Modular development and application of platform QSP models to support a broad R&D portfolio

Examples from immuno-oncology and respiratory therapeutic areas

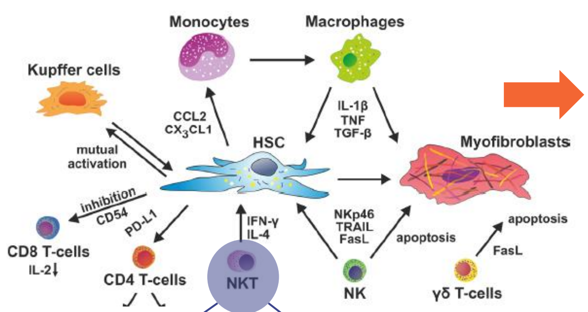
Loveleena Bansal
Scientific Leader, GSK

Outline

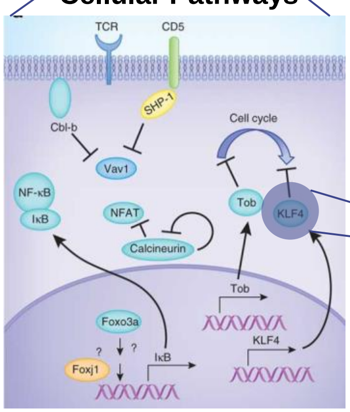
- Strategy for Developing QSP Models
- Modular Development of a QSP Model for Immuno-Oncology
- QSP Automation Tools
- Application of a QSP Platform Model for COPD Portfolio

Development of Platform QSP Models

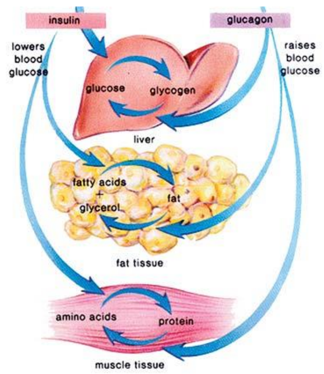
Multi-cellular network



Cellular Pathways

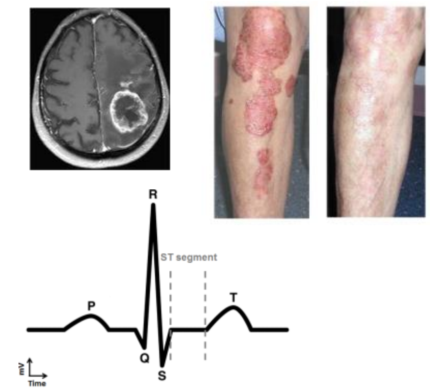


Organs/Tissues



Patient

Clinical Efficacy/ Toxicity Outcomes



Drug Pharmacology

Target ⟷ **Small/ large molecule compounds**

Mechanistic modeling of disease/toxicity pathways at various scales and drug pharmacology to link the effect of ***target engagement*** *to* ***clinical outcomes***

Modeling workflow and application

QSP modeling workflow

Question Outline → Disease Network → Add equations, parameters and validate → Model use

Interdisciplinary team of GSK **modelers and biology scientists** outline the project questions and processes to model

External Partners:

ROSA Drug Development Advisors; InSysBio QSP Company; Immunetrics; applied biomath revolutionizing drug invention; CERTARA; DILIsym; Mount Sinai; University of Oxford; University of Surrey; imi innovative medicines initiative

Internal Resources:

Systems Modeling · QSP Modelers · Post Docs · Computational Biology · Disease Experts

GSK **modelers** use the model to answer project questions.

Stage	Target Validation	Lead Discovery and Opt.	Pre-Candidate	Pre-Clinical	Clinical
QSP/T Application	• *Level of target engagement needed for efficacy*	• *Affinity required to engage the target* • *Modality Selection*	• *Biomarker Selection* • *Dose Predictions (QSP+PK/PBPK)* • *Toxicity evaluations: QST*		• *Selection of right patient population* • *Model refinement and design of next trial*

Strategy for Model Development

- **Prioritization of QSP platform models for key GSK disease areas**
- **Modular development to allow re-use of developed models**
  - Built a matrix of disease and modules to help prioritization

Diseases (columns) / **Modules** (rows)

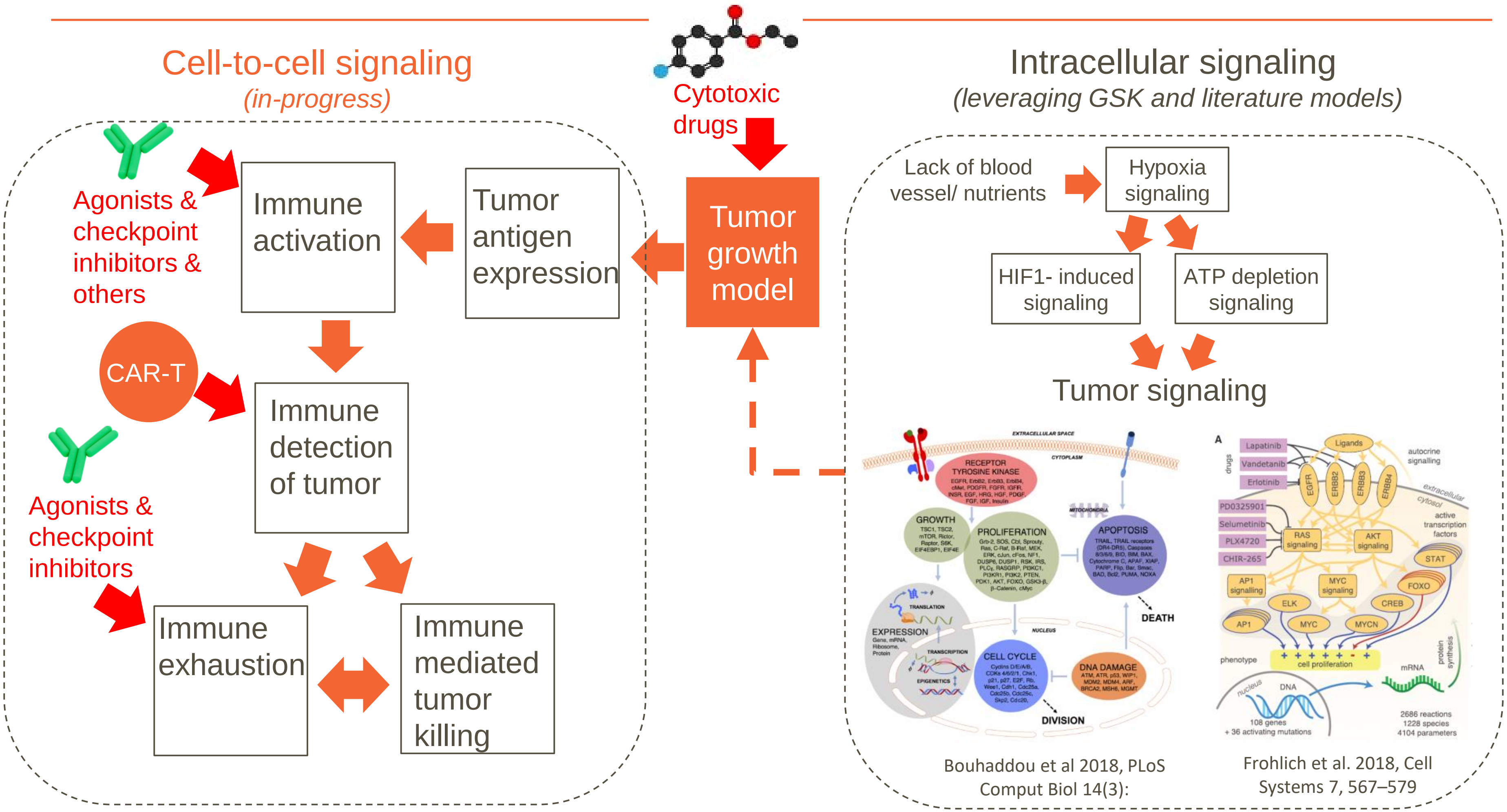
Modules	Oncology	Asthma	COPD	Arthritis	Lupus	Fibrosis	HIV	psoriasis	CV disease	acne	Alzheimer's	IBD	AMD	Neuromuscular	Allergy	Acute lung injury	Obesity	Irritable bowel syndrome	ALS	Atopic Dermatitis	Bacterial infection	[illegible] in kidney	HCV	DILI	CV Tox	Rash	Phospholipidosis	Total
Inflammation		1	1	1	1	1		1	1	1		1	1		1	1				1	1	1		1	1	1		18
T-cell	1	1	1	1	1		1	1		1		1			1					1	1	1	1	1		1		16
Macrophage		1	1	1		1	1	1		1		1			1						1					1		11
Intracellular protein production and proteolysis					1				1		1			1		1			1		1	1		1			1	10
Apoptosis		1	1		1				1					1		1					1	1		1			1	10
Resolution of inflammation/ fibrosis		1	1						1						1	1					1	1		1	1	1		10
Neutrophils		1	1												1	1					1	1				1		7
ROS formation and effect			1		1				1		1					1						1			1	1	1	9
Dendritic cell				1			1	1				1								1	1							6
Angiogenesis	1			1				1	1				1			1						1			1			8
Muscle activity-energy									1					1		1	1					1			1			6
B-cells		1		1	1										1								1			1		6
Barrier function								1				1				1				1	1					1	1	7
Mitochondria			1						1							1			1					1	1			6
Mast cell		1		1											1								1			1		5
Aging			1	1									1															3
Oxygen transport	1		1						1							1									1			5
Wound healing				1									1															2
Membrane permeability												1		1										1	1		1	5
Synaptic transmission											1			1				1							1			4
Bacterial/ mixed culture growth										1		1								1	1							4
Eosinophils		1													1					1						1		4
Network of neurons/processing											1							1	1	1								4
Microglia																			1		1							2
Neuro-muscular junction														1				1	1									3
virus replication							1																1					2
Mucosal immune system																					1							1
Heart pumping and ECG									1													1			1			3
Keratinocyte biology								1		1										1						1		4
Complement system	1												1															2
Drusen													1															1
Sebum/sebocyte										1			1															2
Calcium signaling														1											1			2
Food movement												1						1										2
Food processing to energy																	1							1				2
[illegible] system																	1											1
Astrocytes																			1									1
Neuronal cell biology											1																	1
Protein aggregation											1																1	2
Cell cycle and growth	1		1																								1	3
Hepatocyte biology																							1	1		1		3
Monocytes						1		1															1					3
Osteoclast				1																								1
[illegible]				1																								[illegible]

