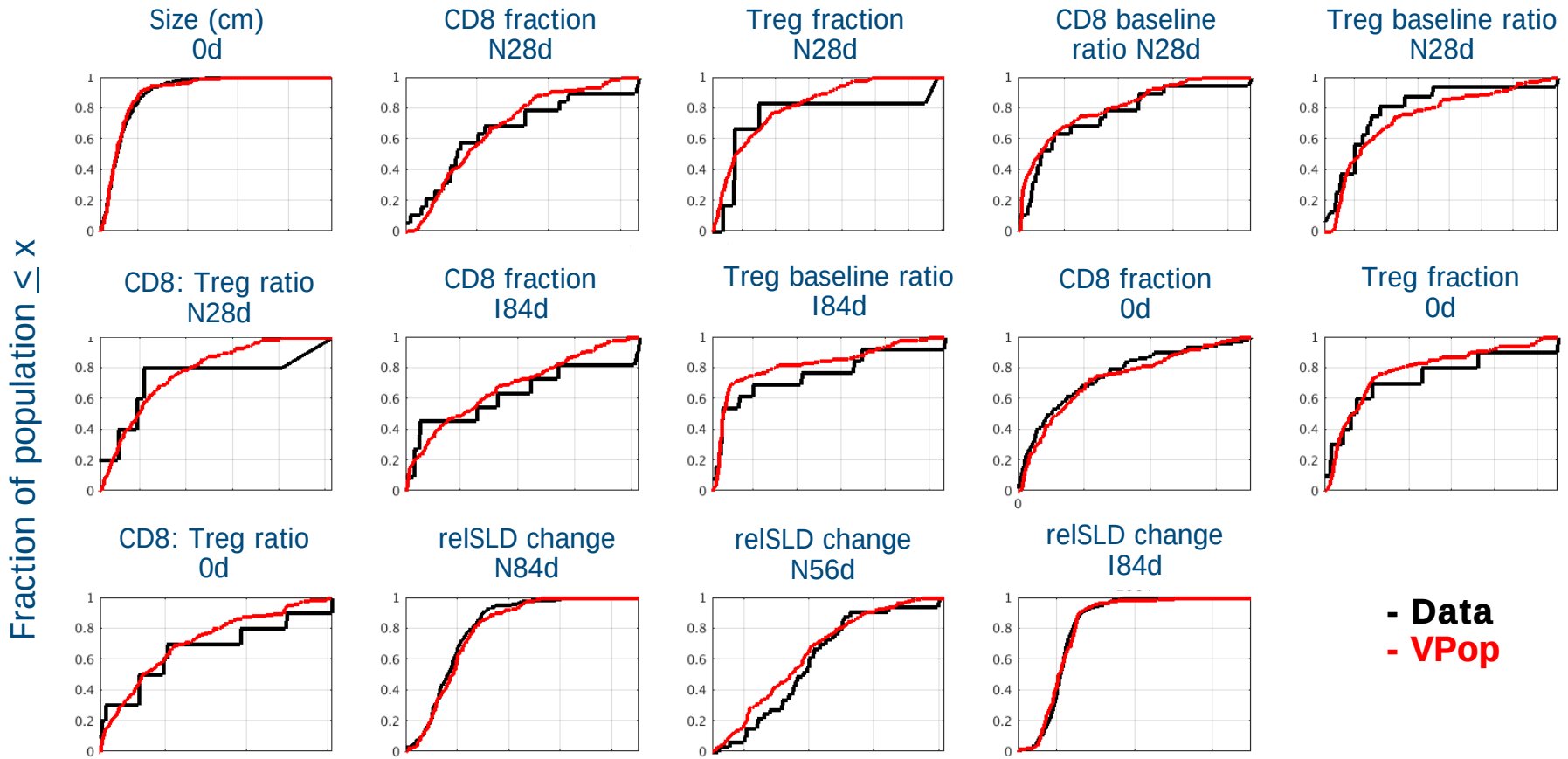
Response calibration

- 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***.

