Mechanistic modeling of the cancer-immunity cycle: a platform approach in I-O

Brian J. Schmidt, PhD

ASCPT

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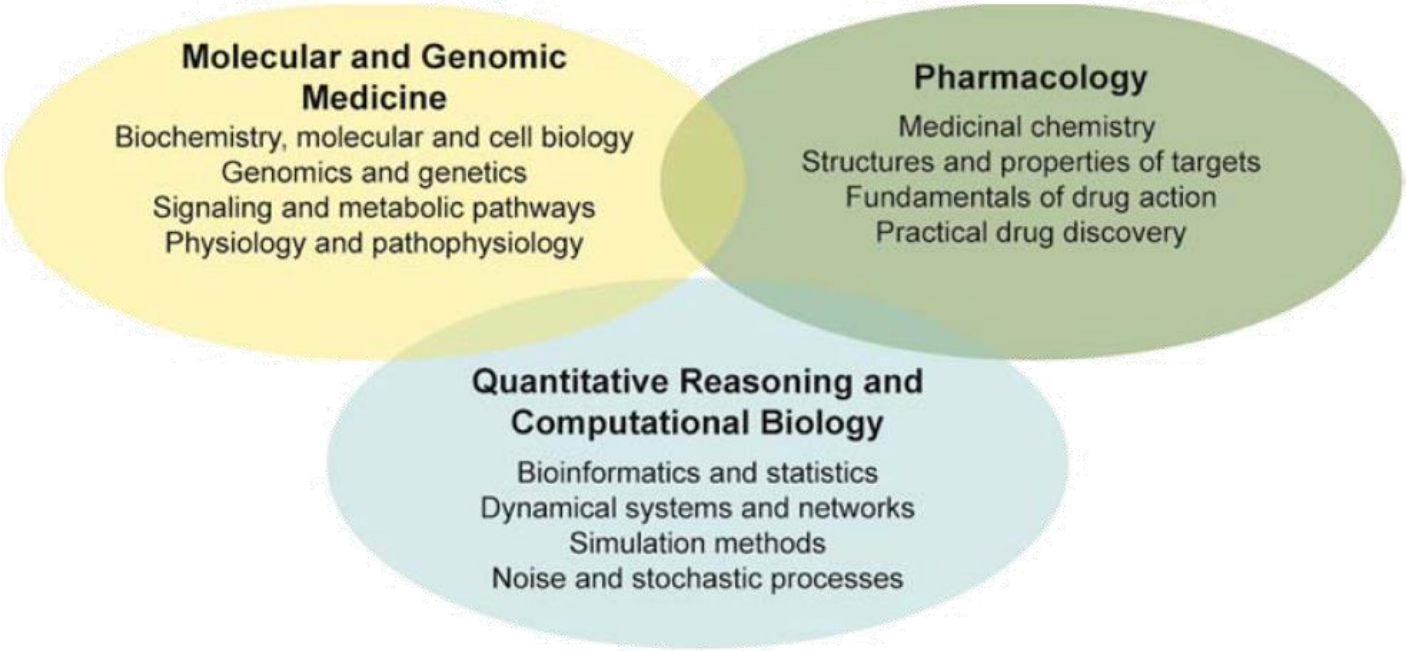
Bristol-Myers Squibb

Agenda

- Discussion of quantitative systems pharmacology (QSP) and mechanistic QSP platform models
- QSP at Bristol-Myers Squibb
- Melanoma immuno-oncology QSP platform
  - Melanoma I-O QSP platform biological scope
  - Pathway-level results in a virtual patient (VP)
- Example with virtual populations (VPops)
- Software & infrastructure considerations

Quantitative (and) Systems Pharmacology

A multidisciplinary science that takes a mathematical approach to pharmaceutical R&D by integrating methodologies from pharmaceutical sciences, engineering, and systems biology.



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,

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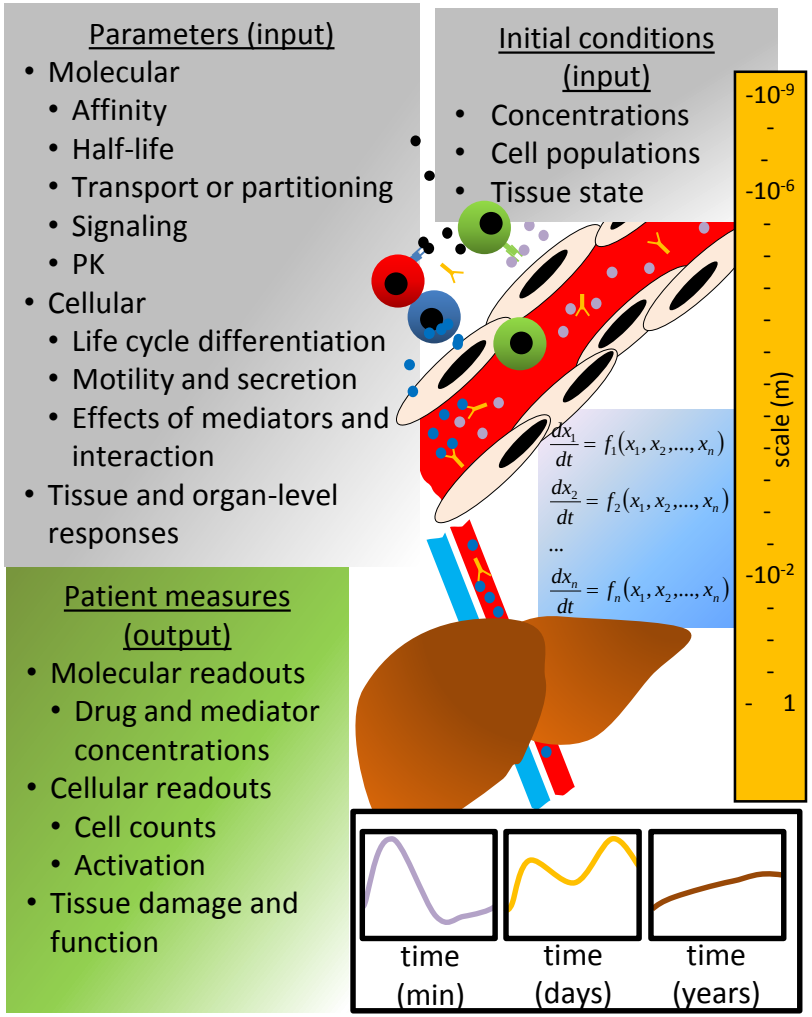
QSP platform model scope



- **QSP platform models mechanistically link target modulation to disease outcome**
- **System focus: can create the link before trial data are available for a new intervention/therapy**
- **Mechanistic (biomarker) and outcome data are used to calibrate the model for related therapies or to evaluate model performance**
- **Models are refined as additional data are available**
- **Potentially resource-intensive but broad application**

Schmidt, B. J., et al. (2013). "Mechanistic systems modeling to guide drug discovery and development." Drug Discov Today 18(3-4): 116-127

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QSP at BMS

- **6 Dedicated QSP modelers in Quantitative Clinical Pharmacology group (we're hiring!)**
- **Substantial & continued investment in platform development and approaches**

Oncology & Immuno-Oncology

- Melanoma I-O Platform
- Antibody-Drug Conjugate Platform
- Physiologically-Based Tumor Receptor Occupancy

Immunoscience

- Rheumatoid Arthritis
- Immunogenicity

Cardiovascular Disease

- Heart Failure
- Coagulation/Thrombosis

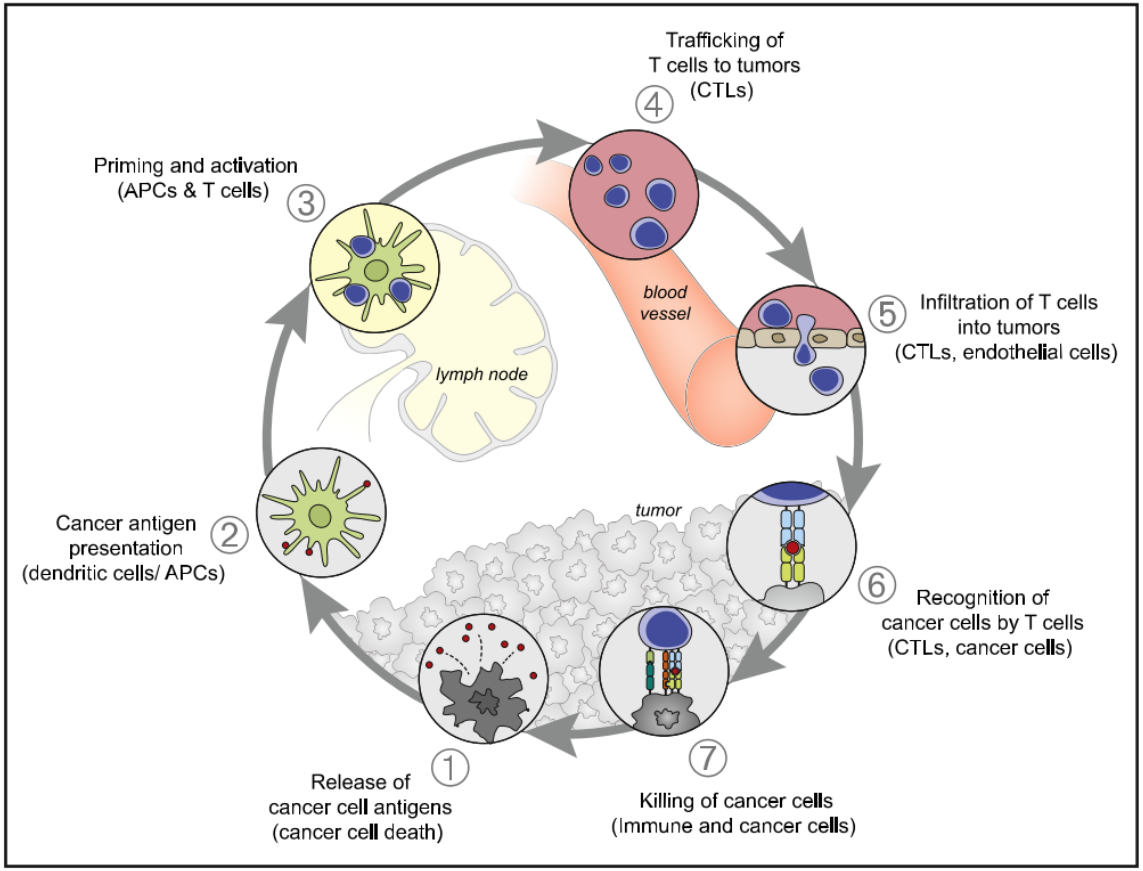
Fibrosis

- Nonalcoholic Steatohepatitis

Additional Platform Resources

- Diabetes/Metabolic Diseases

Melanoma immuno-oncology platform biological scope: cancer-immunity cycle



Chen, D. S. and I. Mellman (2013). "Oncology meets immunology: the cancer-immunity cycle." Immunity 39(1): 1-10.
RightsLink License 3814541352883.

