ASCPT 2019: From Molecule to Patient
Session: Connecting Cell Biology to Patient Populations:
Clinical Applications of Multi-Scale Systems Pharmacology

Bridging Mechanistic Models & Patient Data in Virtual Clinical Trials

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QSP (Quantitative & Systems Pharmacology)

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 – October, 2011

Peter K. Sorger (co-chair), Sandra R.B. Allerheiligen (co-chair)

Darrell R. Abernethy, Russ B. Altman, Kim L. R. Brouwer, Andrea Califano, David Z. D'Argenio, Ravi Iyengar, William J. Jusko, Richard Lalonde, Douglas A. Lauffenburger, Brian Shoichet, James L. Stevens, Shankar Subramaniam, Piet Van der Graaf and Paolo Vicini

Rebecca Ward (editor)

*"We require better quantitative models of pharmacological **mechanism at all scales**, starting with single targets and drugs and scaling to vertically and horizontally integrated **multi-scale models**."*

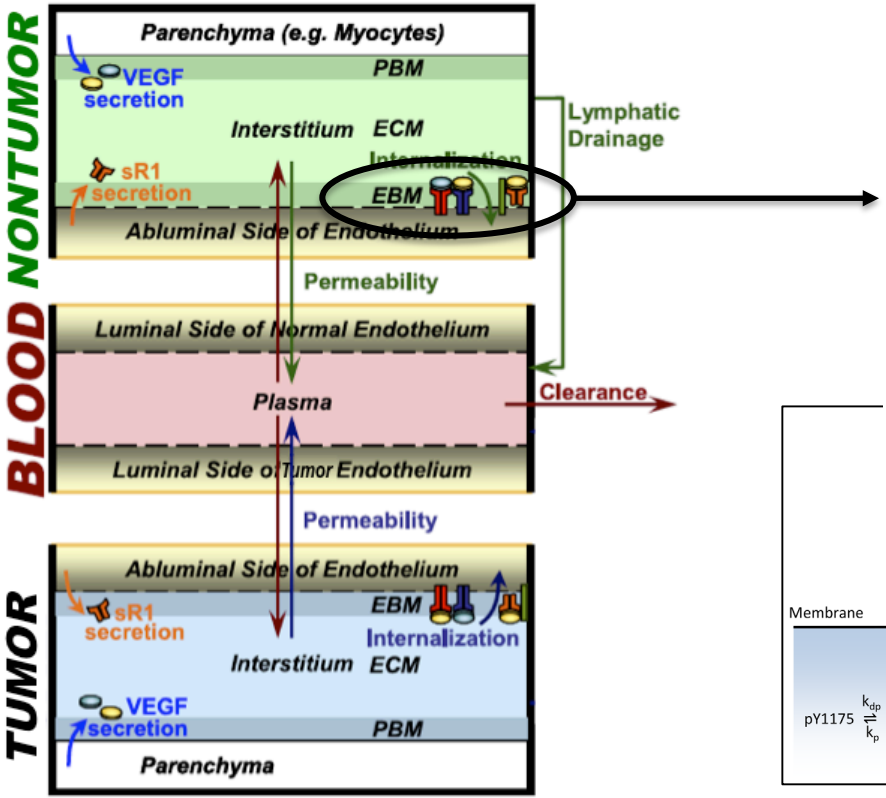
‘Mechanism at all scales’ moves us from drug-centered modeling to target-centered modeling

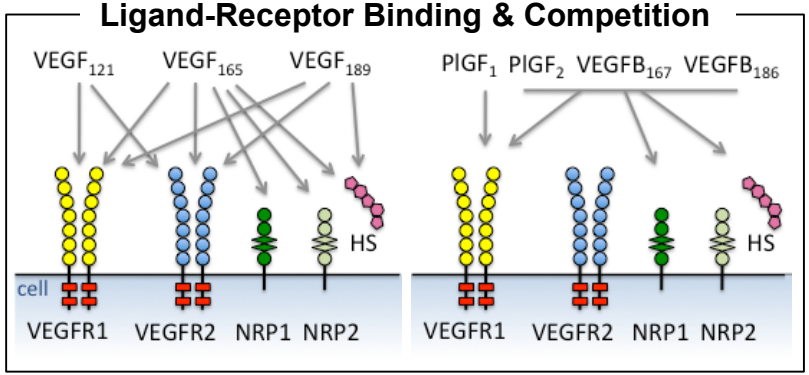
By moving from ‘drug-first’ modeling to ‘target-first’ modeling, we can build platforms that enable simulation and comparison of different therapies (and combinations) in a common framework.