QSP Lead: Yougan Cheng

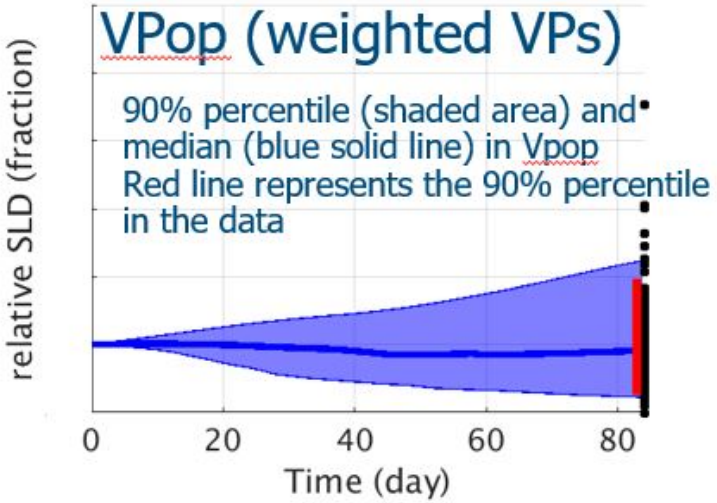
VPop captures clinical distributions

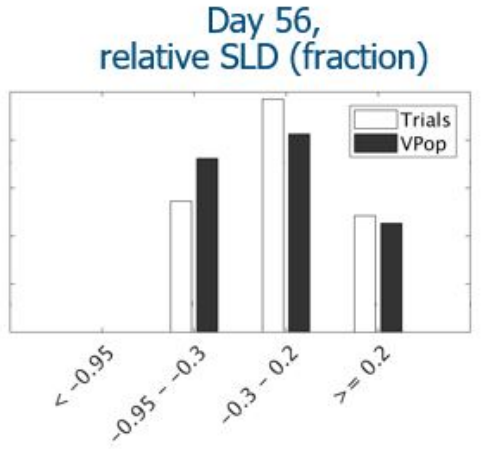


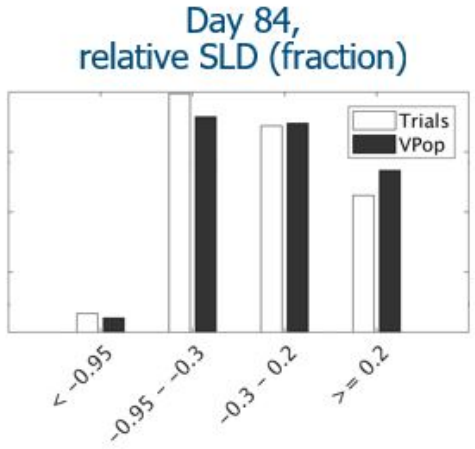
Cumulative distribution functions (CDFs) shown

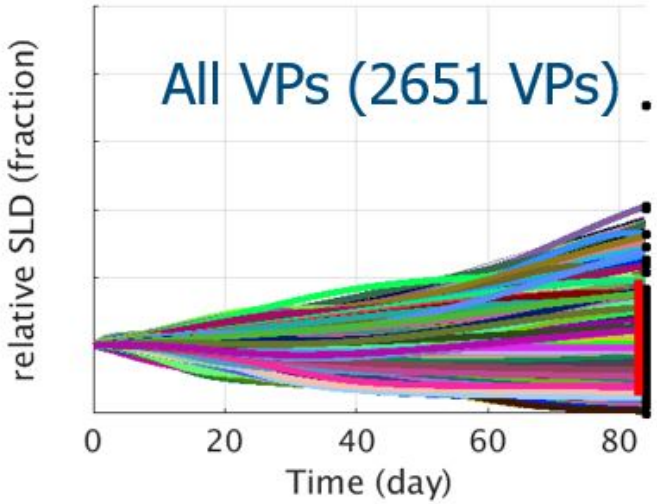
QSP Lead: Yougan Cheng

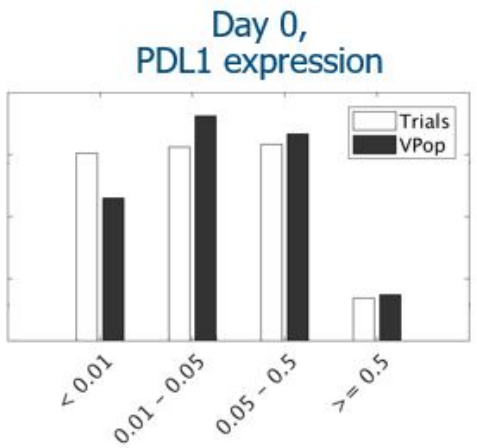
Nivolumab: simulated lesion response and PDL1