Melanoma immuno-oncology platform: staged development

Pilot (Stage 1)

1. Map development
   - Lesion
   - Blood
   - Cells
   - Mediators
   - Interactions
   - Therapies
2. Equations
3. Parameterize, calibrate one VP

5 months

Complete cancer-immunity cycle (Stage 2)

1. Map development
   - Lymph node
   - Tumor lymphoid structures
   - Angiogenesis
   - Metastatic potential
   - Cytokine regulation expansion
   - Additional cell types
   - Additional therapeutic target pathway modulation
2. Equations
3. Parameterize
4. Calibrate a set of VPs

18 months

- Develop mechanistic hypotheses
- Starting point for virtual populations
- Compare options for combination therapies

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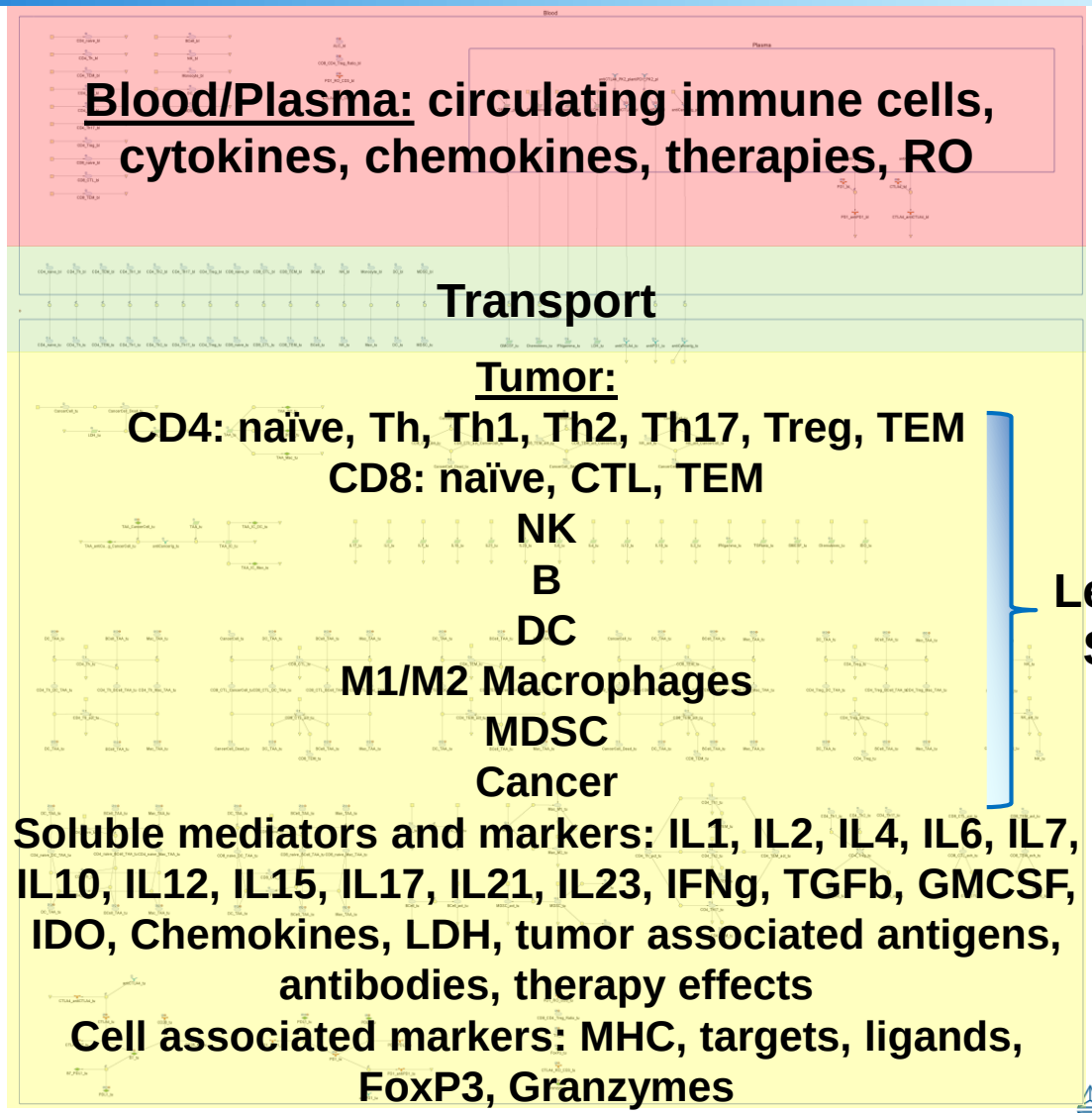
Melanoma immuno-oncology pilot project: cells, cytokines, and biomarkers

149 species
249 reactions
1014 parameters



Development tool:
MATLAB SimBiology

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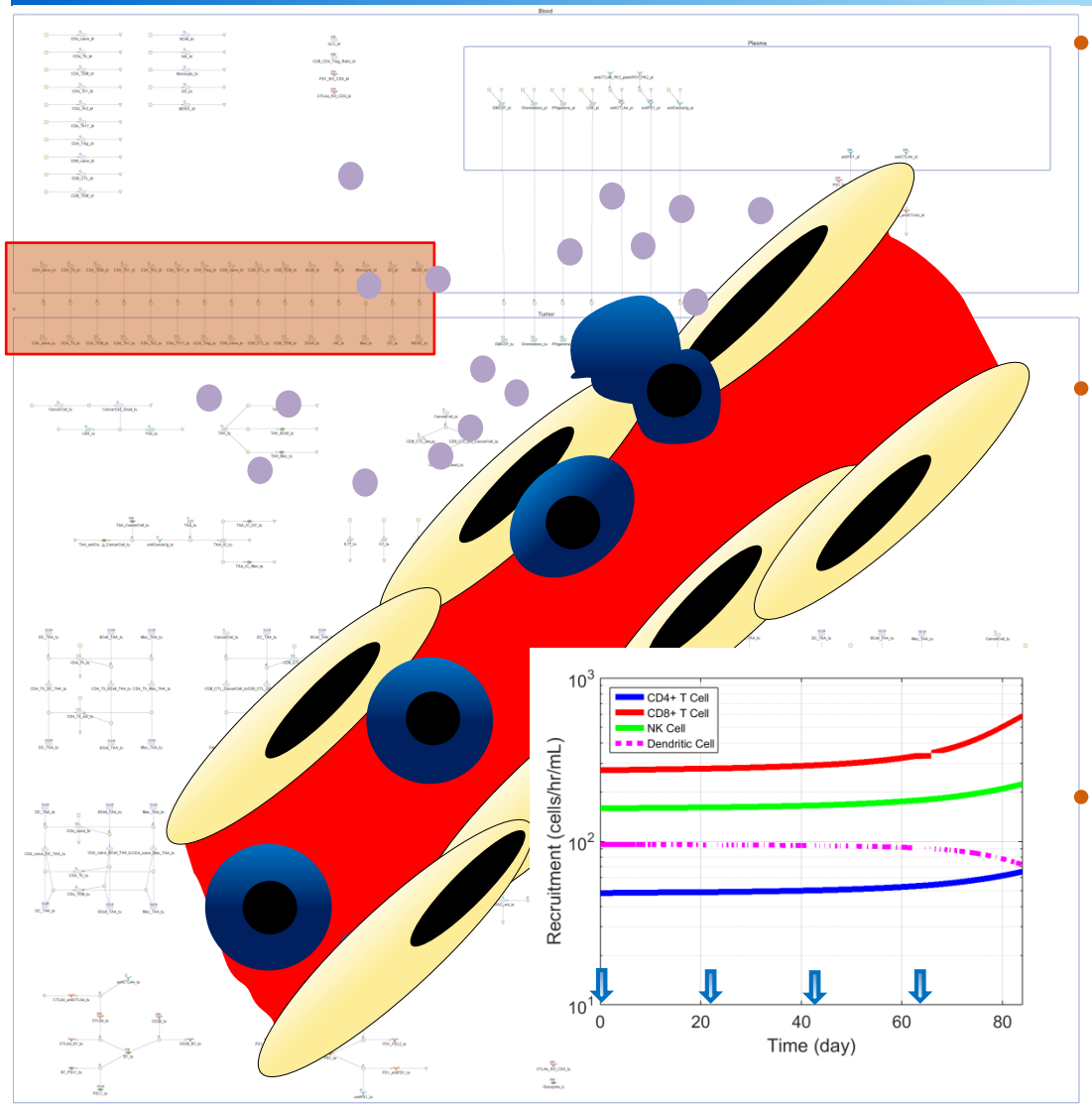
Representation of the cancer-immunity cycle: immune cell trafficking and tumor infiltration



- I-O therapy administered in example simulation to enable an effective immune response
- Pool of immune cells in blood represents production of immune cells throughout the body (e.g., lymph nodes, bone marrow)
- Tumor infiltration is regulated by chemokines released within the tumor microenvironment