Modular Development of a QSP Model for Immuno-Oncology

Modeling done by Roy Song (GSK)

Multi-scale QSP/T model for Immuno-oncology

Model development at the cellular and tissue level



Bouhaddou et al 2018, PLoS Comput Biol 14(3):

Frohlich et al. 2018, Cell Systems 7, 567–579

- **Predict cell composition (TME)**
- **Identify biomarkers**
- **Predict efficacious/ safe doses**
- **Evaluate combination therapy**

- Predict average cellular growth / death rates by drugs
- Identify emergent properties of cellular effect by drugs

QSP/T IO Model Components

Model framework is built around the Hallmarks of Cancer

	Cell modules	Effector modules	Cell-cell interaction modules
Tissue compartments	Cell-types	Soluble effectors	Surface receptors (molecules)
Lymph (ln)	Tumor cell (prototypical solid)	GM-CSF/ M-CSF	MHC-1 & -2
Blood (bld)	Dendritic cell	IFNg	CD80/86
TME (ts)	Type 1 & 2 Macrophages	TNFa	CD40/40L
	MDSC	TGFb	PD1/PD-L1
	B cells	IL-1/2/4/5/6/10/12	OX40
	Th0/1/2/17/Reg (CD4+) T cells	IL-13/15/17/18/23	CTLA4
	Naïve CD8+ / mature CTL T cells	CCL1/2/17/20/22	
	NK cells	CXCL1/5/9/10/11	

- 3 Tissue compartments
- 15 major cell-types with different states and transitions throughout different tissue compartments
- Production of 18 types of cytokines and 10 types of chemokines
- Tracking of 6 types of surface receptors/ligands
- Lends itself to modular development

Cell modules

Tissue compartments	Cell-types	Soluble effectors	Surface receptors (molecules)
Lymph (ln)	Tumor cell (prototypical solid)	GM-CSF/ M-CSF	MHC-1 & -2
Blood (bld)	Dendritic cell	IFNg	CD80/86
TME (ts)	Type 1 & 2 Macrophages	TNFa	CD40/40L
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	Naïve CD8+ / mature CTL T cells	CCL1/2/17/20/22	
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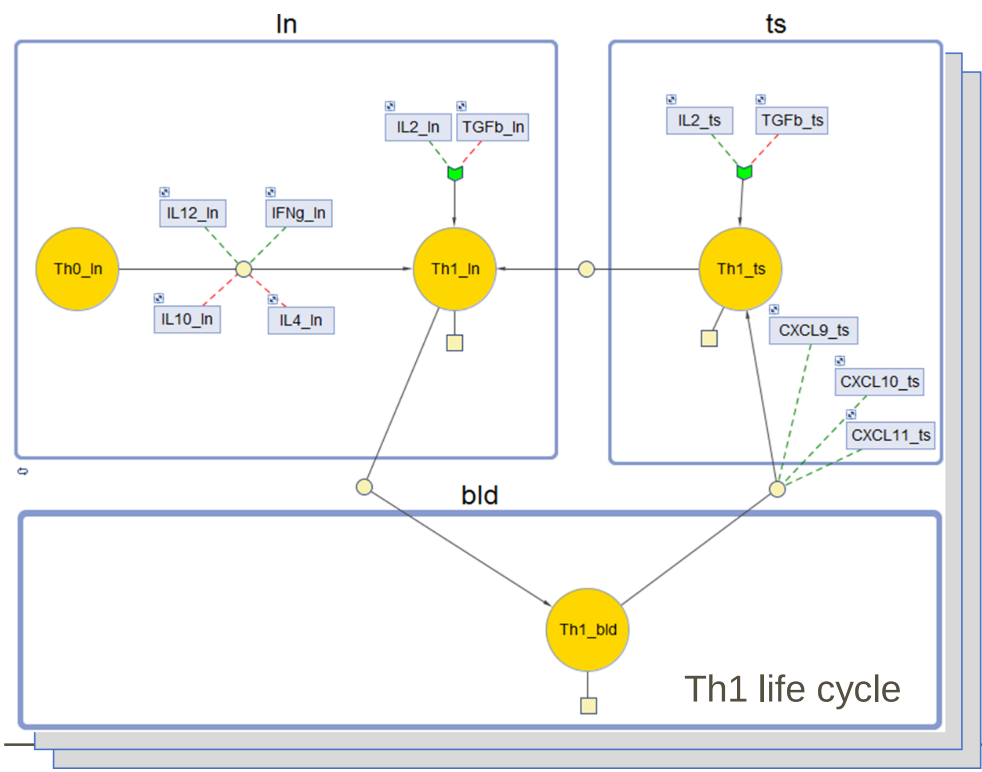

Each cell module describe the life cycle of one cell-type

- Different cell states (active, mature, differentiated, exhausted)
- Cell processes (proliferation, apoptosis, migration)
- Regulation of cell states and transitions by soluble effectors

Benefits:

- Each cell module can represent an *in-vitro* experiment, allows easier parameterization
- Easier to make changes as needed in these individual cell modules vs. “full model”

Effector modules

Tissue compartments	Cell-types	Soluble effectors	Surface receptors (molecules)
Lymph (ln)	Tumor cell (prototypical solid)	GM-CSF/ M-CSF	MHC-1 & -2
Blood (bld)	Dendritic cell	IFNg	CD80/86
TME (ts)	Type 1 & 2 Macrophages	TNFa	CD40/40L
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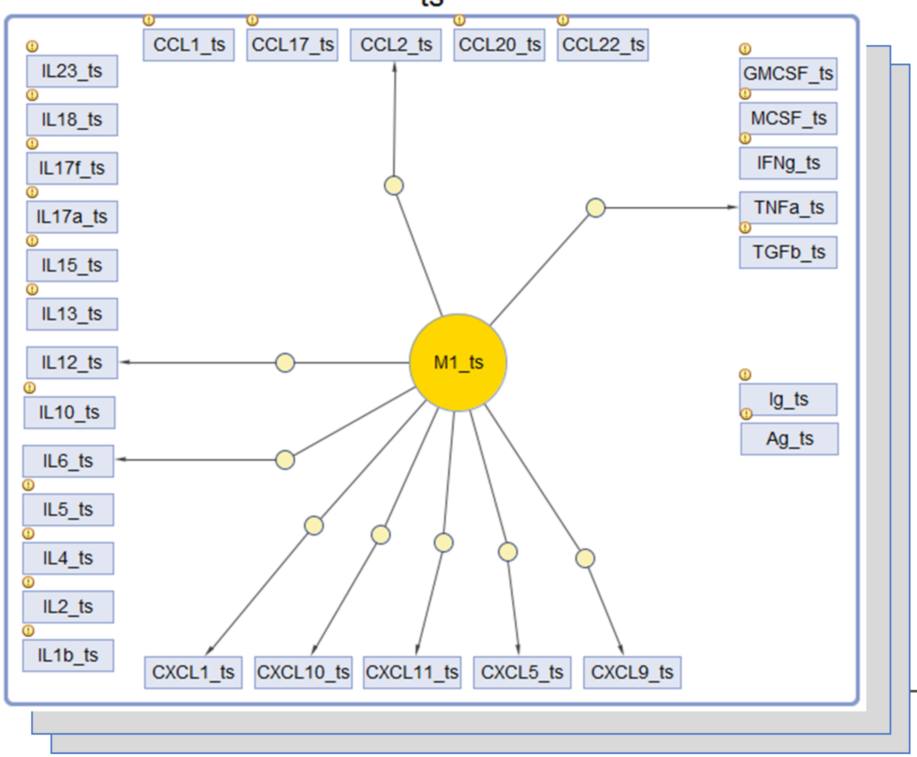
	Naïve CD8+ / mature CTL T cells	CCL1/2/17/20/22	
	NK cells	CXCL1/5/9/10/11	