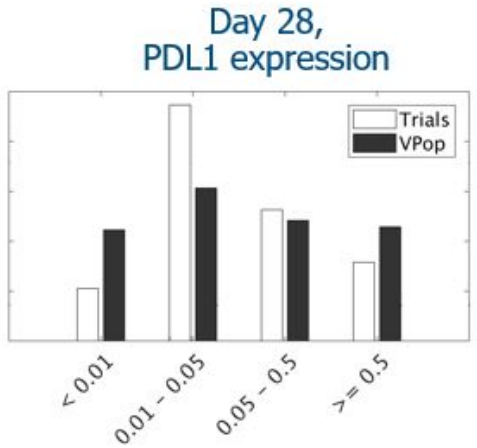






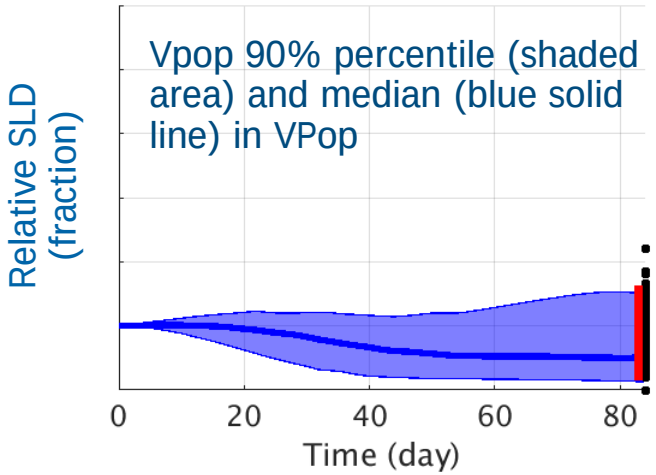


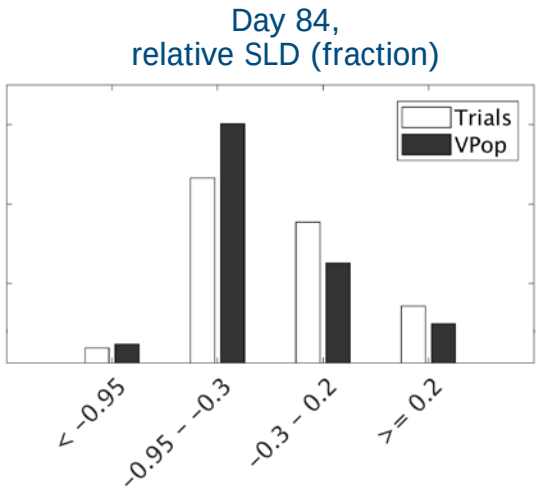


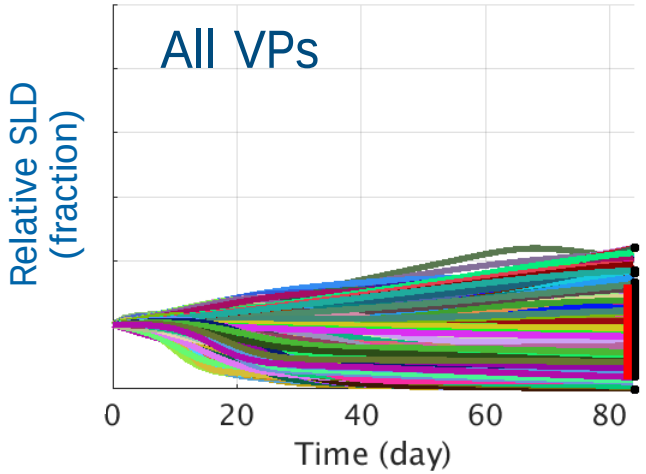


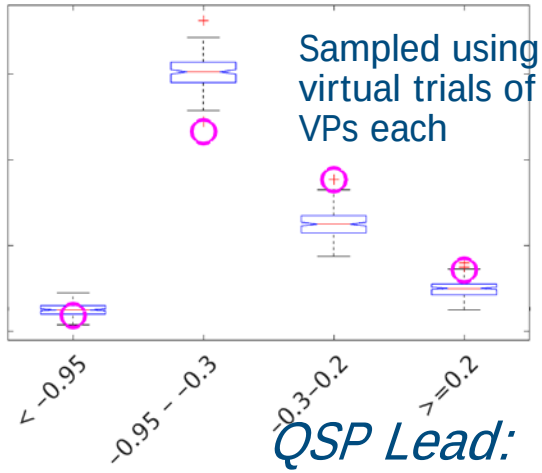
QSP Lead: Yougan Cheng

Model validation: BLIND PREDICTION of nivolumab & ipilimumab combo therapy



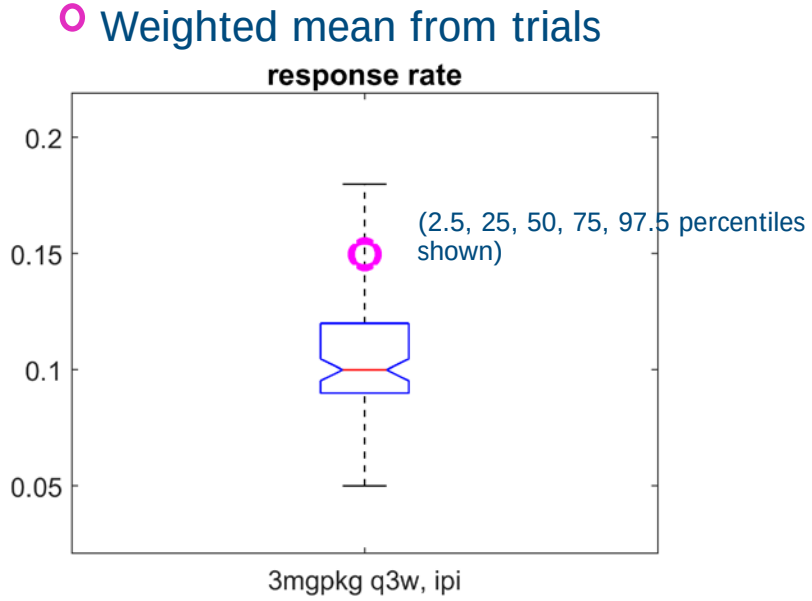






QSP Lead: Yougan Cheng