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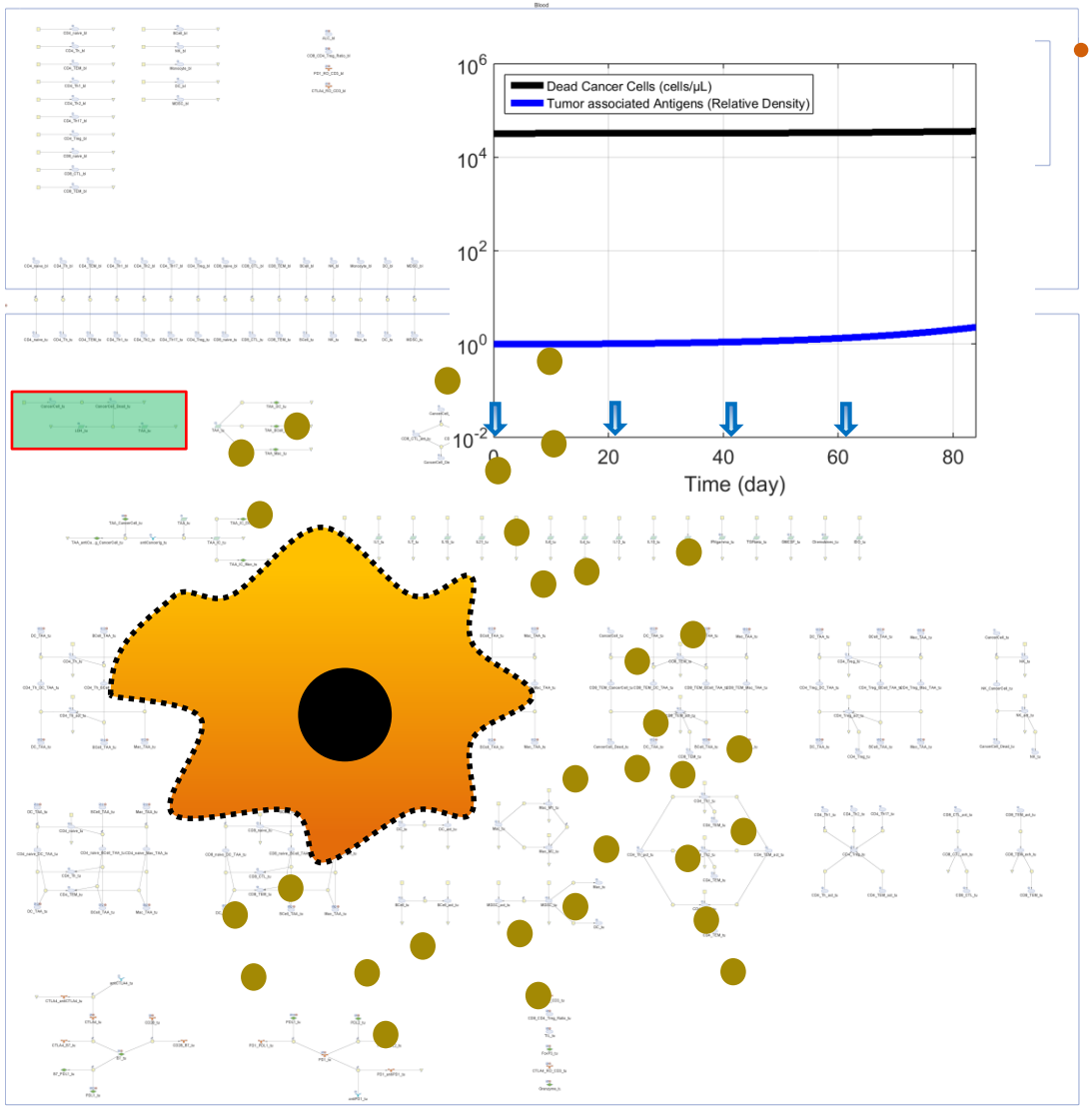
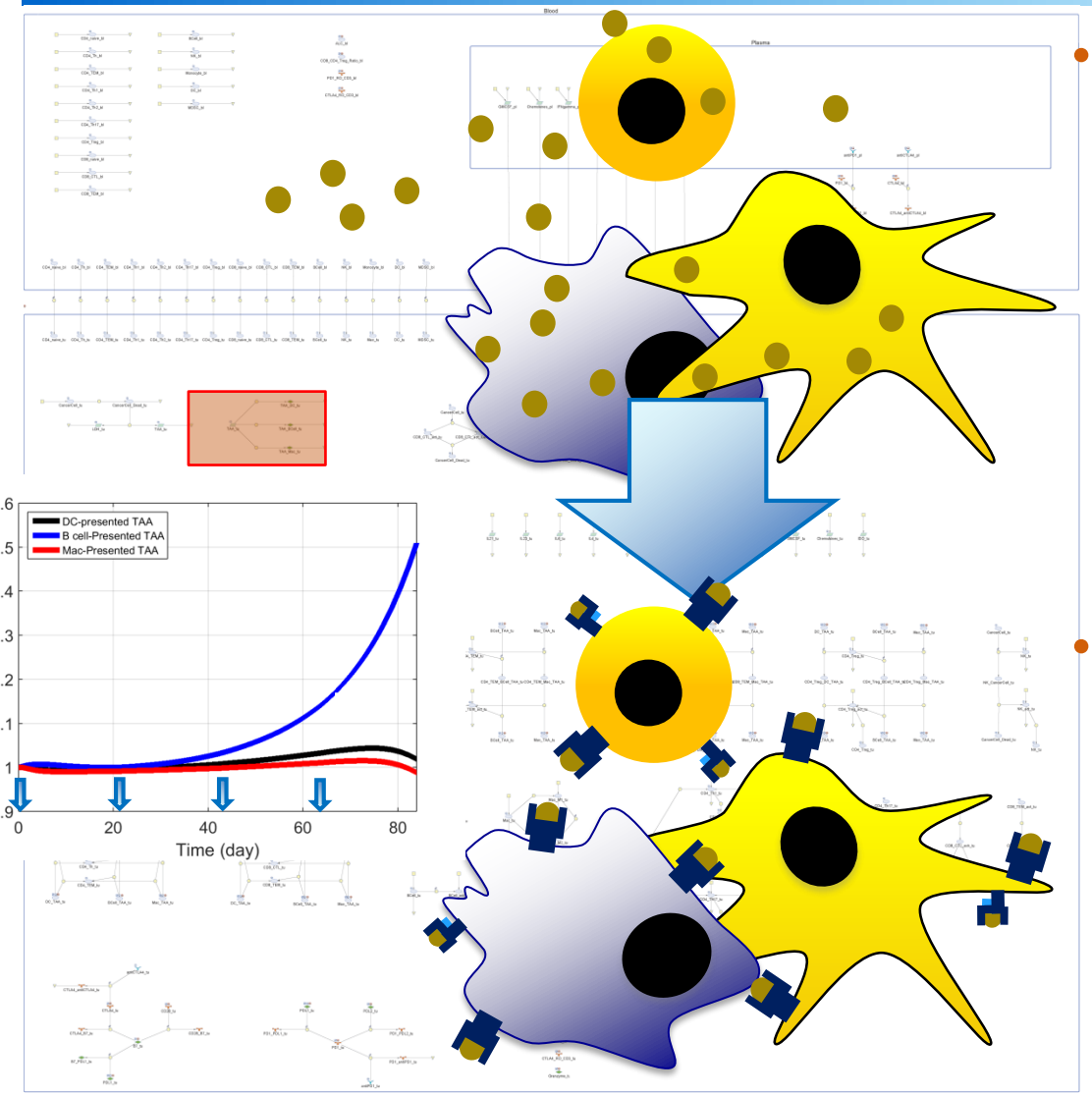
Representation of the cancer-immunity cycle: release of cancer antigens



- Dead cancer cells release components, that can can serve as tumor-associated antigens (TAA)

Representation of the cancer-immunity cycle: cancer antigen presentation



- Released TAA in tumor can be internalized, processed, and presented by dendritic cells, macrophages, and B cells within the tumor or lymph node (stage 2)
- The level of TAA presented per APC contributes to the degree of T cell activation

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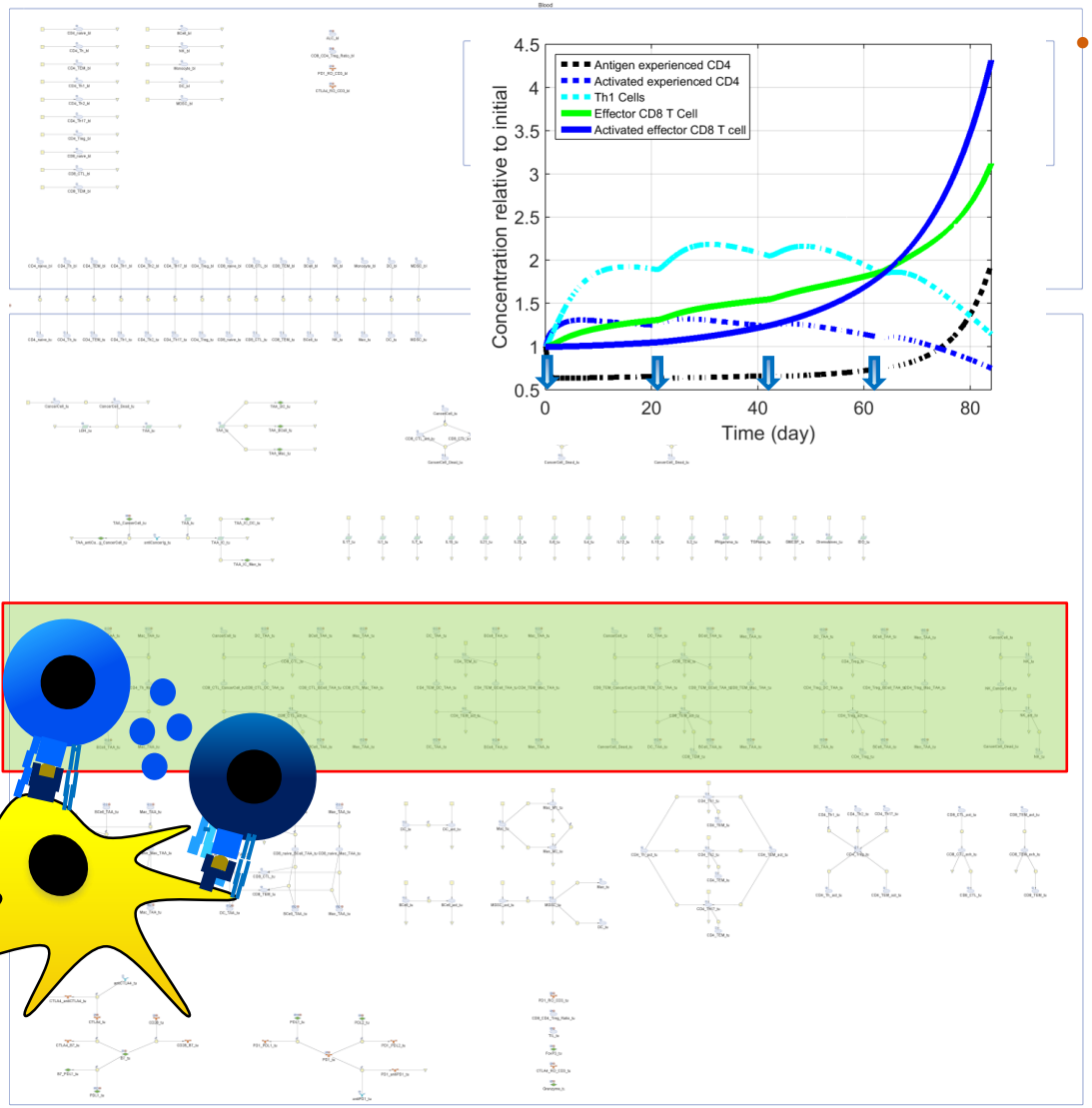
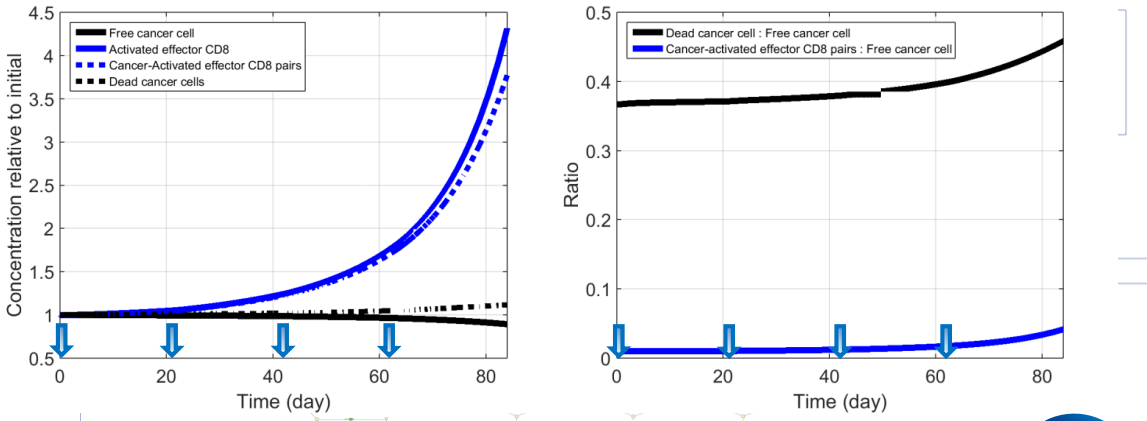
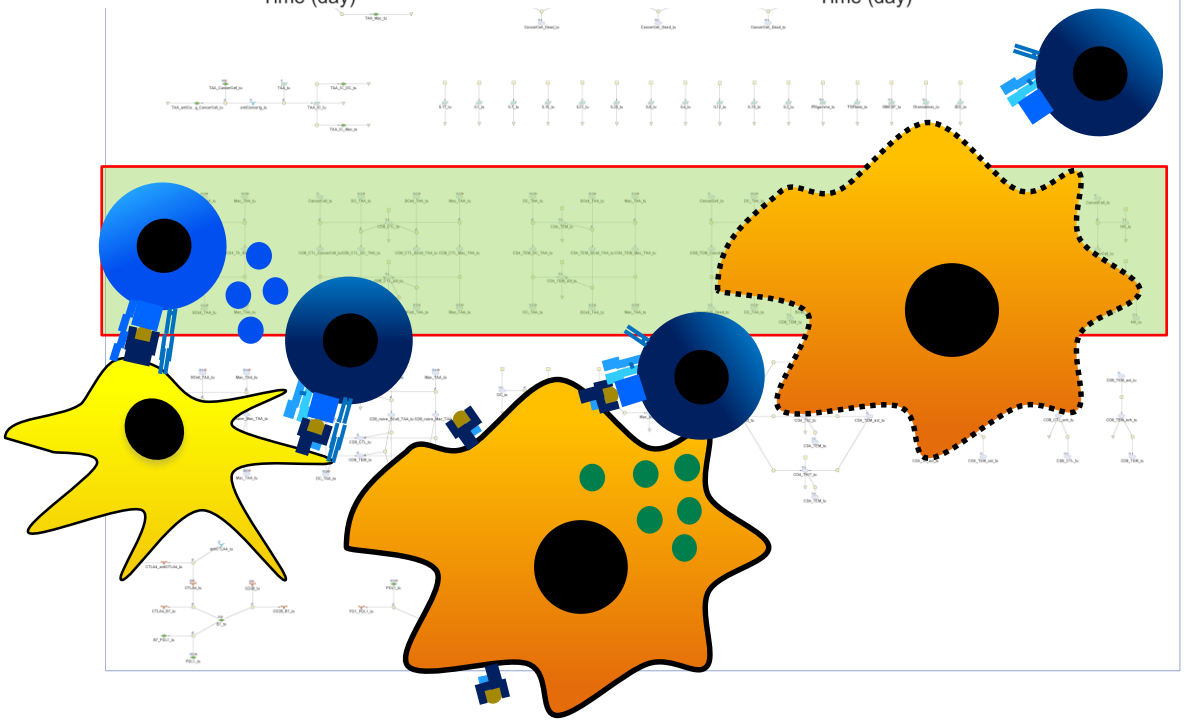
Representation of the cancer-immunity cycle: cancer cell recognition (1 of 3)