Effector production by M1 macrophage

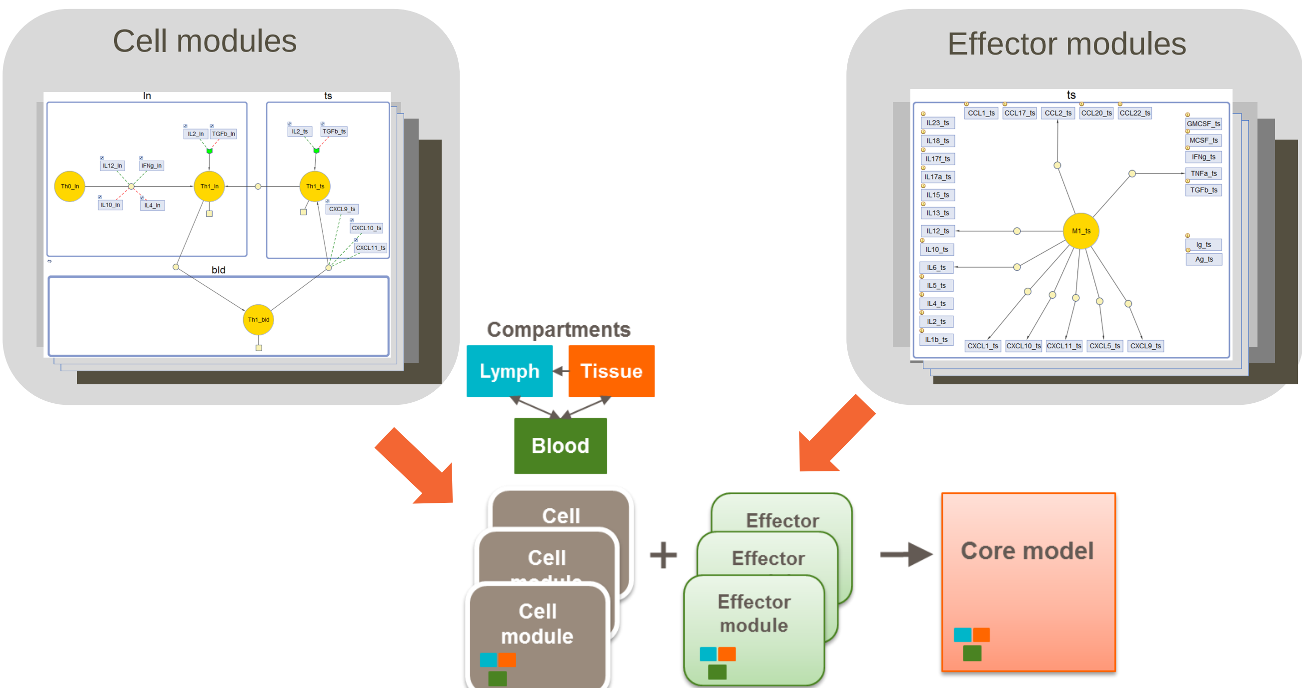
Each effector module describe the production of cytokines and chemokines for each cell-type

Benefits:

- Each effector module can represent an *in-vitro* experiment, allows easier parameterization
- Easier to make changes as needed in these individual effector modules vs. "full model"

Building the core IO model from cell and effector modules

Tissue compartments	Cell-types	Soluble effectors	Surface receptors (molecules)
Lymph (ln)	Tumor cell (prototypical solid)	GM-CSF/ M-CSF	MHC-1 & -2
Blood (bld)	Dendritic cell	IFNg	CD80/86
TME (ts)	Type 1 & 2 Macrophages	TNFa	CD40/40L
	MDSC	TGFb	PD1/PD-L1
	B cells	IL-1/2/4/5/6/10/12	OX40
	Th0/1/2/17/Reg (CD4+) T cells	IL-13/15/17/18/23	CTLA4
	Naïve CD8+ / mature CTL T cells	CCL1/2/17/20/22	
	NK cells	CXCL1/5/9/10/11	



Co-receptors have different expression dynamics

		Resting T cell	Stimulated T cell				
Receptor	Data type (RNA or Protein)	Receptor conc.	Detectable expression	Peak expression	Receptor conc.	Receptor t1/2	Ref.
OX40	RNA	No	12 h	24 h			1,2
	Protein		24 h	40-48 h	~15,000/cell	2 h without ligand 30 min with ligand	
PD1	RNA	Very low	2-24 h	48-72 h	NA	NA	3
CTLA4	RNA	No	0 h	24-48 h			4,5,6
	Protein	No	4 h	24-48 h	NA	2 h	

References

1 Soroosh, P., Ine, S., Sugamura, K., and Ishii, N. (2006). OX40-OX40 Ligand Interaction through T Cell-T Cell Contact Contributes to CD4 T Cell Longevity. The Journal of Immunology 176, 5975–5987

2 Watanabe, N., Kuriyama, H., Sone, H., Neda, H., Yamauchi, N., Maeda, M., and Niitsu, Y. (1988). Continuous internalization of tumor necrosis factor receptors in a human myosarcoma cell line. J. Biol. Chem. 263, 10262–10266.

3 Chemnitz, J.M., Parry, R.V., Nichols, K.E., June, C.H., and Riley, J.L. (2004). SHP-1 and SHP-2 Associate with Immunoreceptor Tyrosine-Based Switch Motif of Programmed Death 1 upon Primary Human T Cell Stimulation, but Only Receptor Ligation Prevents T Cell Activation. The Journal of Immunology 173, 945–954.

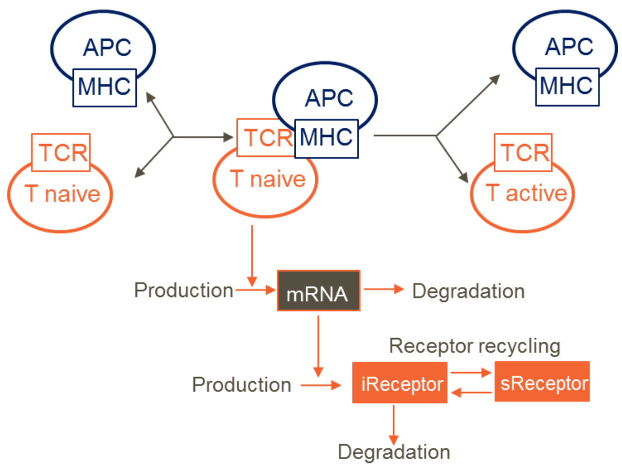
4 Egen, J.G., and Allison, J.P. (2002). Cytotoxic T Lymphocyte Antigen-4 Accumulation in the Immunological Synapse Is Regulated by TCR Signal Strength. Immunity 16, 23–35.

5 Linsley, P.S., Greene, J.L., Tan, P., Bradshaw, J., Ledbetter, J.A., Anasetti, C., and Damle, N.K. (1992). Coexpression and functional cooperation of CTLA-4 and CD28 on activated T lymphocytes. Journal of Experimental Medicine 176, 1595–1604

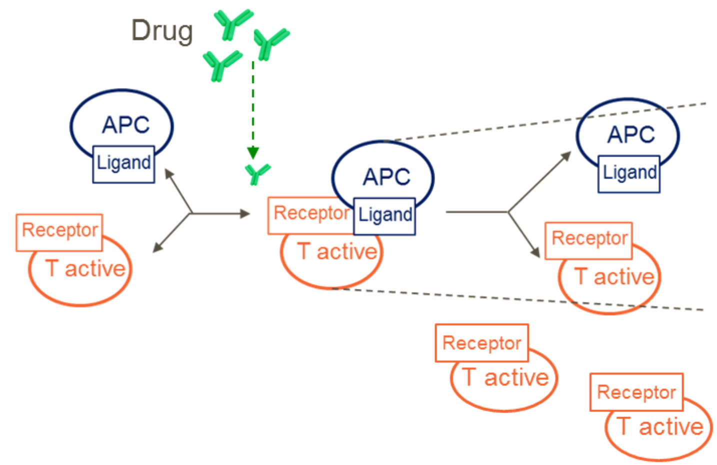
6 Knieke, K., Hoff, H., Maszyna, F., Kolar, P., Schrage, A., Hamann, A., Debes, G.F., and Brunner-Weinzierl, M.C. (2009). CD152 (CTLA-4) Determines CD4 T Cell Migration In Vitro and In Vivo. PLOS ONE 4, e5702.

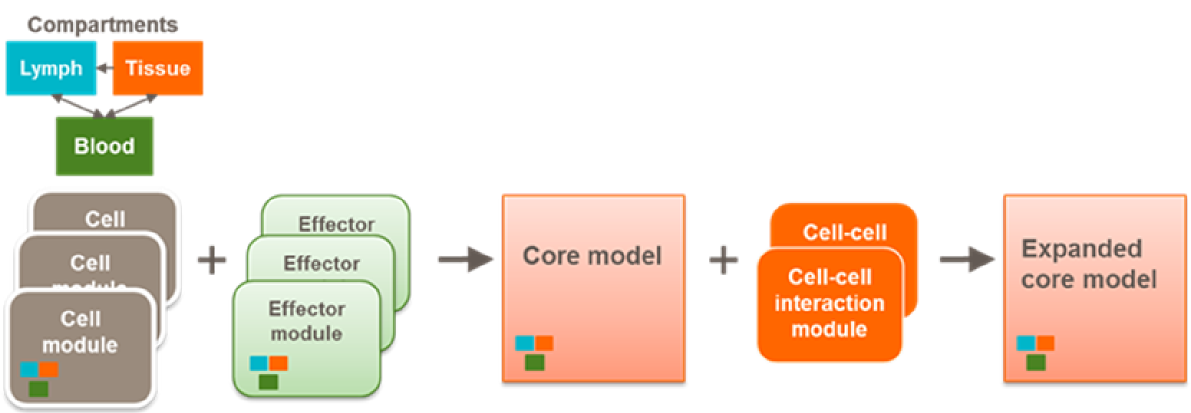
Modeling Co-receptor expression dynamics and effect on Tcells