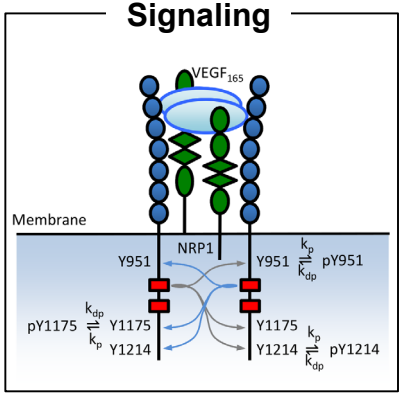
These models can include the target’s complex and dynamic environment, including interaction networks.

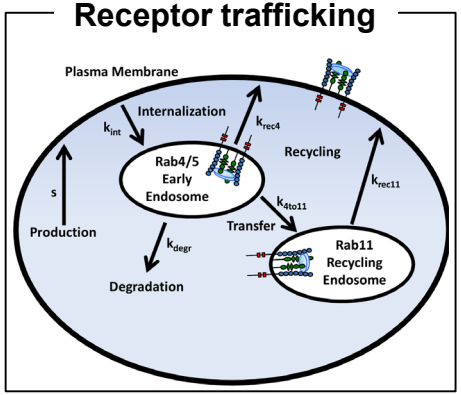
Changing perspective to detailed mechanism of action allows us to simulate more complex therapies and multi-step clinical protocols.

Multiscale mechanistic models combine **physiology** with detailed **molecular and cellular biology**









Clegg and Mac Gabhann, PLoS Comp Biol 2015

The models are built on mechanisms (the obligatory intimidating equation slide)

Secretion from cells

Sequestration in extracellular matrix

$$\frac{d[V_{165}]_N}{dt} = q^N_{V165} - k_{on,V165,MEBM}[V_{165}]_N[M_{EBM}]_N + k_{off,V165,MEBM}[V_{165}M_{EBM}]_N$$
$$- k_{on,V165,MECM}[V_{165}]_N[M_{ECM}]_N + k_{off,V165MECM}[V_{165}M_{ECM}]_N$$
$$- k_{on,V165,MPBM}[V_{165}]_N[M_{PBM}]_N + k_{off,V165MPBM}[V_{165}M_{PBM}]_N$$

Binding to cell surface receptors

$$- k_{on,V165,R1}[V_{165}]_N[R_1]_N + k_{off,V165R1}[V_{165}R_1]_N - k_{on,V165,R2}[V_{165}]_N[R_2]_N$$
$$+ k_{off,V165R2}[V_{165}R_2]_N - k_{on,V165,N1}[V_{165}]_N[N_1]_N + k_{off,V165N1}[V_{165}N_1]_N$$

$$- k_{on,V121,A}[V_{165}]_N[A]_N + k_{off,V165A}[V_{165}A]_N$$

Drug targeting

$$-\left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_N}\right)\frac{[V_{165}]_N}{K_{AV,N}} + k^{BN}_{pV}\frac{S_{NB}}{U_N}\frac{U_B}{U_p}[V_{165}]_B$$

Vascular permeability and lymphatic transport

Stefanini et al, Cancer Res 2010

The models are built on mechanisms (the obligatory intimidating equation slide)

$$\frac{d\,[R2_{pY1175}]}{dt}$$

Binding/Unbinding Reactions

$$= k_{off,V\cdot R2}[V\cdot R2_{pY1175}] - k_{on,V\cdot R2}[V][R2_{pY1175}]$$

$$+ k_{off,(M\cdot V)\cdot R2}[M\cdot V\cdot R2_{pY1175}] - k_{on,(M\cdot V)\cdot R2}[M\cdot V][R2_{pY1175}]$$