Model validation: BLIND PREDICTION of ipilimumab after progression on nivolumab



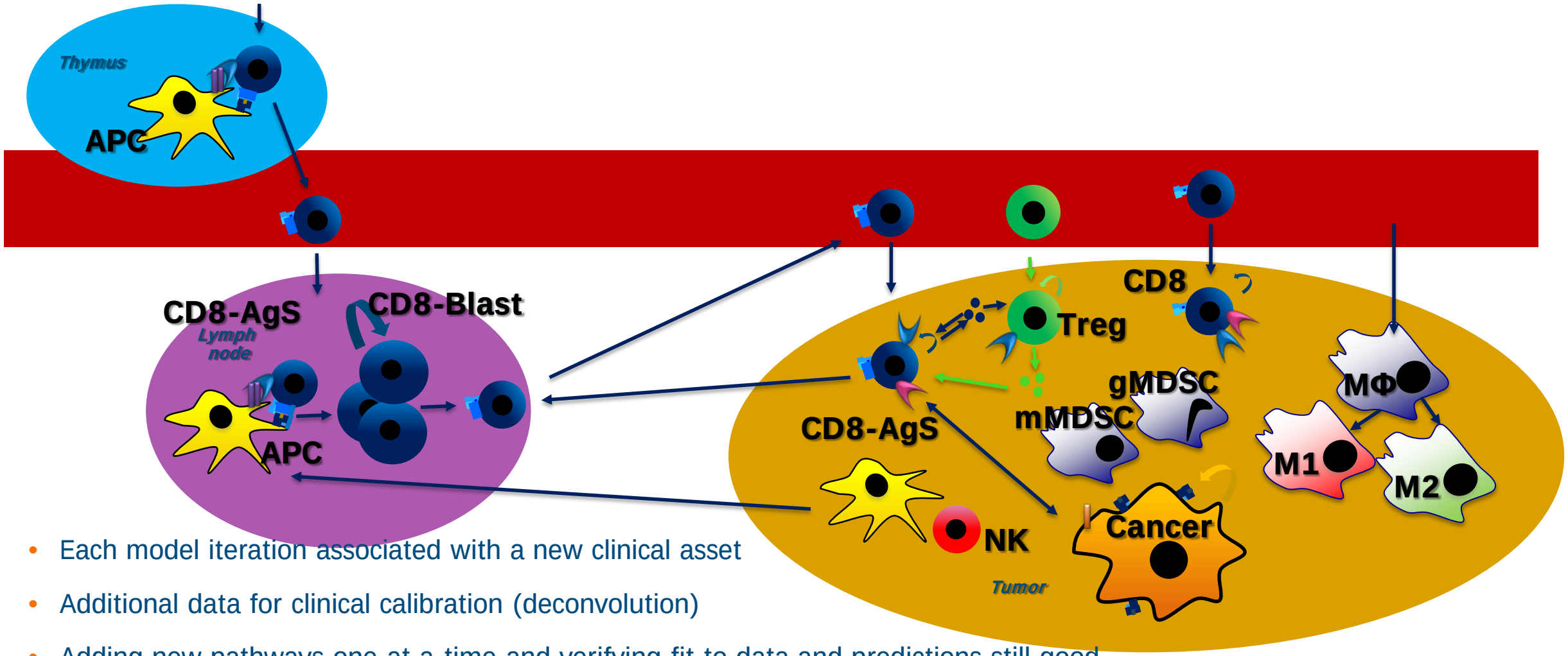
- Ipilimumab efficacy after progression on anti-PD1 therapy in melanoma:
  - 0.5 (N=8) Jacobsoone-Ulrich A, et al. Melanoma Res. 2016
  - 0.1 (N=40) Bowyer S, et al. Br J Cancer. 2016
  - 0.22 (N=9) Aya F, et al. Future Oncol. 2016
  - 0.16 (N=47) Zimmer L, et al. Eur. J. Cancer 2017
  - 0.13 (N=97) 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)