Co-receptor expression following Tcell activation via MHC-TCR interaction



Co-receptor-ligand driven expansion or exhaustion of Tcells



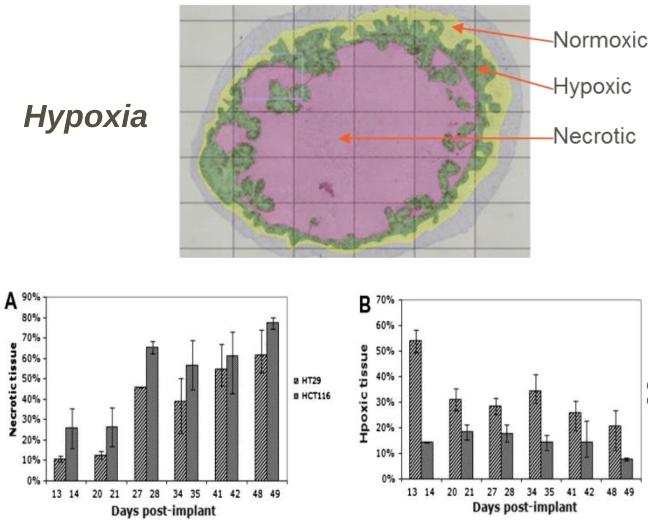


<u>Model components</u>

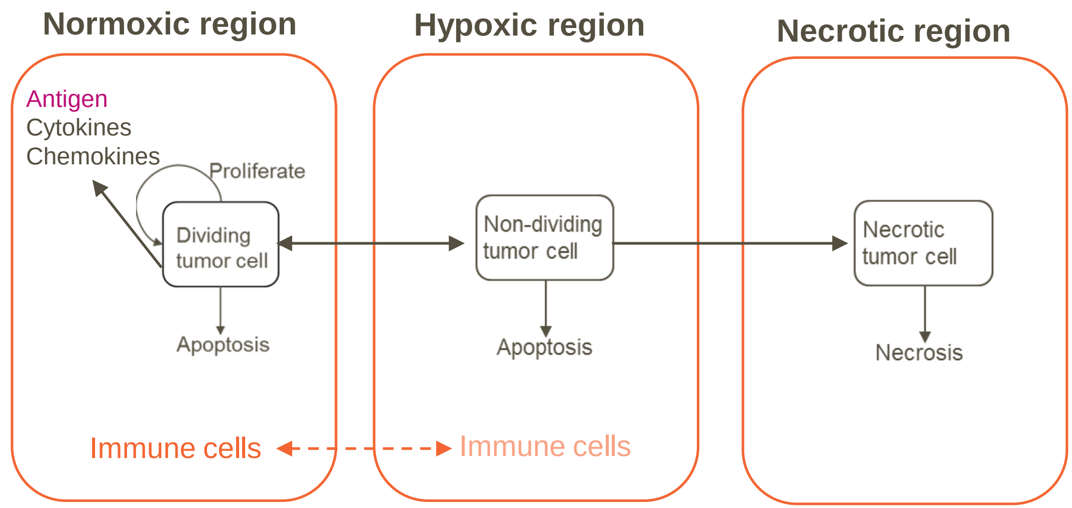
Compartments:	5
Parameters:	647
Reactions:	1940
Rules:	82
Species:	546

Modeling Tumor Growth and Heterogeneity

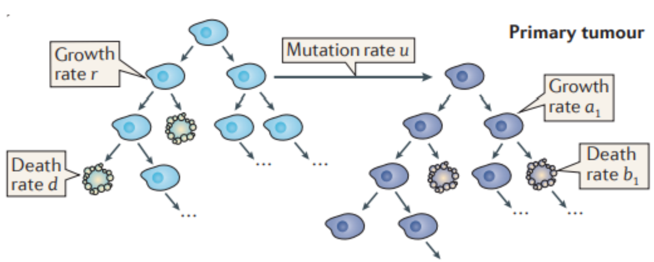
Hypoxia



Ribba, B., et al (2011). European Journal of Cancer *47*, 479–490.

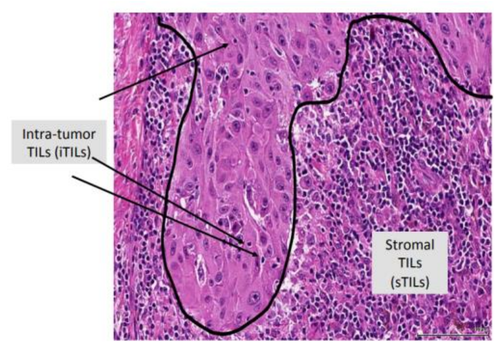


Mutational rate reflected by antigen production



↑Mutation rate ↑Antigen ↓Mutation rate ↓Antigen

Immune Cells

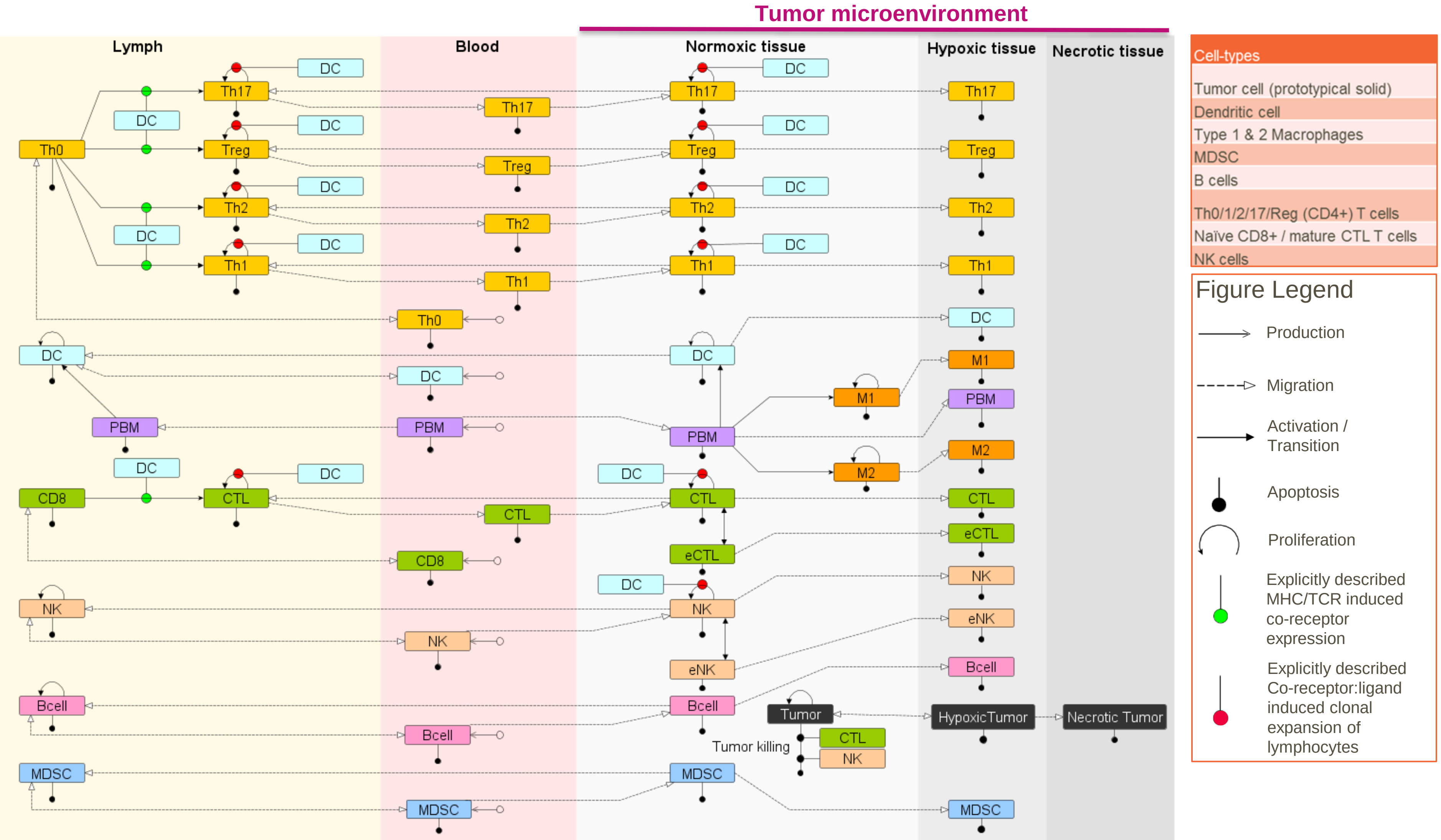


- TILs mainly in stroma or in outer tumor region
- Cytokine and chemokine production and co-receptor expression by tumor impacts immune cells migration and function

Altrock, P.M., Liu, L.L., and Michor, F. (2015). Nature Reviews Cancer *15*, 730–745.