Trafficking Processes

$$- k_{intn,R2_{pY1175}}[R2_{pY1175}] + k_{rec4,R2_{rab45,pY1175}}[R2_{rab45,pY1175}]$$

$$+ k_{rec11,R2_{rab11,pY1175}}[R2_{rab11,pY1175}] + k_{p,Y1175,R2}[R2]$$

$$- k_{dp,Y1175,R2_{pY1175}}[R2_{pY1175}] - k_{p,Y951,R2_{pY1175}}[R2_{pY1175}]$$

$$+ k_{dp,Y951,R2_{pY951-pY1175}}[R2_{pY951-pY1175}] - k_{p,Y1214,R2_{pY1175}}[R2_{pY1175}]$$

$$+ k_{dp,Y1214,R2_{pY951-pY1214}}[R2_{pY951-pY1214}]$$

Phosphorylation/Dephosphorylation Reactions

Clegg and Mac Gabhann, PLoS Comp Biol 2015

In many cases, we have the parameters we need to build detailed mechanistic models …

Anatomy/Geometry

Microvessel network

Tumor cell packing

Interstitial space, ECM

Basement membranes

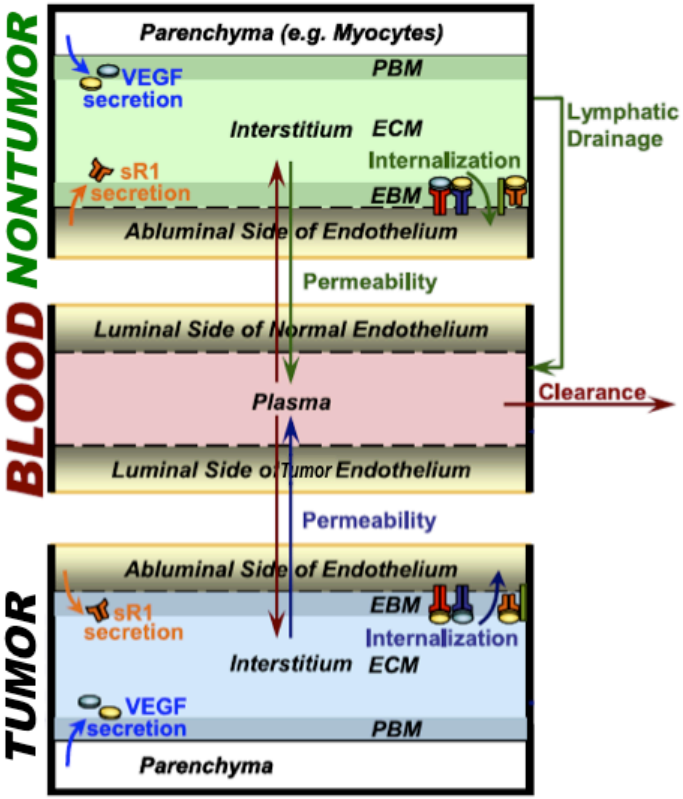
Ligands/Receptors

Receptor density

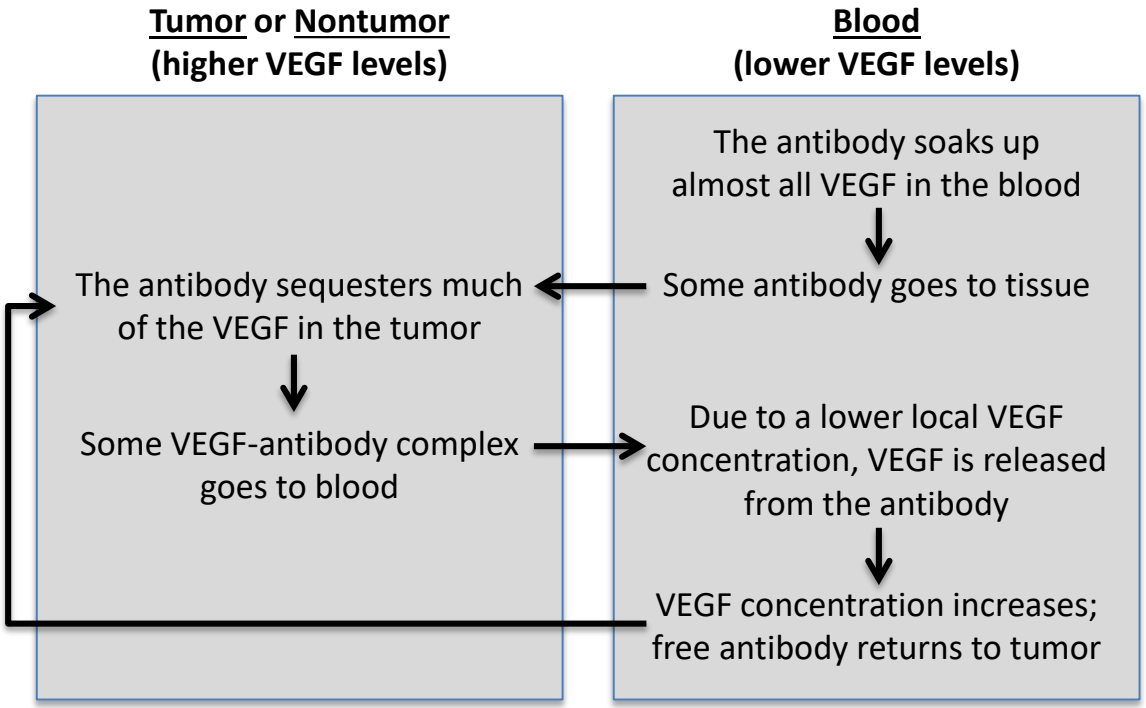
Ligand secretion rate, concentrations

Ligand-receptor binding kinetics

Extracellular matrix sequestration



… and these can lead to key mechanistic insights, such as a shuttling mechanism for bevacizumab



Stefanini et al, Cancer Res 2010

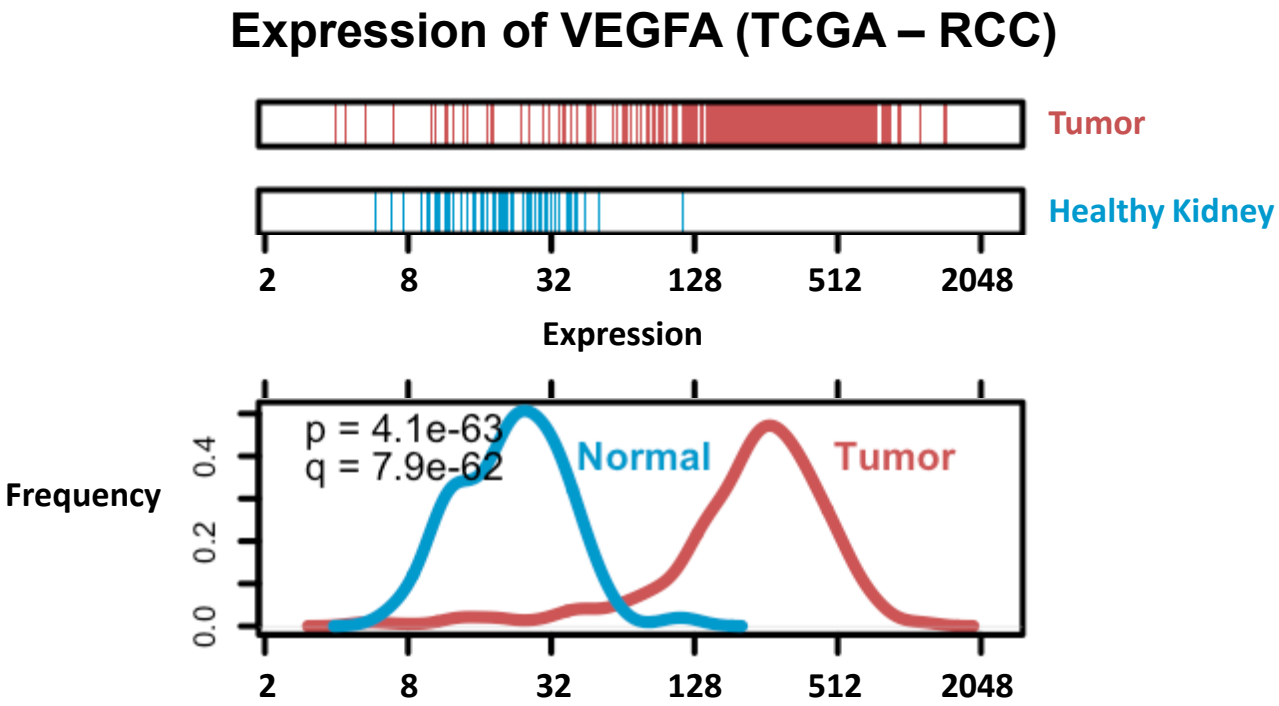
Understanding **variability across the population** is crucial for predicting likelihood of treatment success

Population pharmacokinetics (PopPK) studies one element of variability across patients. It can help to decrease variability in drug exposure, typically by informing dosing and scheduling.