- **Presentation of TAA can activate CD4+ and CD8+ T cells**

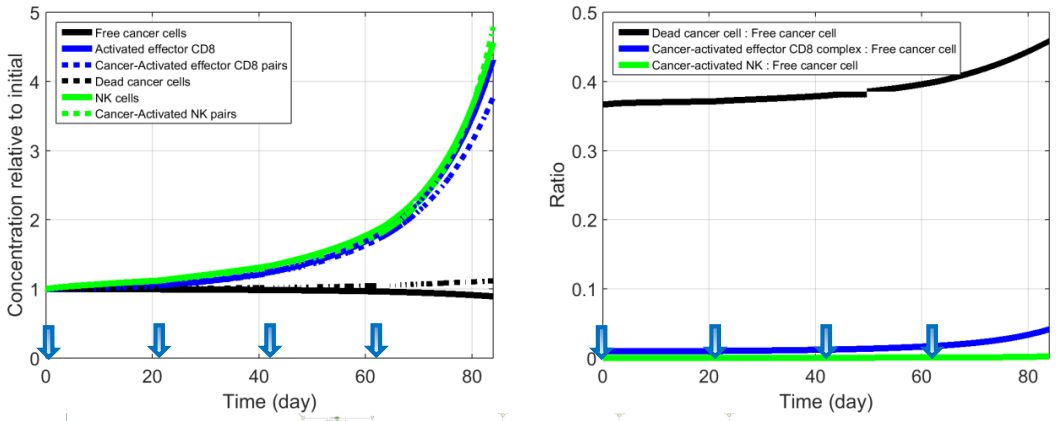
Representation of the cancer-immunity cycle: cancer cell recognition (2 of 3)

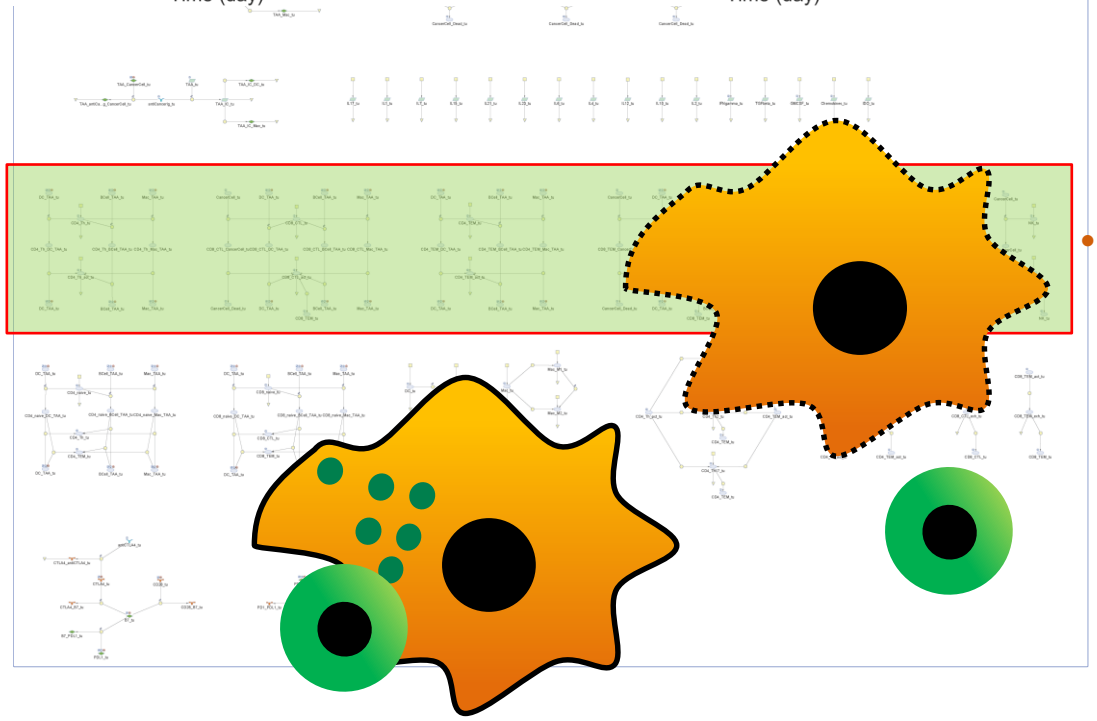




- Presentation of TAA can activate CD4+ and CD8+ T cells
- CD8+ T cells can directly bind to cancer cells presenting MHC-TAA complexes
  - APC are protected from CD8+ CTL-mediated killing
  - Cancer cells are killed by activated CD8+ CTL

Representation of the cancer-immunity cycle: cancer cell recognition (3 of 3)





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- CD8+ T cells can directly bind to cancer cells presenting MHC-TAA complexes
  - APC are protected from CD8+ CTL-mediated killing
  - Cancer cells are killed by activated CD8+ CTL
- **Natural killer (NK) cells detect downregulated MHC I expression on the cancer cells**
  - **This leads to NK cell activation and direct killing of the cancer cells**

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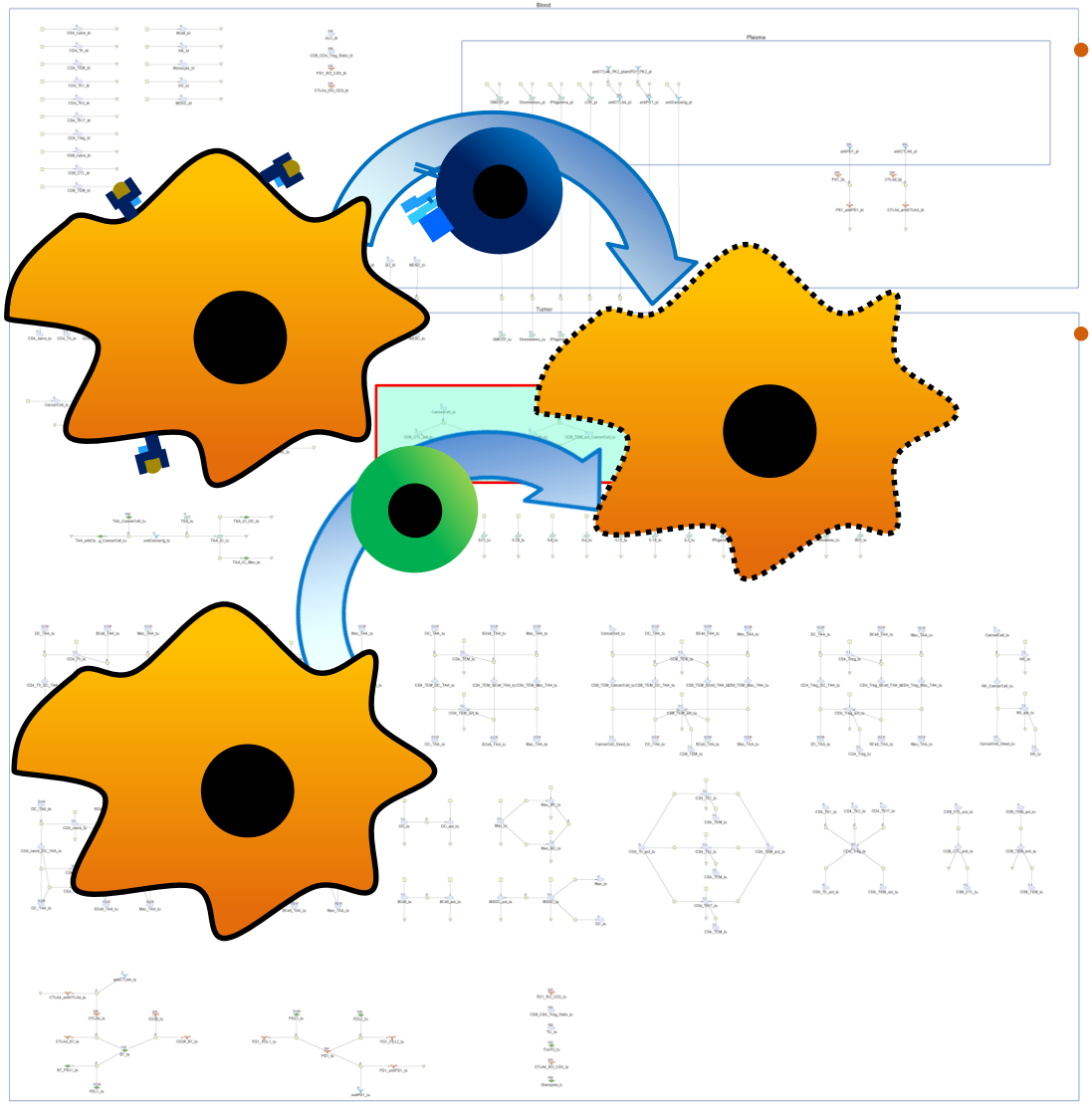
Representation of the cancer-immunity cycle: cancer cell killing