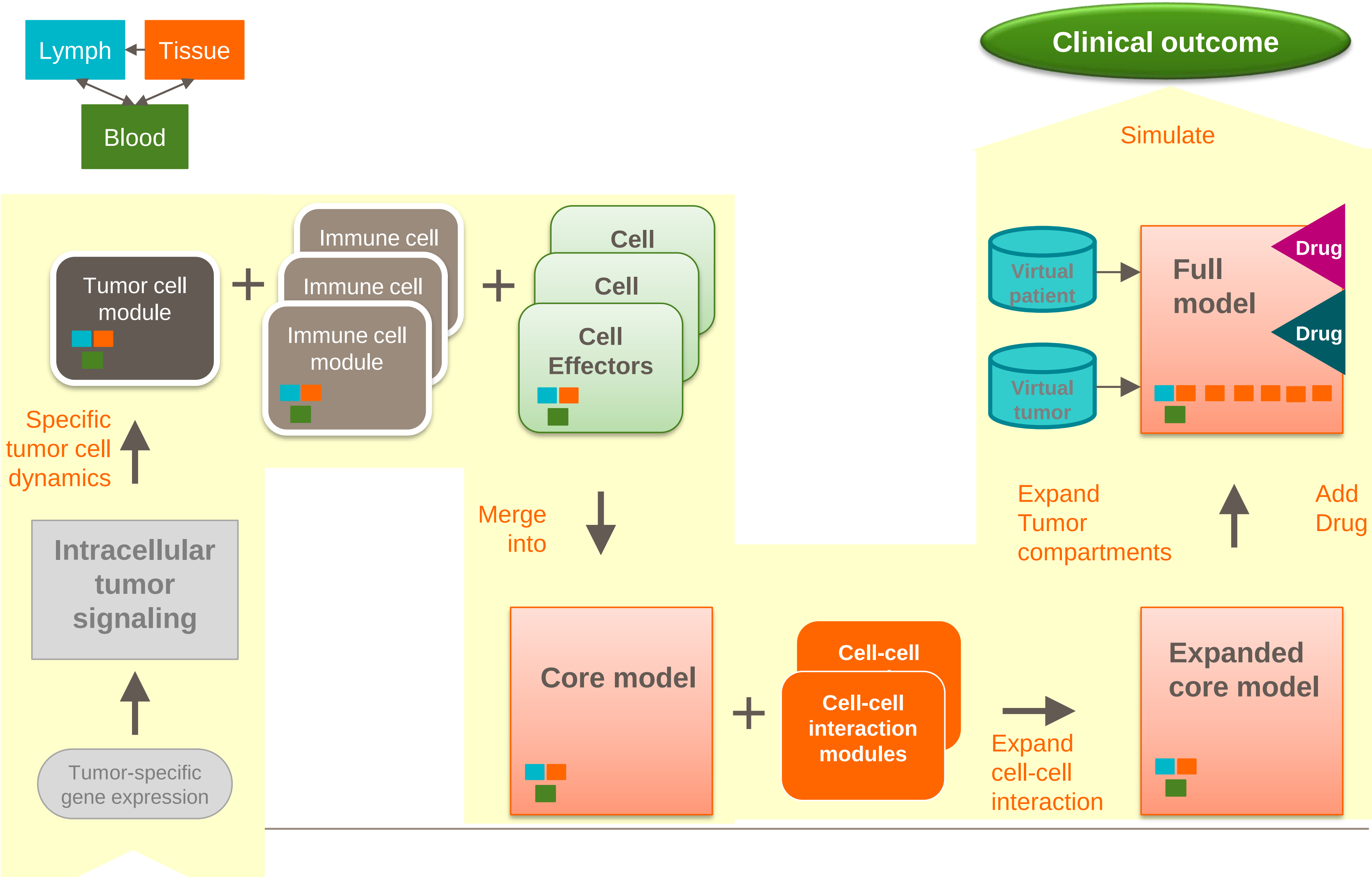
Hendry, S., et al. (2017). Advances in Anatomic Pathology *24*, 235–251.

Immune Cells in Tumor Microenvironment



No proliferation or effector production in hypoxic region

Immuno-oncology QSP Model Modular Development



QSP Automation Tools

QSP Automation Tools

Model Development → **Model Qualification** → **Model Simulations** → **Model Deployment**

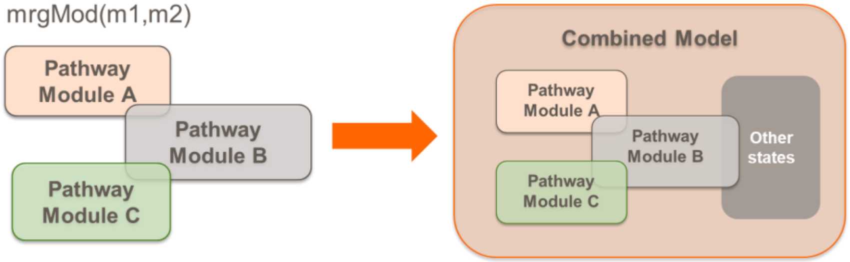
Model Development
- **Module development**
- **Model operations** (compare, merge, copy, multiply)
- **Parameter database**

Model Qualification
- **Debugging tools**
- **Automated calibration** of model states
- **Model checking** with literature data

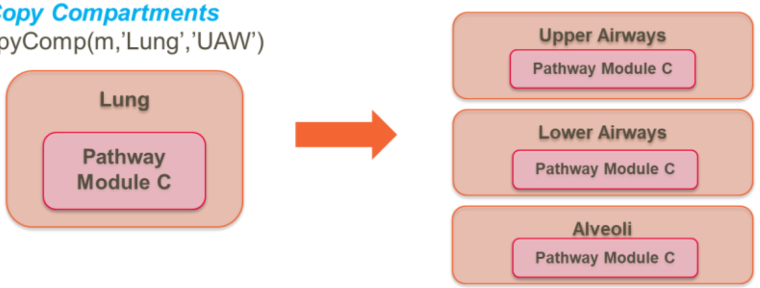
Model Simulations
- Plotting tools
- **Virtual patient simulations**
- **Sbml import/ export tools**

Model Deployment
- **Web-based model simulations (SimPod)**
- **Web-based model layout/ diagram**

Merge models
mrgMod(m1,m2)



Copy Compartments
cpyComp(m,'Lung','UAW')



Completed
On-going

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Tissue	Fluid	Cell	Effector	Process	ParameterTyp	ParameterID	Value	Unit	Description	Min	Max	Mean
		Mast cell	TSLP	Activation	base rate	EC50_tslp_act_MC_base	100000	pM	base EC50 for MC activation by	100000	100000	100000
		Eosinophils	TSLP	Migration	EC50	EC50_tslp_vcam_migr_eo	8	pM	EC50 for EO migration stimulati	8	8	8
Alveolar			Elastin Fibers		level	EF_al_HS_prev	3.5E+09	pM	elastic fiber concentration in al	3E+09	4E+09	3.5E+09
					Activating factor	FEV1_max_ref	4	L	maximum value of FEV1 in refe	2.8	6	4
		Th0	IL10	Differentiation	IC50	IC50_IL10_dif_Th0	50	pM	IC50 for inhibitory effect of IL10 on differentiation of Th0			
		iDC	IL10	Differentiation	IC50	IC50_IL10_dif_iDC	48	pM	IC50 for IL-10 effect on dendriti	48	48	48
		iMph	IL10	Differentiation	IC50	IC50_IL10_dif_iMph	48	pM	IC 50 for IL-10 effect on M1 polarization			
			IL10	Synthesis	IC50	IC50_IL10_ot_CCL19_syn	50	pM	IC50 for inhibitory effect of IL10 on sythesis of CCL19 by other ti			
		Cilia	IL13	Production	IC50	IC50_IL13_Cil_prod	70.33	pM				
		Th0	IL15	Apoptosis	IC50	IC50_IL15_apo_Th0	50	pM	IC50 for inhibitory effect of IL15 on apoptosis of Th0			
		CD8	IL15	Apoptosis	IC50	IC50_IL15_cd8_apo	50	pM	IC50 for IL-15 effect on apoptosis of CD8+ cells			
		Cilia	IL1b	Production	IC50	IC50_IL1b_Cil_prod	32000	pM				
		Goblet	IL1b	Production	IC50	IC50_IL1b_Gob_prod	32000	pM				
		Th0	IL4	Differentiation	IC50	IC50_IL4_dif_Th0	50	pM	IC50 for inhibitory effect of IL4 on differentiation of Th0			
			IL6		IC50	IC50_IL6	2.951345	pM	IC50 for IL-6 inhibitory effect or	2.951345	2.951345	2.951345
		CTL	TGFb	Killing	IC50	IC50_TGFb_CTL_kill	500	pM	IC50 for TGFb effect on cytotoxic interaction of CTL with target c			
		iDC	TGFb	Differentiation	IC50	IC50_TGFb_dif_iDC	3.03	pM	IC50 for TGFb effect on iDC deif	3.03	3.03	3.03
		iMph	TGFb	Differentiation	IC50	IC50_TGFb_dif_iMph	3.03	pM	IC 50 for TGFb effect on M1 pola	3.03	3.03	3.03
		Th1	TGFb	Proliferation	IC50	IC50_TGFb_pro_Th1	5	pM	IC50 for TGFb effect on Th1 proliferation			
		Th2	TGFb	Proliferation	IC50	IC50_TGFb_pro_Th2	5	pM	IC50r for TGFb effect on Th2 proliferation			
					IC50	IC50_zileut	850000	pM	IC50 for LTA4 production by Zile	850000	850000	850000
Plasma			IL25		level	IL25_pl	2.210287	pM	Interleukin 25 in plasma	2.210287	2.210287	2.210287
Alveolar			IgA		level	IgA_al	16895659	pM	Fixed concentration of IgA_aw	16895659	16895659	16895659
Airway			IgA		level	IgA_aw	16895659	pM	Fixed concentration of IgA_aw	16895659	16895659	16895659
Plasma			IgA		level	IgA_pl	16895659	pM	Fixed concentration of IgA_pl f	16895659	16895659	16895659
Upper Airway			IgA		level	IgA_uaw	16895659	pM	Fixed concentration of IgA_aw	16895659	16895659	16895659