Pharmacogenomics is another source of variability; SNPs may be biomarkers for therapeutic success (e.g. gefitinib & EGFR)

With detailed multiscale modeling of therapy *mechanism of action*, we can also consider population pharmacodynamics (PopPD) as a source of variability in efficacy from person to person.

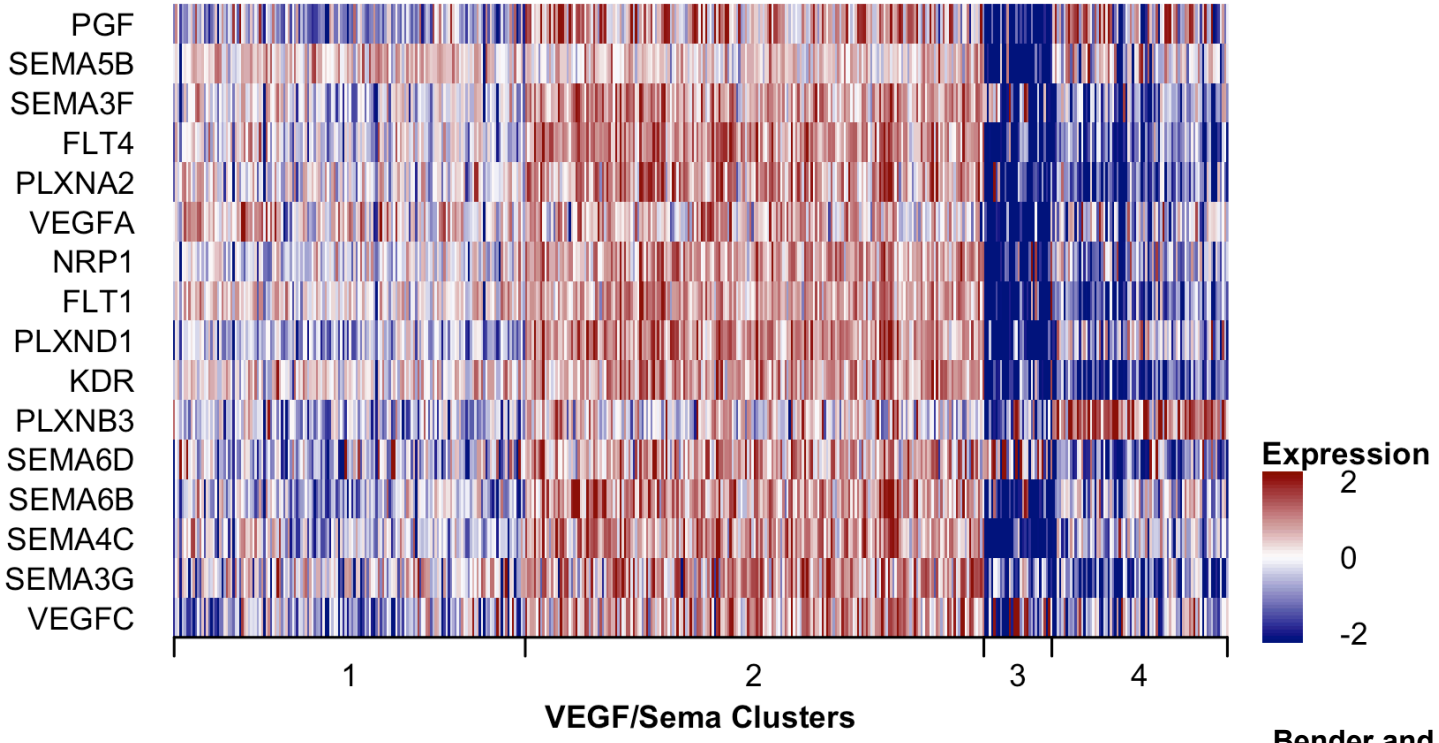
Gene and protein expression can show high variability in the population …