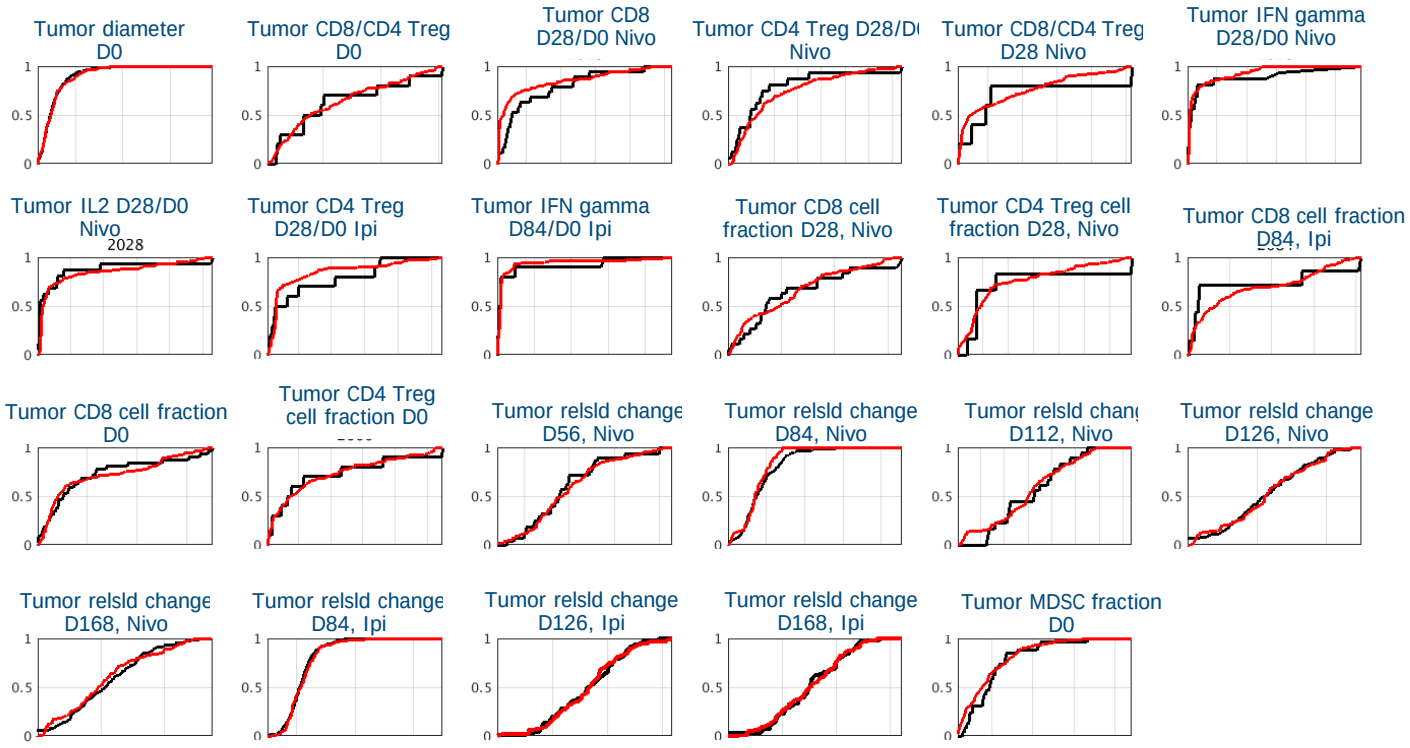
- Proximal PD model predicted some clinical immunological activity at a very low starting dose for drug x early in development, subsequently confirmed
- Current model impacts with development team
  - Model predicts drug x has a biphasic dose response in anti-PD-1 progressed MEL, so far qualitatively 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