- **Database of parameters and species levels**

Completed

On-going

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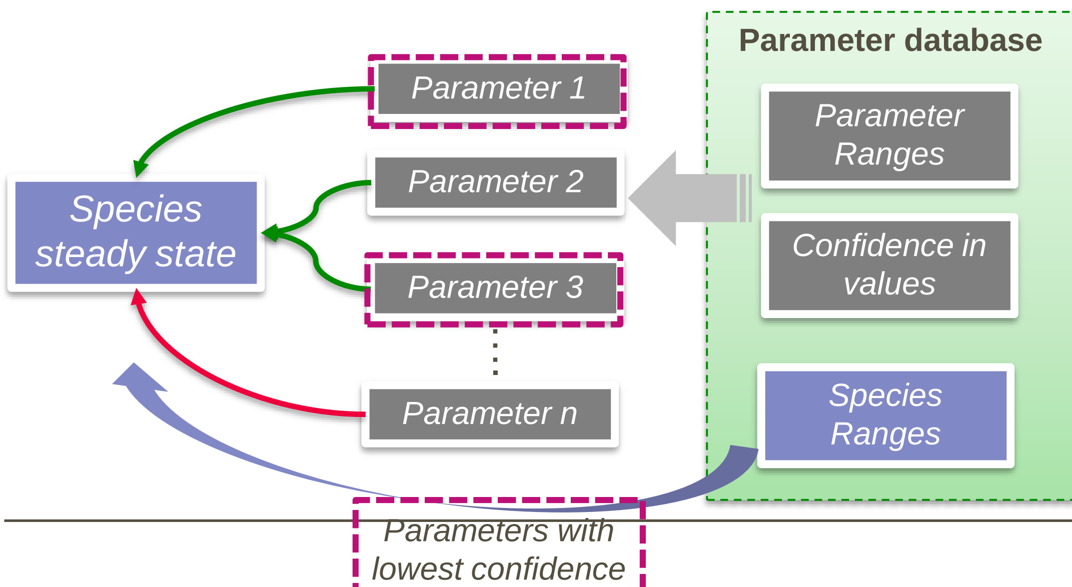

AdjPrms(m,sp)

Optimization problem

Minimize difference in simulated species and clinical ranges

By changing parameters with lowest confidence

Completed
On-going

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res = analyzeModel(m)

Fields	Name	Info	pf	Results
1	'Fluxes'	'Checking fluxes for species'	'fail'	1x1 struct
2	'Reactions'	'Checking reactions in the model'	'fail'	1x6 struct
3	'Units'	'Checking unit assignment'	'pass'	[]

Multiple model checks implemented

Flux checking to see if a species might go negative

res(1).Results

Field	Value
Species	'cyto.TRX'
Name	'cyto.KEAP1ox + cyto.TRX -> cyto.KEAP1 + cyto.TRXox'
RxnRate	'kTrx * cyto.KEAP1ox * cyto.H2O2'
RxnObj	1x1 Reaction

Negative flux for cyto.TRX but reaction rate doesn't depend on it

res(2).Results **Inconsistencies in reaction and reaction rates**

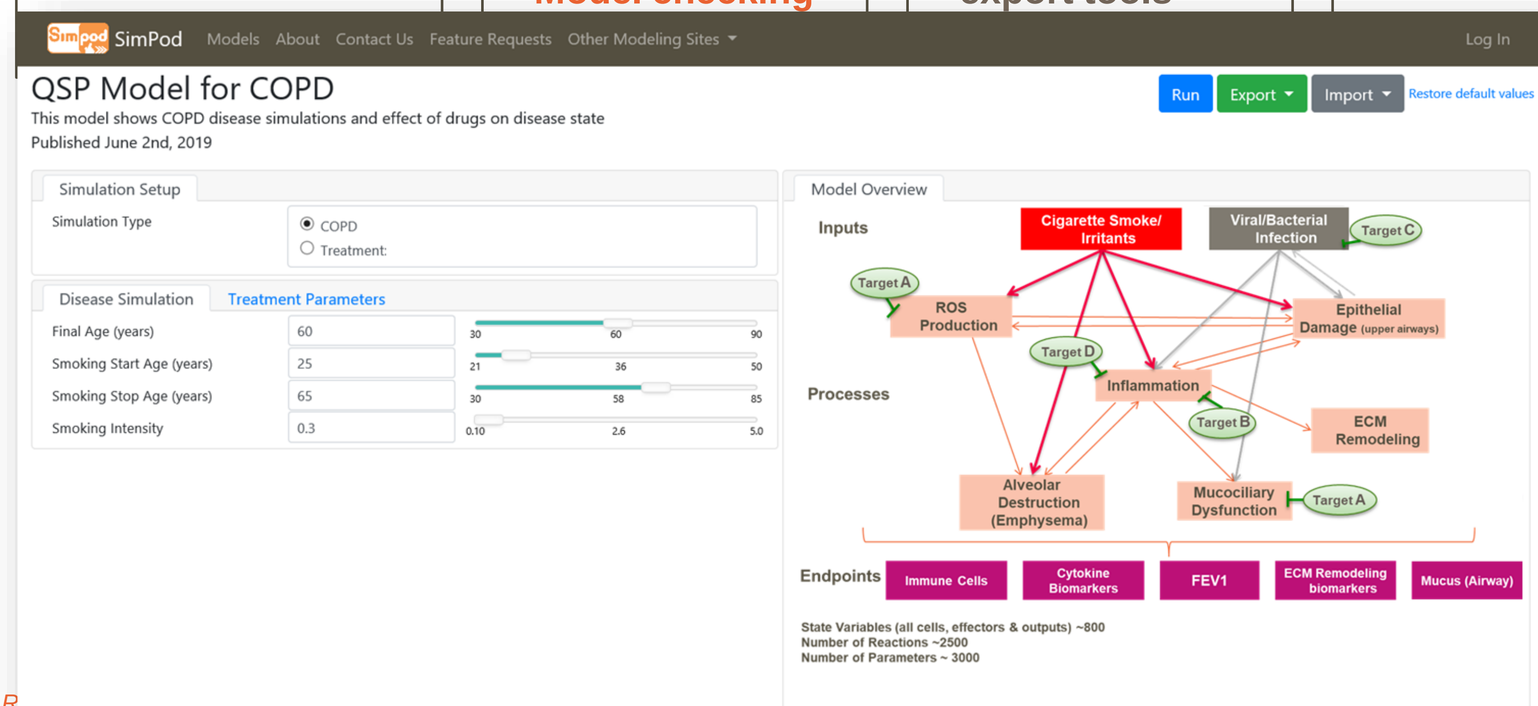
RxnObj	Name	RxnRate	Species
1x1 Reaction	'cyto.KEAP1ox + cyto.TRX -> cyto.KEAP1 + cyto.TRXox'	'kTrx * cyto.KEAP1ox * cyto.H2O2'	'cyto.H2O2'
1x1 Reaction	'cyto.KEAP1ox + cyto.TRX -> cyto.KEAP1 + cyto.TRXox'	'kTrx * cyto.KEAP1ox * cyto.H2O2'	'cyto.TRX'
1x1 Reaction	'cyto.TRXox -> cyto.TRX'	'kTR * cyto.TR * cyto.TRXox * cyto.NADPH / (KTRTRX * K...	2x1 cell

Completed

On-going

QSP Automation Tools

Model Development	Model Qualification	Model Simulations	Model Deployment
• **Module development** • **Model operations** (compare, merge, copy, multiply)	• **Debugging tools** • **Automated calibration** of model states • **Model checking**	• Plotting tools • **Virtual patient simulations** • **Sbml import/ export tools**	• **Web-based model simulations (SimPod)** • **Web-based model layout/ diagram**



Completed

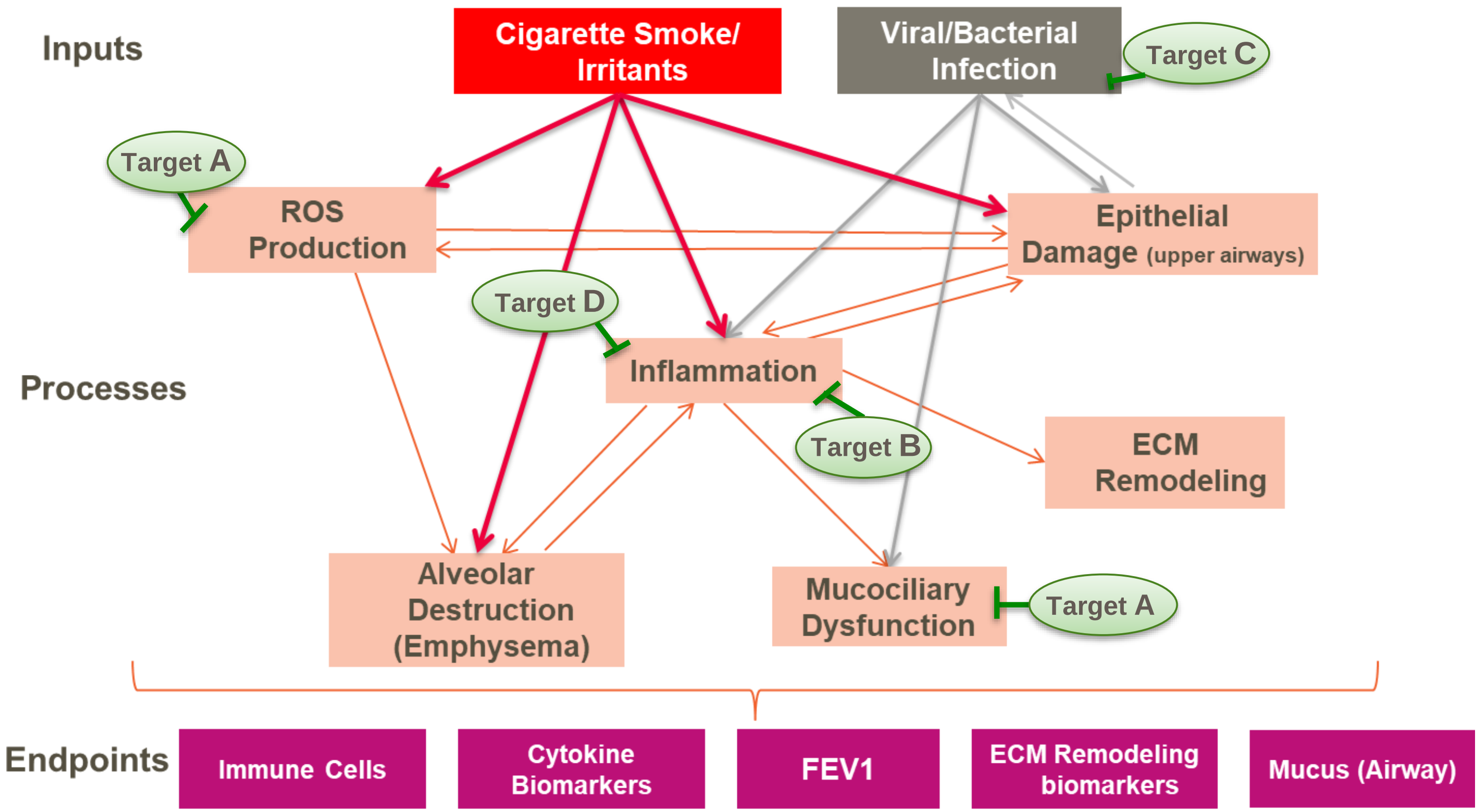
On-going

Application of a QSP Platform Model for COPD Portfolio

Modeling done by Cibele V. Falkenberg (GSK)