Bender and Mac Gabhann

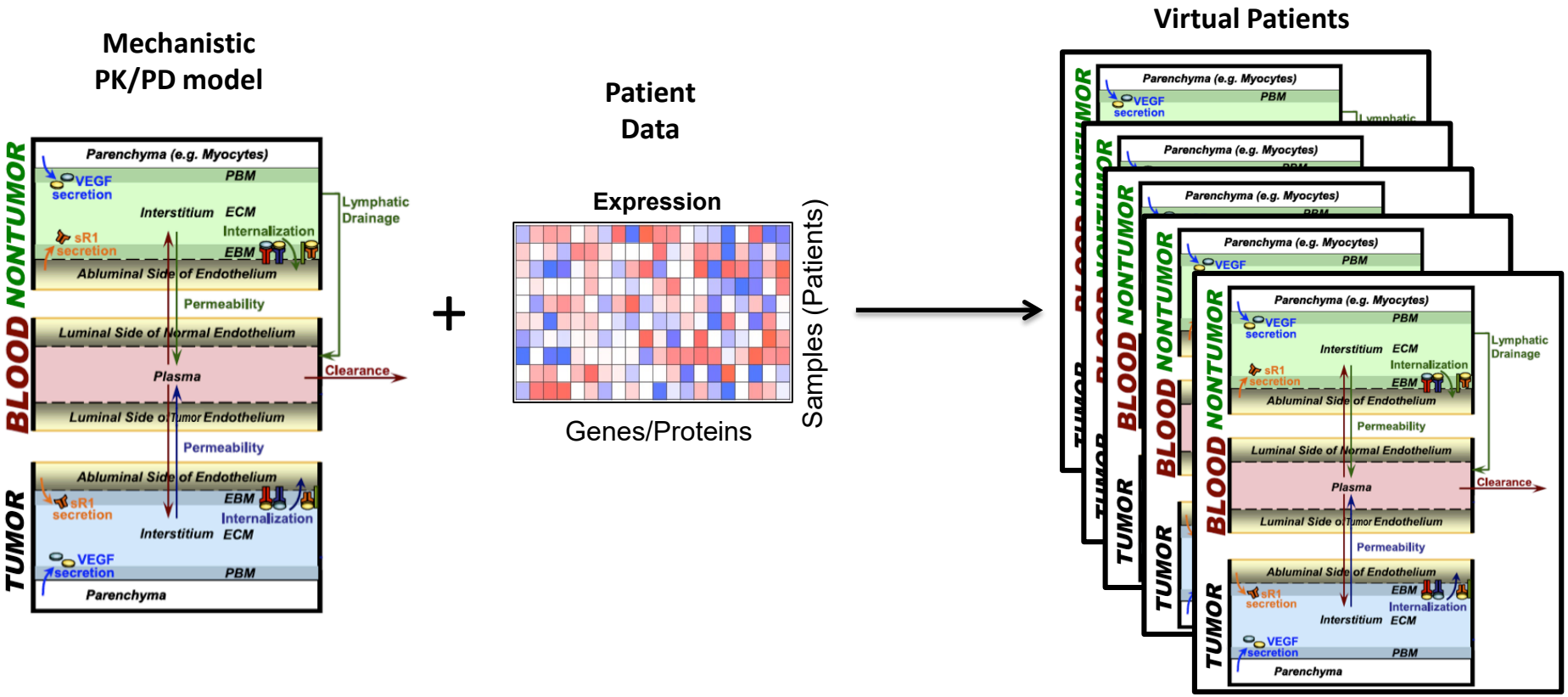
… and variability can be high for multiple components in the network

Expression of multiple network genes (TCGA – RCC)