- Activated CD8+ T cells and NK cells carry out additional killing of the cancer cells
- Activation and cytokines contribute to exhaustion of CD8 T-cells and upregulation of exhaustion markers

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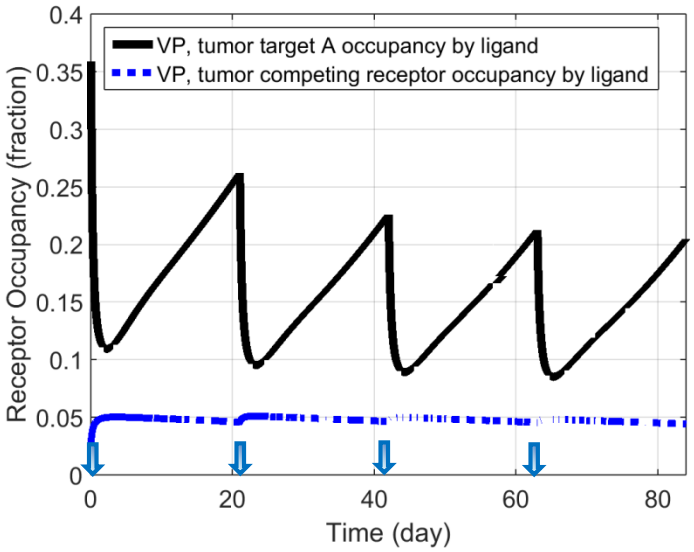
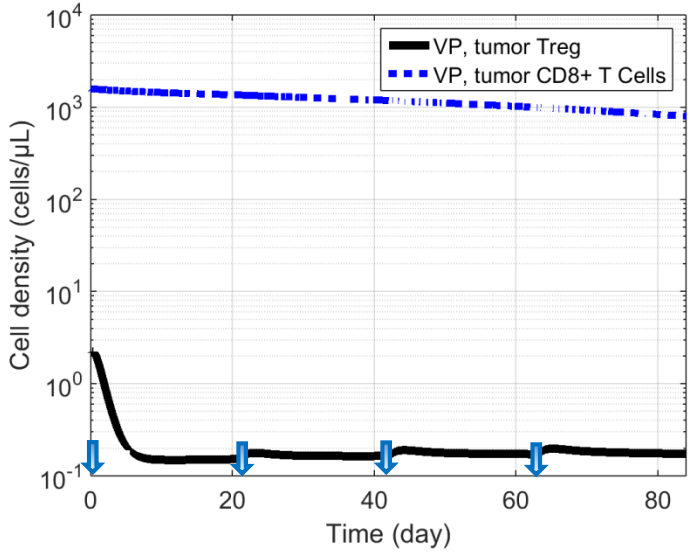
Therapy A proximal PD





- **Two therapies implemented**
- **Typical values used for PK**
- **Multiple effects of engagement of target A**
  - **Free target A ligand to bind to a competing receptor**
  - **Target A is expressed on T regs: antibody-dependent cell-mediated cytotoxicity**

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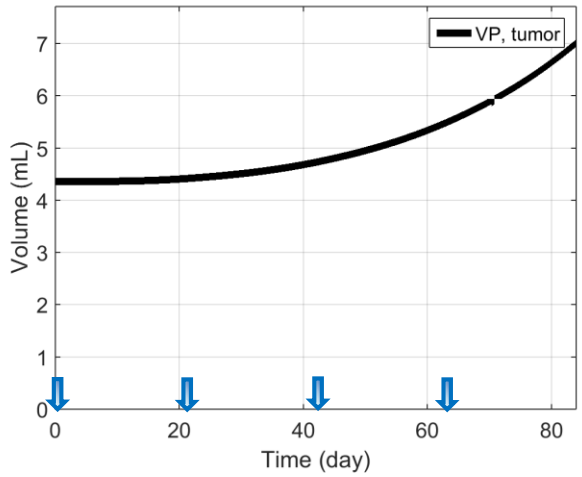
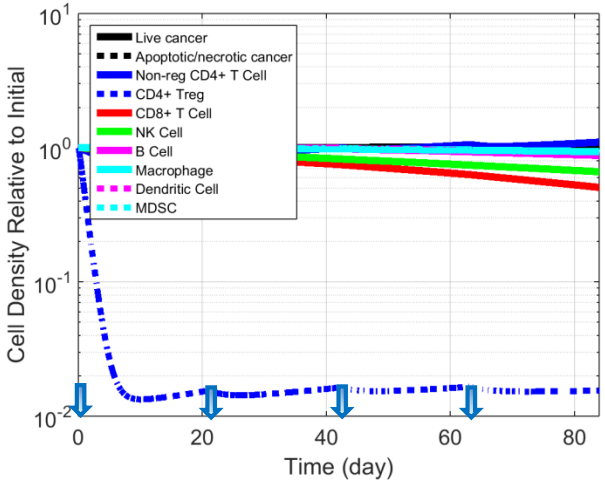
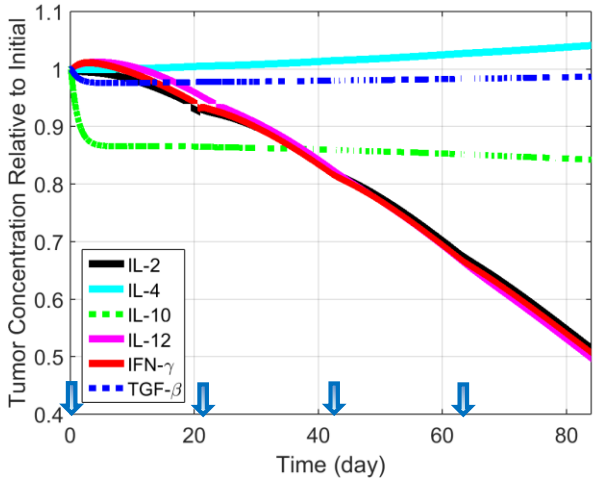
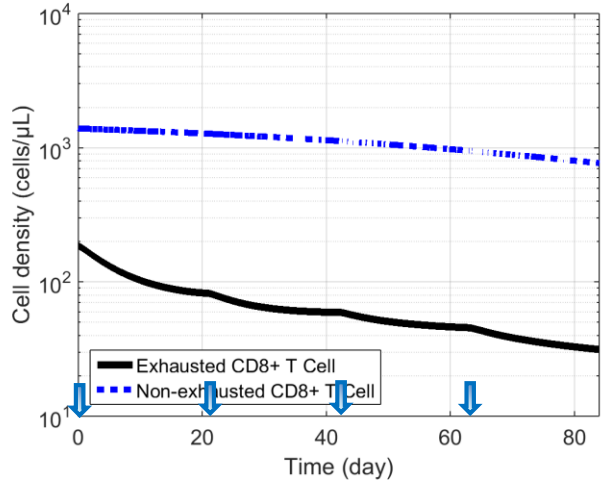
Pilot VP: response to therapy A









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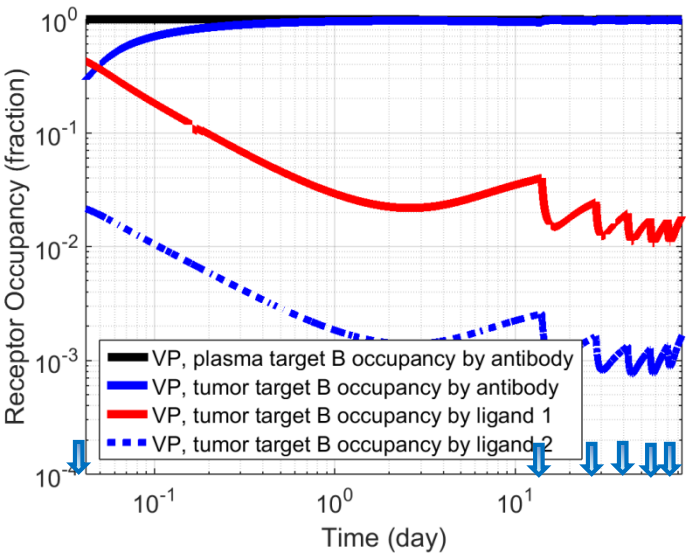
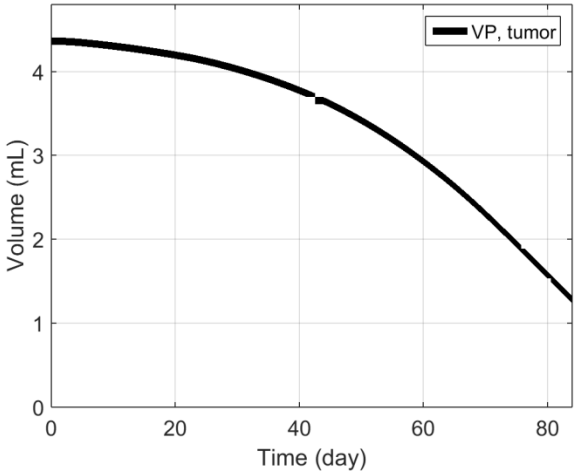
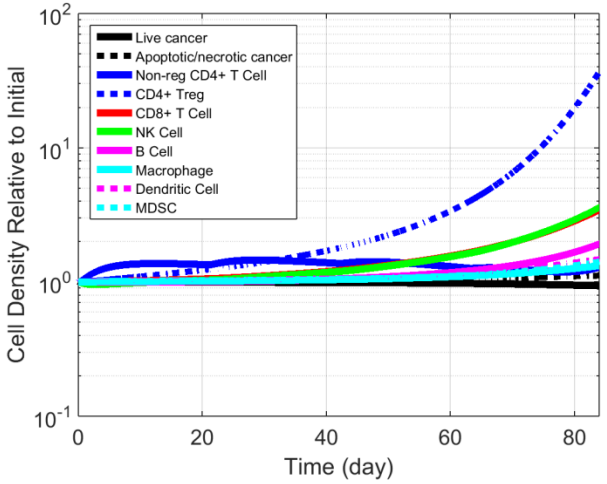
Therapy B proximal PD

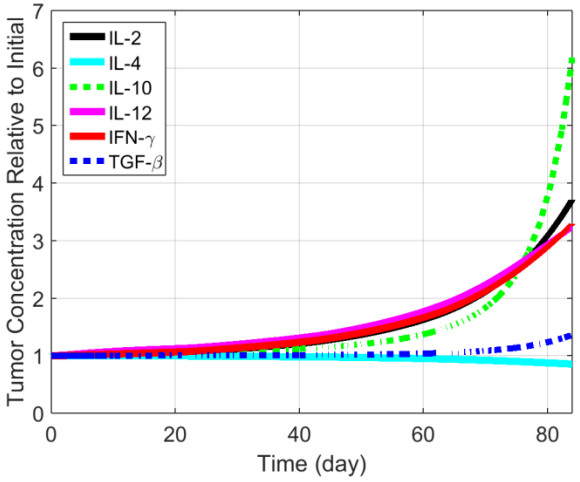


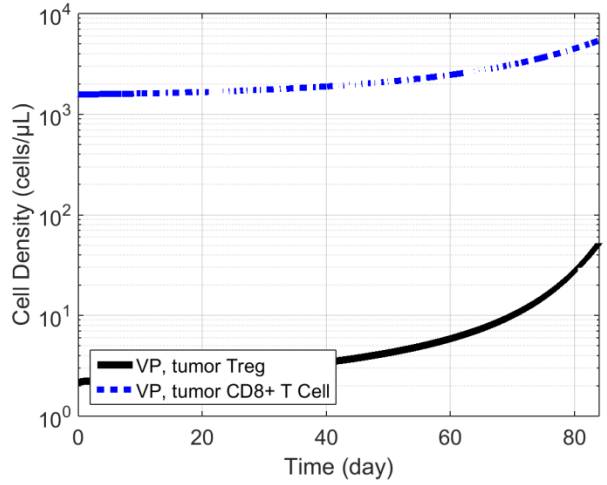
- **Target B receptor occupancy is shown following infusion**
  - **Therapy B**
  - **Target B ligand 1**
  - **Target B ligand 2**
- **Simulations account for affinity as well as expression**