COPD QSP Platform Overview

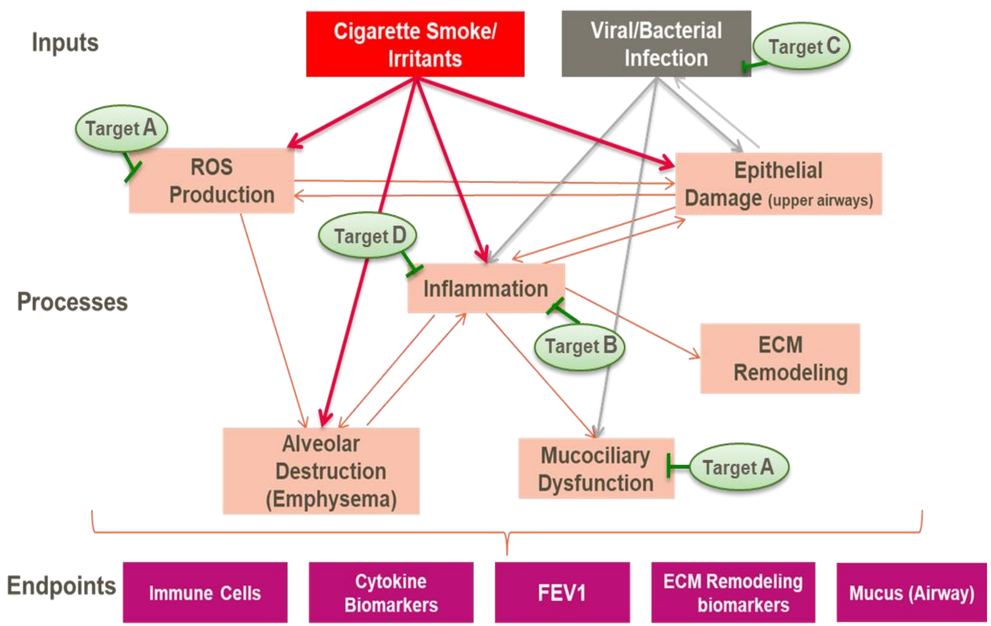
- Chronic Obstructive Pulmonary disease (COPD) is caused by long term exposure to irritants, primarily by cigarette smoke
- Complex disease, with coupled processes involving altered immune and tissue cell populations, leading to inflammation, mucus production and tissue destruction.



Model Development Team: GSK Modelers, GSK Respiratory Scientists, CRO (InSysBio)

COPD QSP Platform Overview

Model Development using Cell and Effector Modules

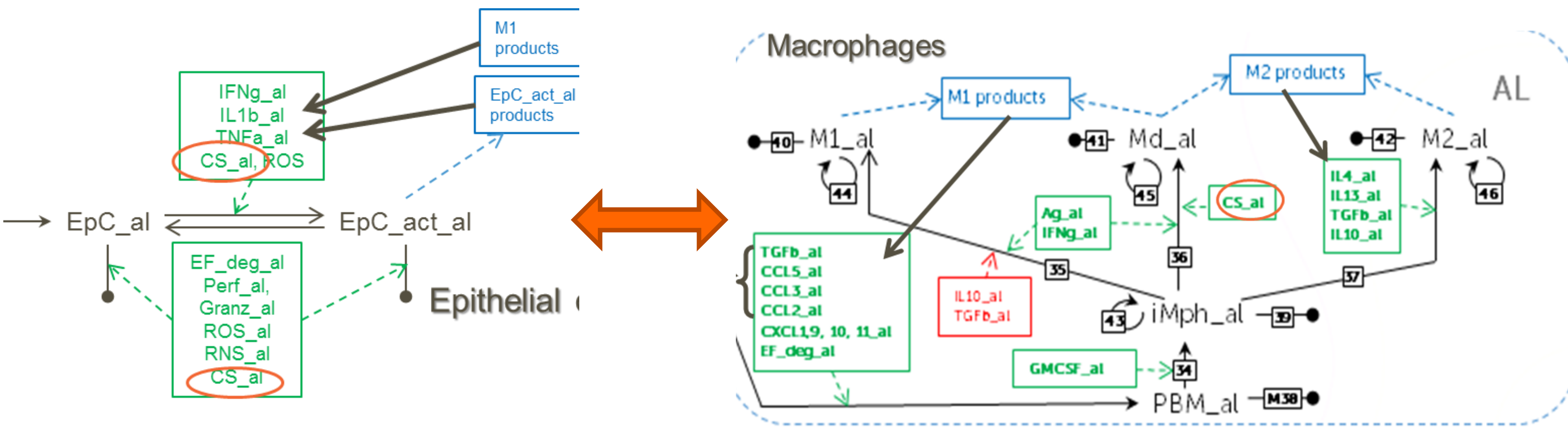


Model Components	
6 Tissue Compartments	Lymph Node, Blood, Bone Marrow, Lung (Alveolar, Upper Airways, Lower Airways)
19 Cell types	PBM, M1,M2 DC, Th0, Th1, Th2, Th17, Treg, CD8_naive, CTL, Neutrophils, Epithelial, endothelial, Eosinophils etc
118 Cell states	active, inactive, M1 M2 etc (for all compartments)
309 Cell processes	origination, maturation, proliferation, migration, activation, apoptosis (for each cell type)
56 Regulators	**55** (cytokines, chemokines, other effectors)

State Variables (all cells, effectors & outputs) ~800
Number of Reactions ~2500
Number of Parameters ~ 3000

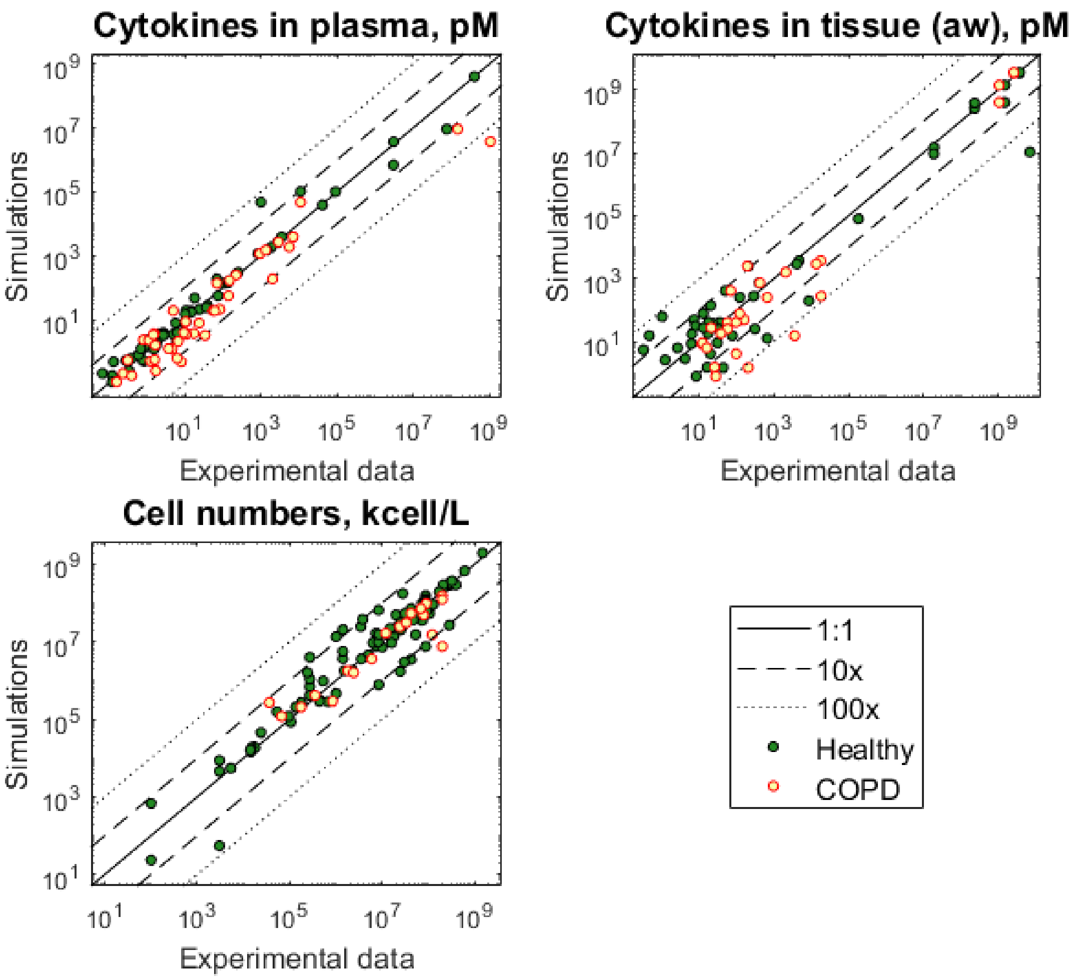
Cigarette Smoke driven disease progression

In the model, cigarette smoke (CS) is responsible for the transition from healthy to the COPD state.