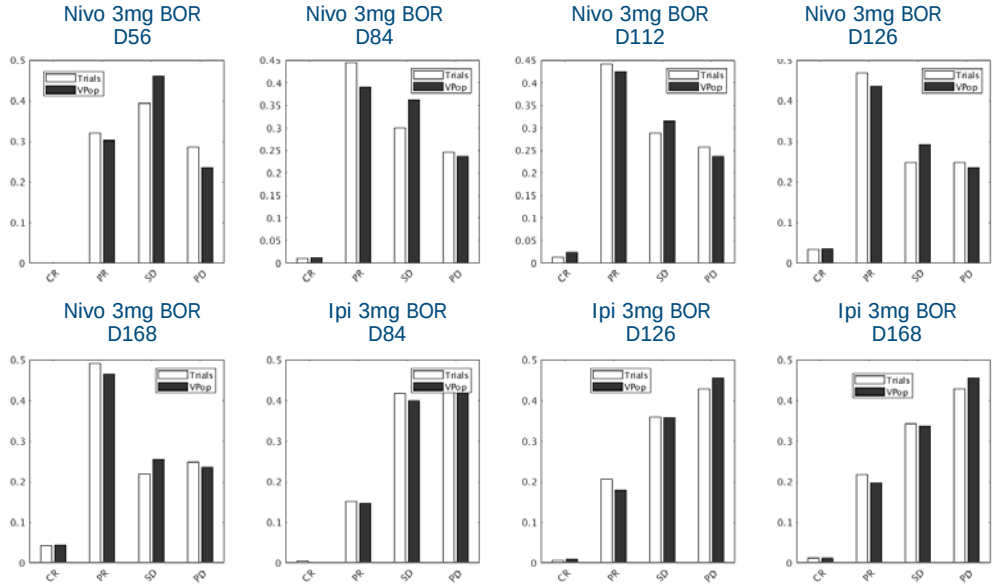


- Each model iteration associated with a new clinical asset
- Additional data for clinical calibration (deconvolution)
- Adding new pathways one-at-a-time and verifying fit to data and predictions still good
- gMDSC/mMDSC, M1/M2 macrophage polarization, NK life cycle, DC maturation, soluble mediators;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

Calibration of even more tumor endpoint distributions



BOR for ipilimumab and nivolumab Up to 6 months so far



- 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

Acknowledgements

- Session organizers
  - Jeff Saucerman, Feilim Mac Gabhann, Colleen Kuemmel, Sarah Dunsmore
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- BMS CP
  - Akintunde Bello, Amit Roy, Ming Zheng
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