Pilot VP: response to therapy B









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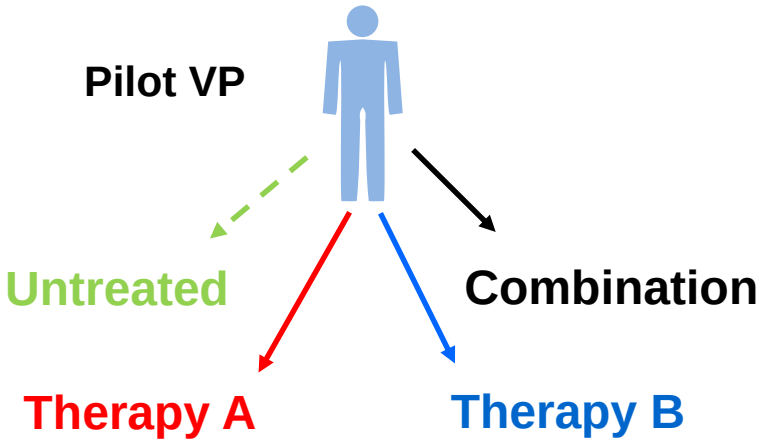
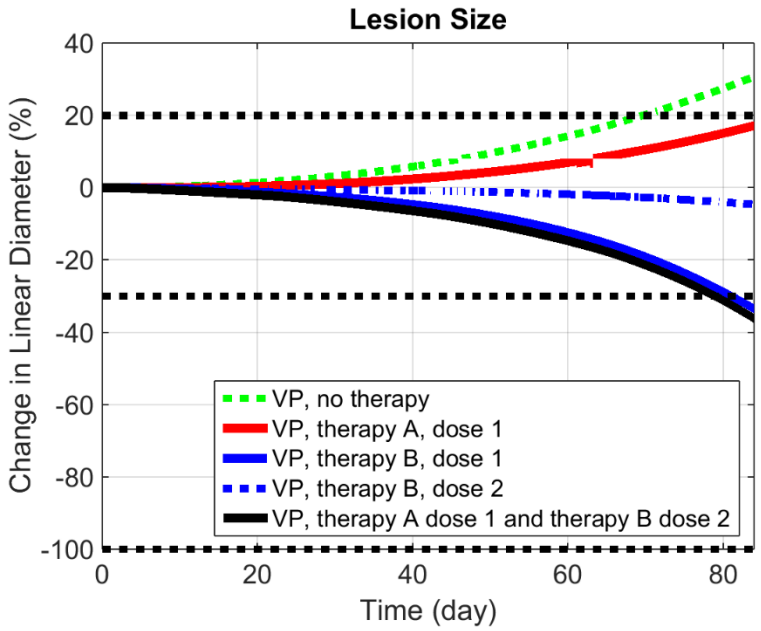
Pilot VP: lesion response to combination therapies





- We have taken the same VP and tested different immuno-oncology therapies
- Note the simulated increased response for the combination relative to monotherapies at the same concentrations
- Will add additional feedback mechanisms in stage 2
- Alternate VPs will facilitate exploring phenotypes that may have greater benefit from the combination
- Develop virtual populations: increase confidence in distribution of response phenotypes

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Stage 2 expansion: cells, cytokines, and other biomarkers

Blood/Plasma

Pilot: circulating immune cells, cytokines, chemokines, RO, therapy A and B

Stage 2: expand immune cells, 3 more therapies (checkpoint inhibitors, agonists)

Transport

Tumor & lymph node

Pilot cell types: CD4: Naïve, Th, Th1, Th2, Th17, Treg, TEM; CD8: Naïve, CTL, TEM; NK, B, DC, M1/M2 Macrophages, MDSC, Cancer

Stage 2 cell types: CD4: TFH , TCM; CD8: TCM; B: Naïve, Plasma (short & long lived), Memory; VEC, LEC, CAF, pDC, N1/N2 Neutrophils, TIE2-Expressing Monocytes, Lymph node fibroblasts

Pilot mediators and markers (21): IL1, IL2, IL4, IL6, IL7, IL10, IL12, IL15, IL17, IL21, IL23, IFNg, TGFb, GMCSF, IDO, ~~Chemokines~~, LDH, tumor associated antigens, therapy A and B

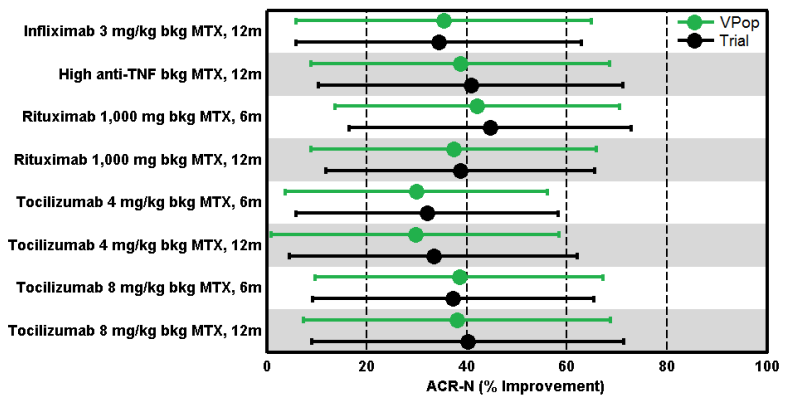
Stage 2 mediators and markers (39): IL18, IFN1, TNFalpha, CXCL8, CXCL9, CXCL12, CCL4, CCL2, CCL5, CCL20, CCL21, CCL22, MCSF, PGE2, ICAM1, VEGFA, VEGFC, Ang2, ECM, MMP, new therapies

Pilot cell associated markers: MHC, target-associated markers, FoxP3, granzymes

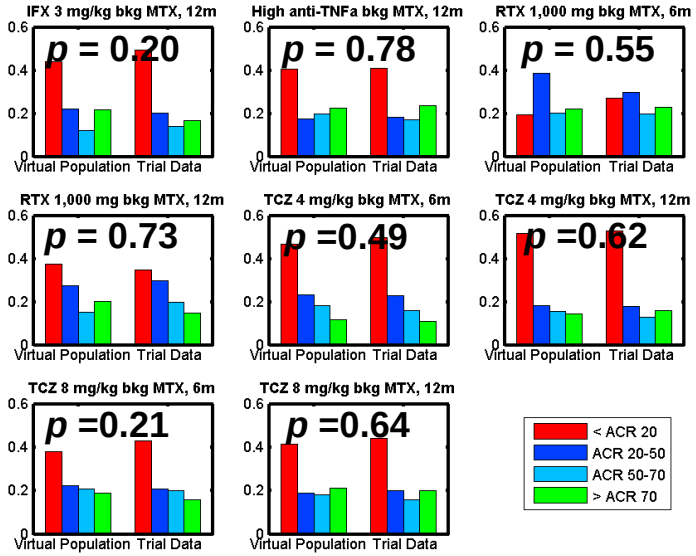
Stage 2 target-associated cell markers

Some of the new processes in Stage 2: hypoxia, vessel and ECM density (metastatic potential), cancer and immune cell migration to the lymph node, adaptive immune response in the lymph node

Trial results for a virtual population: an example in rheumatoid arthritis



p=0.65(0.54)
p =0.28(0.68)
p =0.56(0.99)
p =0.75(0.66)
p =0.10(0.99)
p =0.03(0.99)
p =0.40(0.56)
p =0.24(0.69)



- A cohort of 1,206 VPs was developed algorithmically
- Cohort VPs all exhibit feasible baseline biomarkers and therapeutic responses
- Many virtual populations (768) were created
- Composite goodness-of-fit criterion was acceptable for each virtual population
- Agreement for one virtual population across multiple trials is illustrated
- Virtual population calibration gives a basis for population response extrapolation with new therapies

Schmidt, B. J. et al. (2013). "Alternate virtual populations elucidate the type I interferon signature predictive of the response to rituximab in rheumatoid arthritis." BMC Bioinformatics 14: 221. Originally published by Biomed Central.

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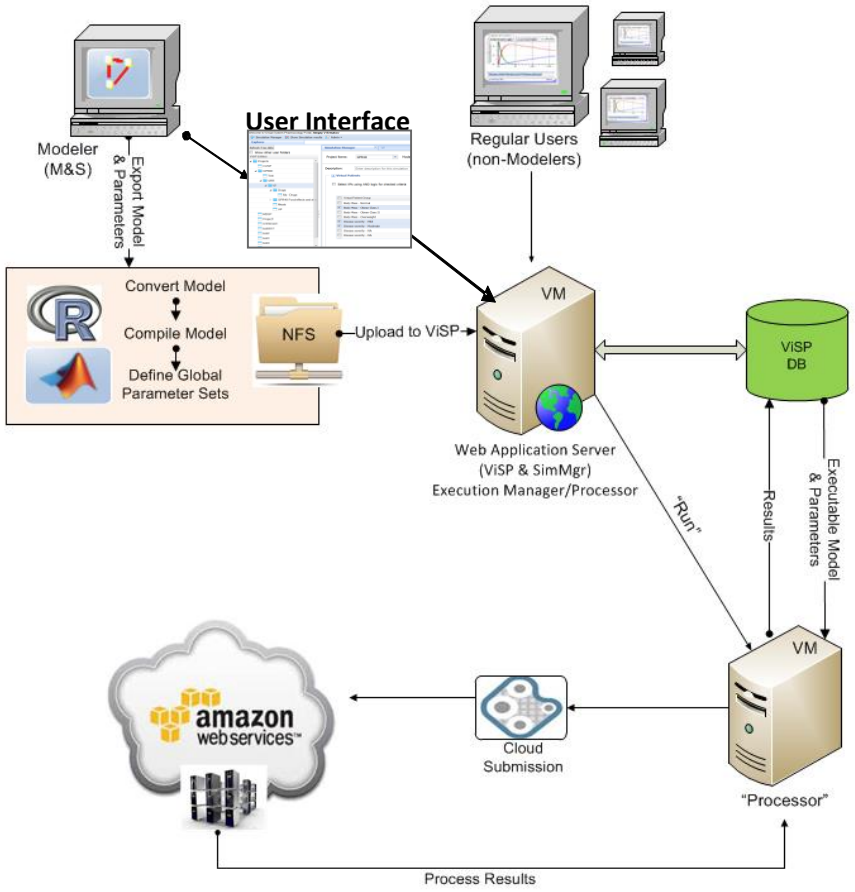
Virtual Systems Pharmacology (ViSP) HPC platform



- **QSP software and infrastructure development are 2-fold:**
  - **Provide tools and interfaces for non-modelers to access simulations (left)**
  - **Provide computing resources for computationally-intensive models and algorithms**

Ermakov, S., et al. (2014). "Virtual Systems Pharmacology (ViSP) software for mechanistic system-level model simulations." Front Pharmacol. 5: p. 232.