Model validation

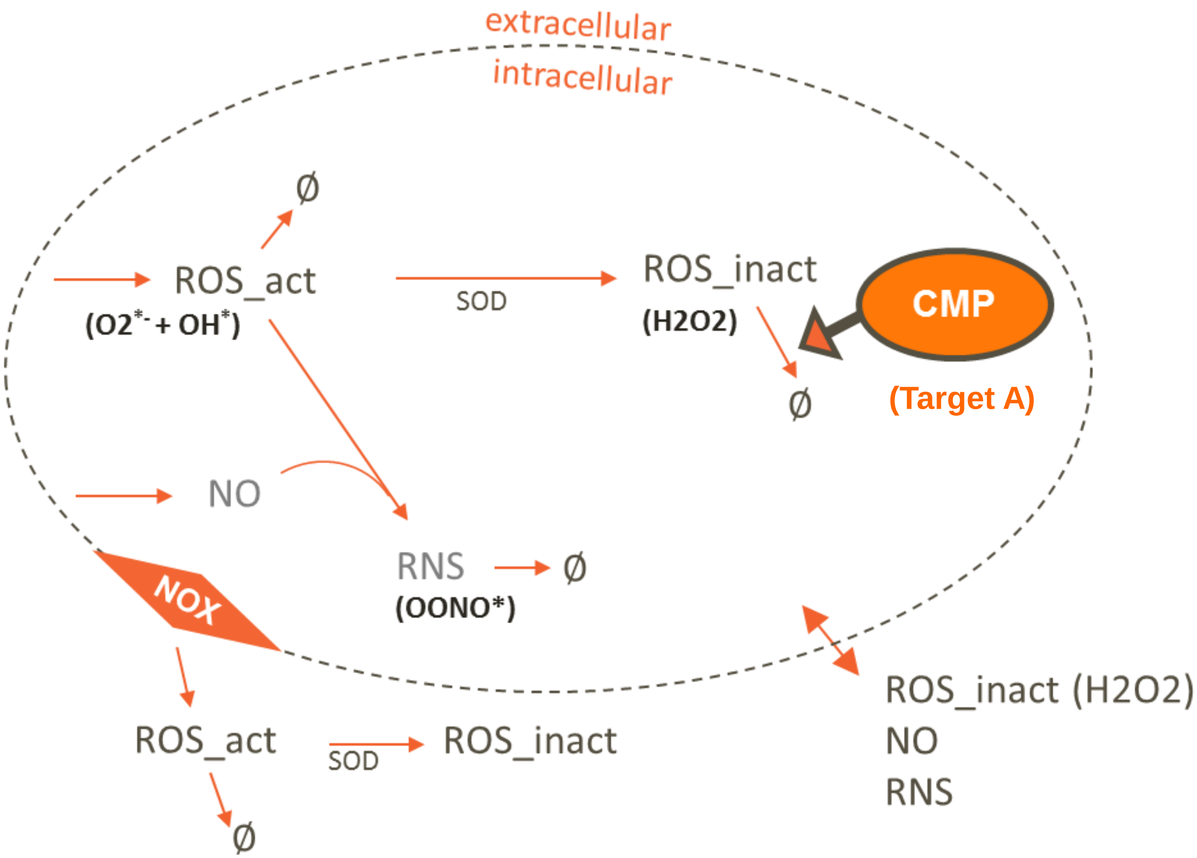
Comparison with Patient Data



Values for cell numbers, cytokines (and chemokines) in plasma and tissue were compared with human data.

- The simulated COPD state was obtained after 40yr exposure to high levels of CS.
- Data in tissue (aw) was calculated using measurements from BAL and sputum.
- Data from publications; number of data points ranging from 2 to 948 for each variable in each publication, mean=35.2;
- When available, variable average was calculated using several publications.

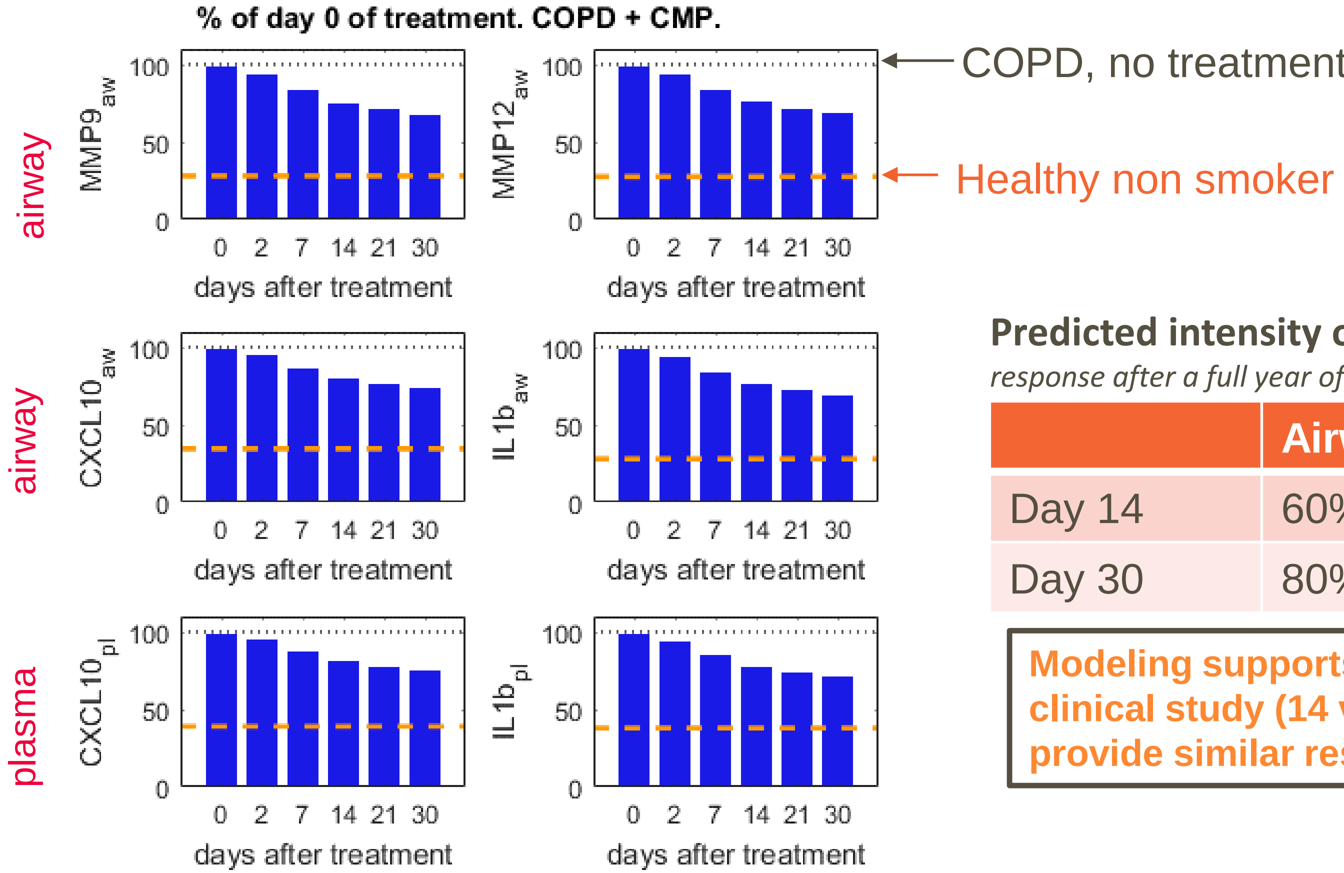
Target A: ROS production and elimination



- The model was updated to account for intracellular production of hydrogen peroxide, and its elimination.
- Target A engagement results in enhancement of the cell's ability to handle hydrogen peroxide.

***Question from Program Team:** How long does it take for biomarker changes resulting from target A modulation to be measurable?*

Target A: QSP Modeling Results



Predicted intensity of response *relative to predicted response after a full year of treatment (preliminary results)*

	Airway	Plasma
Day 14	60%	70%
Day 30	80%	90%

Modeling supports a shorter duration clinical study (14 vs 30 days) would provide similar results.

Target B: COPD model currently applied for efficacious dose prediction to support candidate selection

To hear more details

- **Roy Song,** “Development of immuno-oncology (IO) quantitative systems pharmacology (QSP) model for evaluation of clinical dose for coreceptor-mediated IO therapies”

  SMB Annual Meeting, Montreal, Canada, 22nd-26th July, 2019

- **Cibele Falkenberg,** “Application of a Quantitative Systems Pharmacology (QSP) model of COPD progression for evaluating a novel mechanism targeting oxidative stress and inflammation in the lung”

  ISoP Regional QSP Day 2019, Princeton NJ, 16th July 2019

Acknowledgements

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  - Roy Song
  - Bob Bondi
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  - Herbert Struemper

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  - Heather Jackson
  - Paul Bojczuk

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  - Phil Landis
  - James Callahan
  - Bill Rumsey
  - Heidi Feldser

- **CRO:** InSysBio

Thank you!