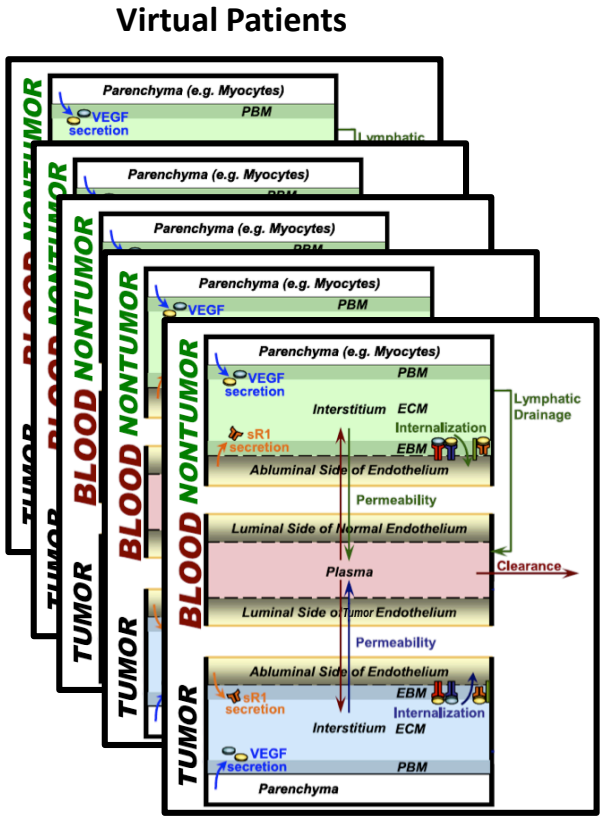
Bender and Mac Gabhann

Use patient data to build a population of hundreds of computational models (one per patient)



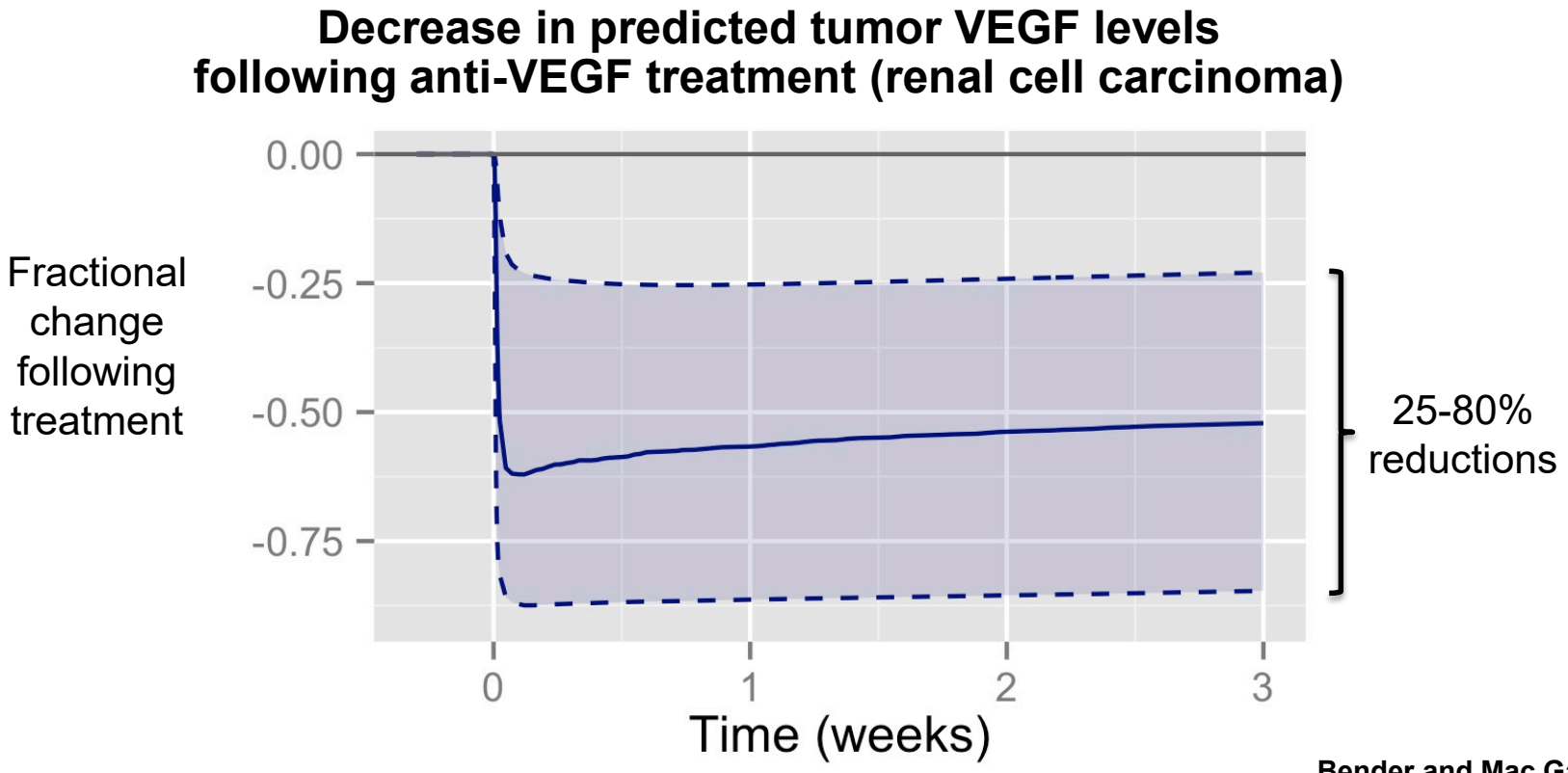
Use these virtual patients to run **virtual clinical trials** (simulate population response to treatment)