Take home

- Mechanistic quantitative systems pharmacology (QSP) modeling platforms can address a variety of questions
  - Elucidate and predict efficacy and biomarker trends
  - Evaluate combinations
  - Dosing strategy
- Modeling platforms are non-trivial
  - Require foresight and planning
  - Continual development, re-use
- Software & infrastructure considerations
  - May require customized development
  - Virtual populations can be resource hungry
  - Cloud computing resources

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- Craig Thalhauser (QSP)
- Sergey Ermakov (former BMS QSP)

Clinical Pharmacology & Pharmacometrics

- Shruti Agrawal
- Amit Roy
- Satyendra Suryawanshi

Genomics

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- Nathan Siemers

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- Andres A. Gutierrez (former BMS)
- Raphael A. Clynes
- Praveen Aanur
- Suba Krishnan

Oncology Discovery

- Maria Jure-Kunkel
- Joe Fargnoli
- Henry Kao

Preclinical Candidate Optimization

- Zheng Yang
- Huadong Sun
- Haiqing Wang

Translational R&D Analytics

- Kaushal Desai

Translational R&D IT

- Marko Miladinov

Clinical Biomarkers

- Jaclyn Neely

ASCPT and Session Chairs

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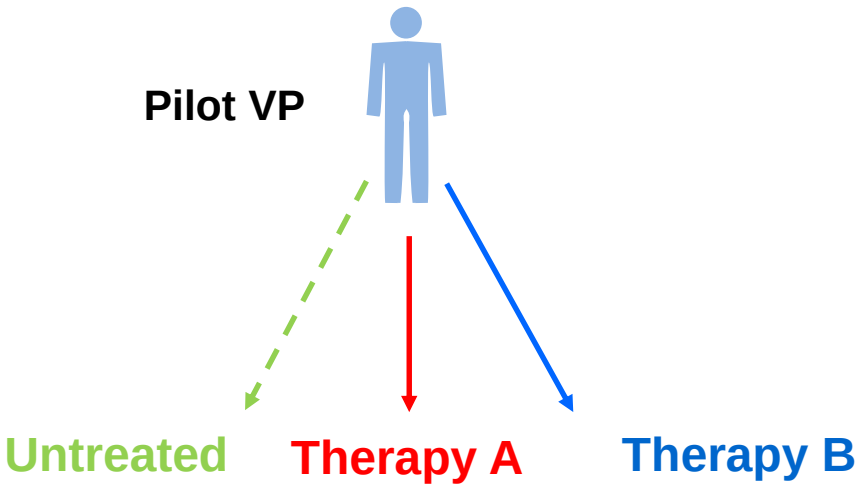
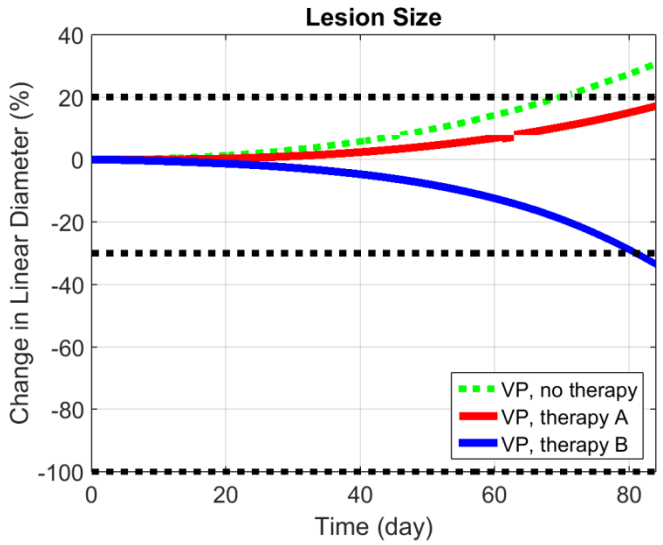
Backup

Therapy implementation with the VP





- We have taken the same VP and tested different immuno-oncology therapies
- Lesion size is calculated based on number of cancer and immune cells in the simulated lesion

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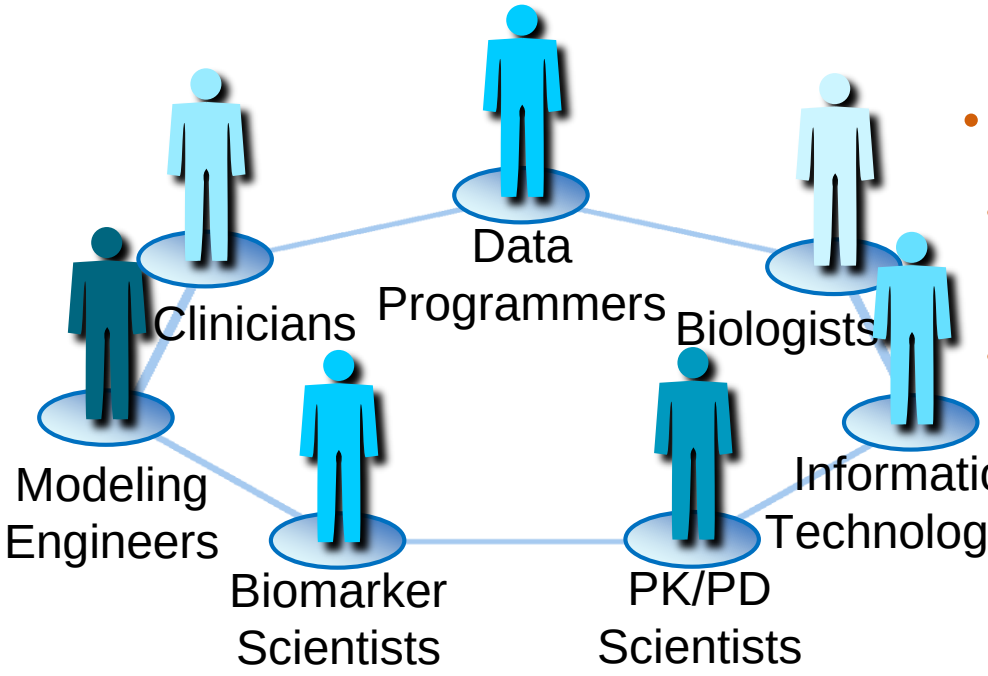
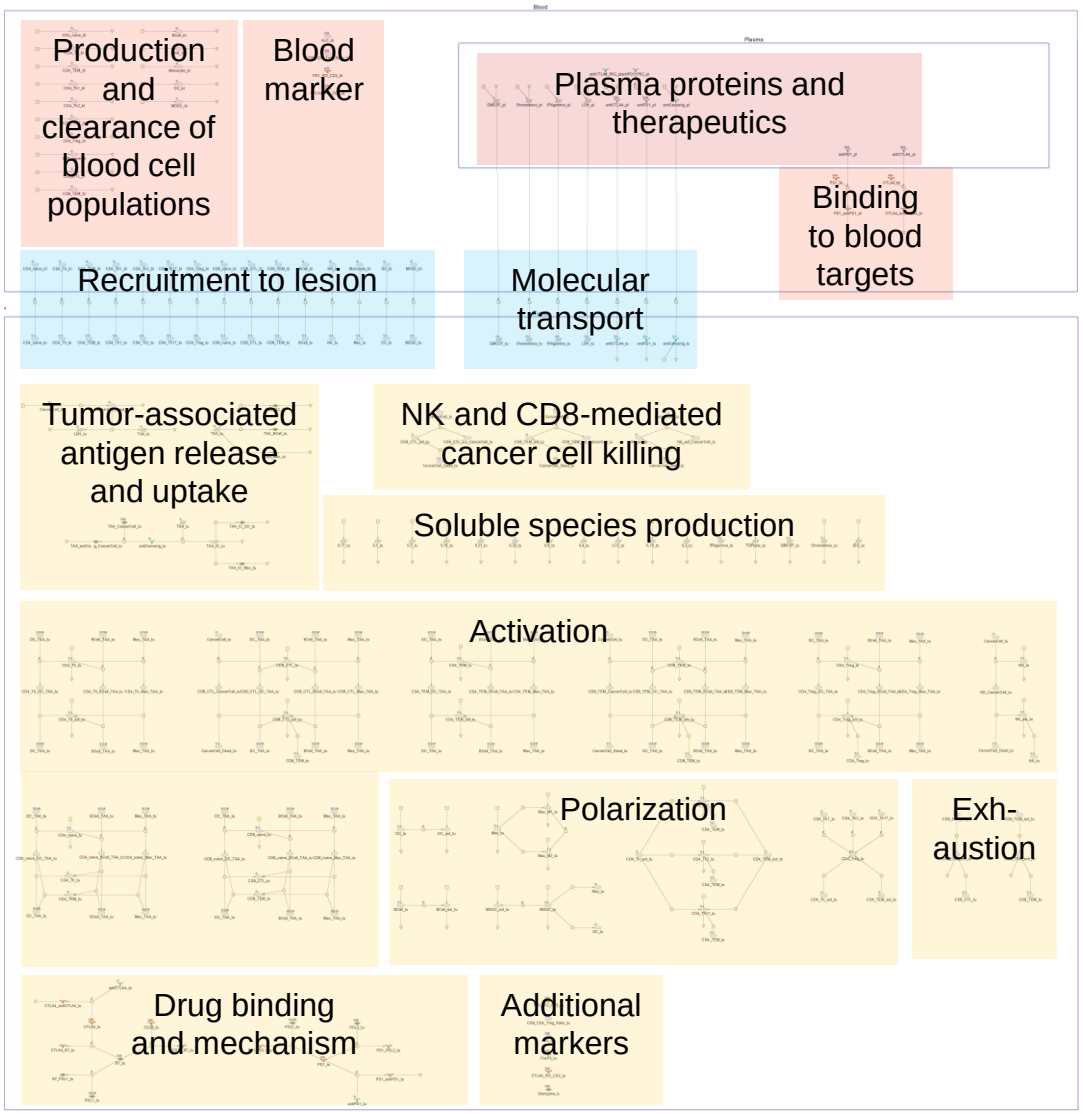
Melanoma immuno-oncology platform: development team



- **Cross-function team of drug development scientists**
- **Leverage external resources to accelerate model development**
- **Information-intensive**
  - **Preclinical and clinical data sets**
  - **Over 500 publications for pilot**

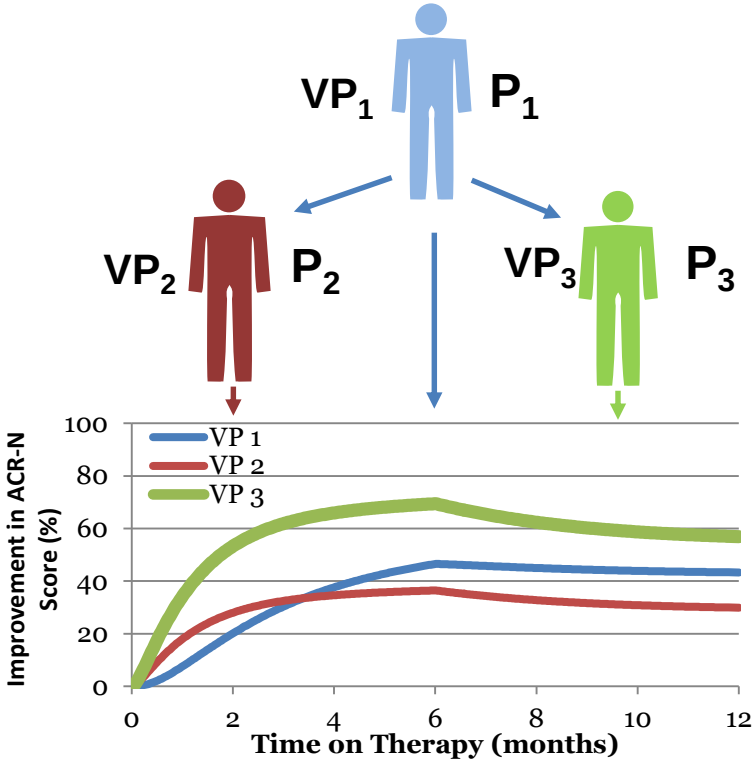
Melanoma immuno-oncology pilot project: processes



- **21 baseline measures of pathology**
- **53 response measures on 10 therapeutic interventions**

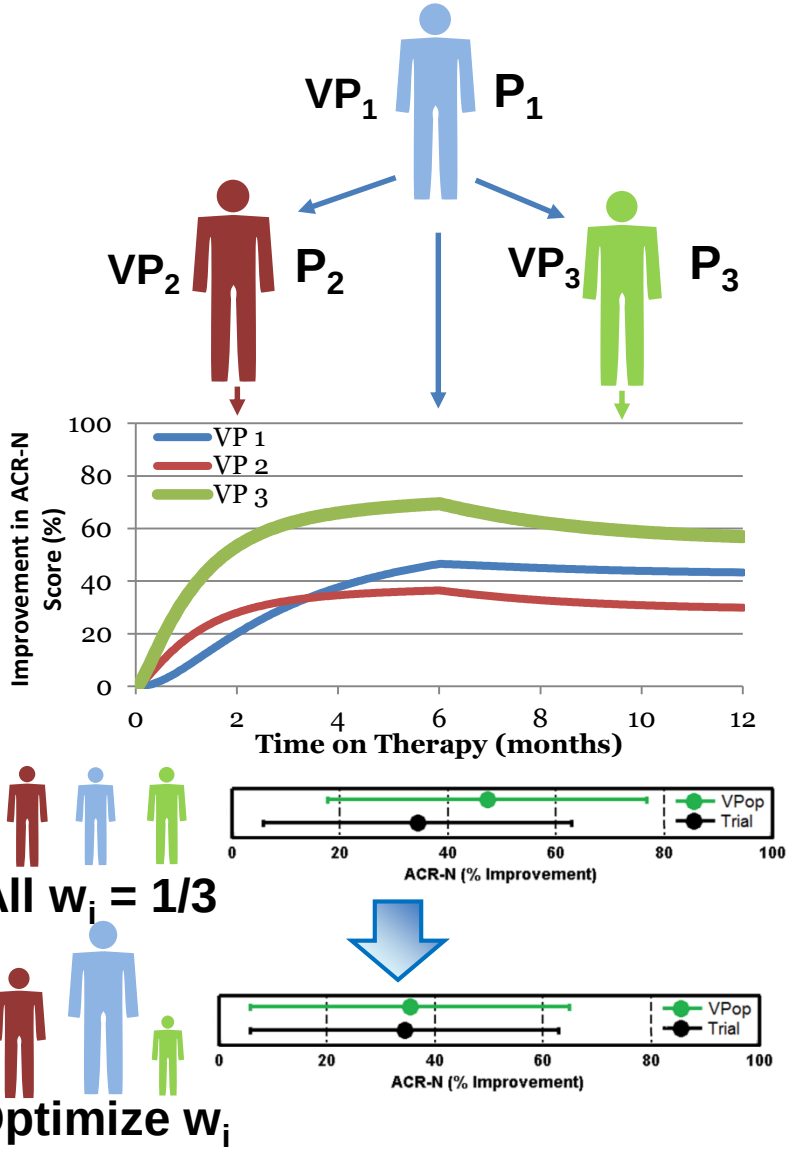
Treatment/Simulation	Measure	Feasible Range for VP
Untreated (Baseline RA)	Plasma C-Reactive Protein	<255 mg/L
	Synovial Tissue Volume Occupied by Cells	<0.95 (Fraction)
	Synovial Sublining B Cell Density	0.48 - 37.92 ($x10^6$ cells/mL)
	Synovial Sublining T Cell Density	0.32 - 408.48 ($x10^6$ cells/mL)
	CD4: CD8 T Cells	1-3 (ratio)
	Circulating $CD28^-/CD4^+$ T Cells	<0.61 (fraction of $CD4^+$ T Cells)
	Circulating Th17 Cells	<0.85 (fraction of $CD4^+$ T Cells)
	Average Synovial NK Cell Density	<6 ($x10^6$ cells/mL)
	Synovial Sublining Plasma Cell Density	9.28 - 119 ($\times10^6$ cells/mL)
	Synovial Macrophage Density	18.16 - 189.36 ($\times10^6$ cells/mL)
	Synovial Lining FLS Density	18 - 104.1 ($\times10^6$ cells/mL)
	Cartilage Degradation Rate	0.1 - 1.5 (mm/yr)
	Bone Metabolism Rate	<-1 - 1 ($x10^{-6}$ mL/hr)
	Serum TNFa Level	<3.6 (ng/mL)
	Serum IL-1Ra	0.1 - 5.2 (ng/mL)
	Serum COMP	2.6 - 32 (µg/mL)
	Serum VEGF	0.025 - 5.5 (ng/mL)
	Serum IL-1	<1.03 (ng/mL)
	Serum Free and Complexed IL-6	<52 (ng/mL)
	Serum Total IL-6R	<0.0185 - 218 (ng/mL)
	Serum Total SGP-130	50 - 1068 (ng/mL)
NSAID, 27.5 ng/ml, 1 year	Improvement in JSN Progression Rate	-25% to 50%
	Improvement in BES Progression Rate	-25% to 50%
	Improvement in ACR-N Score	>-10%
Methotrexate, 14.2mg/wk, 1 year	Plasma C-Reactive Protein	<255 mg/L
	Synovial Tissue Volume Occupied by Cells	<0.95 (Fraction)
	Improvement in JSN Progression Rate	>-25%
	Improvement in BES Progression Rate	>-25%
	Improvement in ACR-N Score	>-25%
Methotrexate, 16.5mg/wk, 1 year	Same feasibility constraints as MTX 14.2	
Adalimumab, 40 mg s.c., and MTX, 1 year, following 1 year on MTX	Same feasibility constraints	
Rituximab, 1000 mg, and MTX, 6 months, following 1 year on MTX	Same feasibility constraints	
Rituximab, 1000 mg, and MTX, 1 year, following 1 year on MTX	Same feasibility constraints	
Tocilizimumab, 4 mg/kg, and MTX, 1 year, following 1 year on MTX	Same feasibility constraints	
Tocilizimumab, 8 mg/kg, and MTX, 1 year, following 1 year on MTX	Same feasibility constraints	
Anakinra, 100 mg s.c., and MTX, following 1 year on MTX	Same feasibility constraints	
Infliximab, 3 mg/kg, and MTX, 1 year, following 1 year on MTX	Same feasibility constraints	
Infliximab, 10 mg/kg, and MTX, 1 year, following 1 year on MTX	Same feasibility constraints	

Alternate VPs simulate variability: example from a rheumatoid arthritis study (1 of 2)



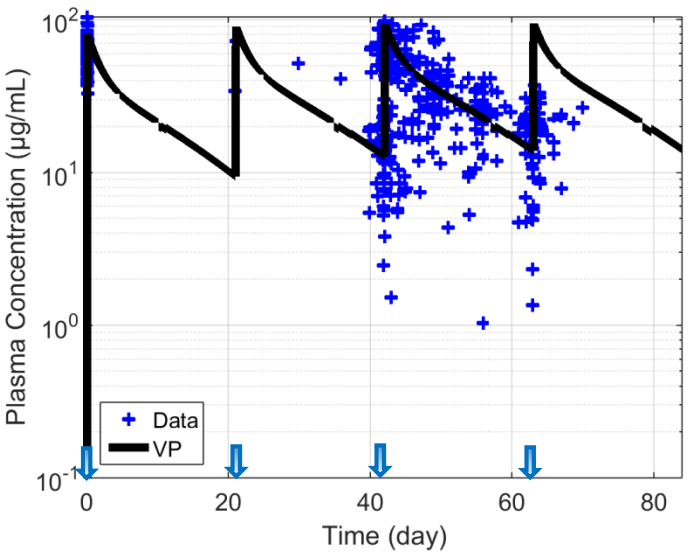
- Alternate VPs can be created to form a VP cohort
- All VPs must meet feasibility criteria
  - Responses to therapies are generally consistent with patient class
  - Pathophysiology (cell counts, concentrations) feasible and in agreement with literature

Alternate VPs simulate variability: example from a rheumatoid arthritis study (2 of 2)



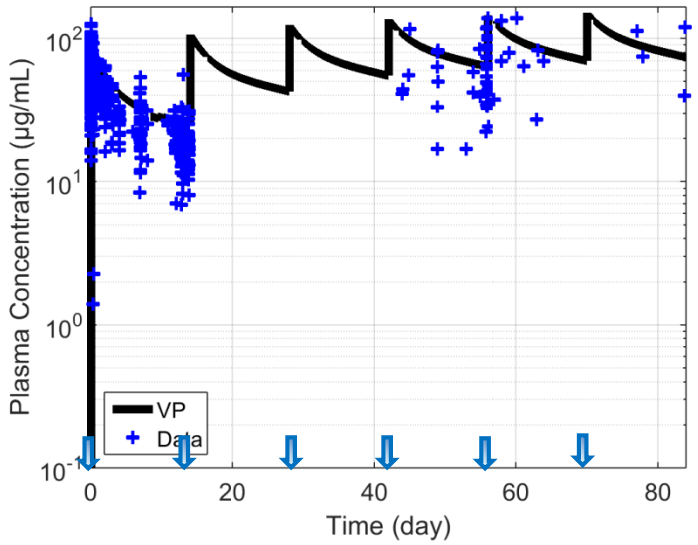
- Alternate VPs can be created to form a VP cohort
- All VPs must meet feasibility criteria
  - Responses to therapies are generally consistent with patient class
  - Pathophysiology (cell counts, concentrations) feasible and in agreement with literature
- Once a cohort of VPs is created, they may not match trial statistics
- "Prevalence" weights can be optimized to improve the match, giving a virtual population
- Algorithms have been developed optimizing prevalence weights

Therapy A PK



- Patient data are shown for comparison
- Previously reported pharmacokinetic parameters were used for the VP

Therapy B PK



- Patient data are shown for comparison
- Previously reported PK parameters were used for the VP