Therapeutic interventions
Target(s)
Dose
Scheduling



Population Outcomes

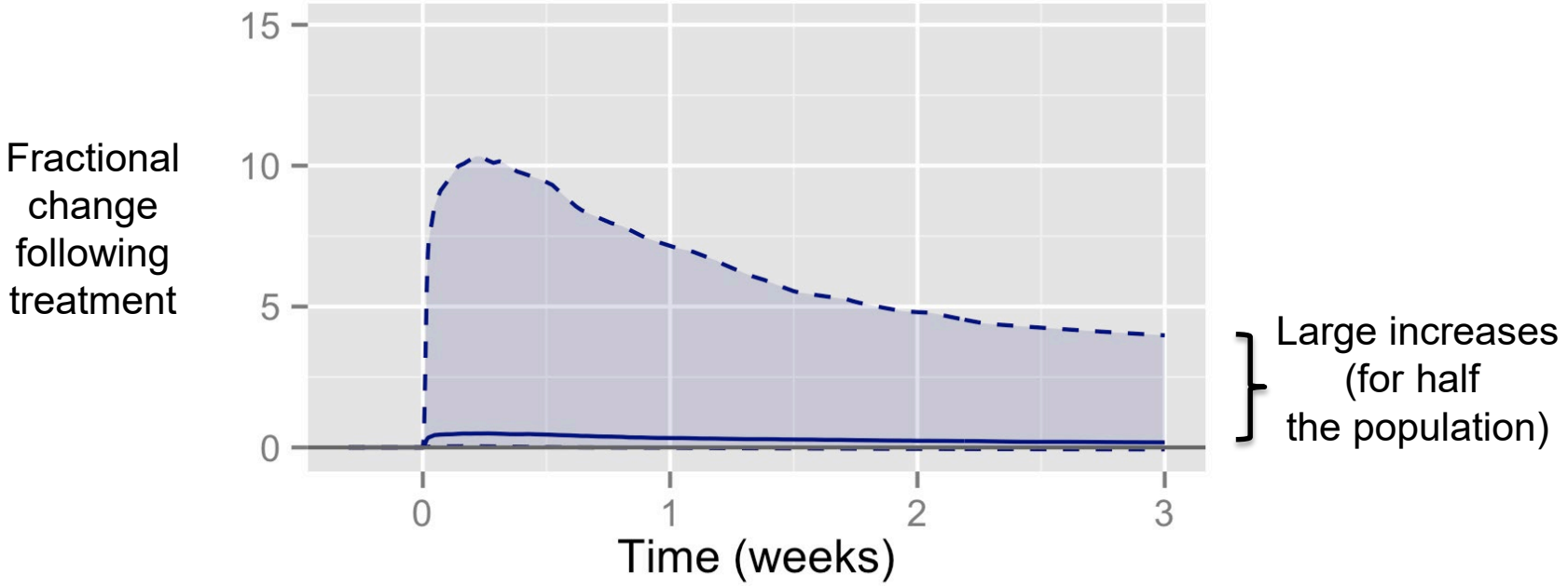
The variability in target response to treatment is high (here, PopPD effects are isolated from PopPK)



Bender and Mac Gabhann

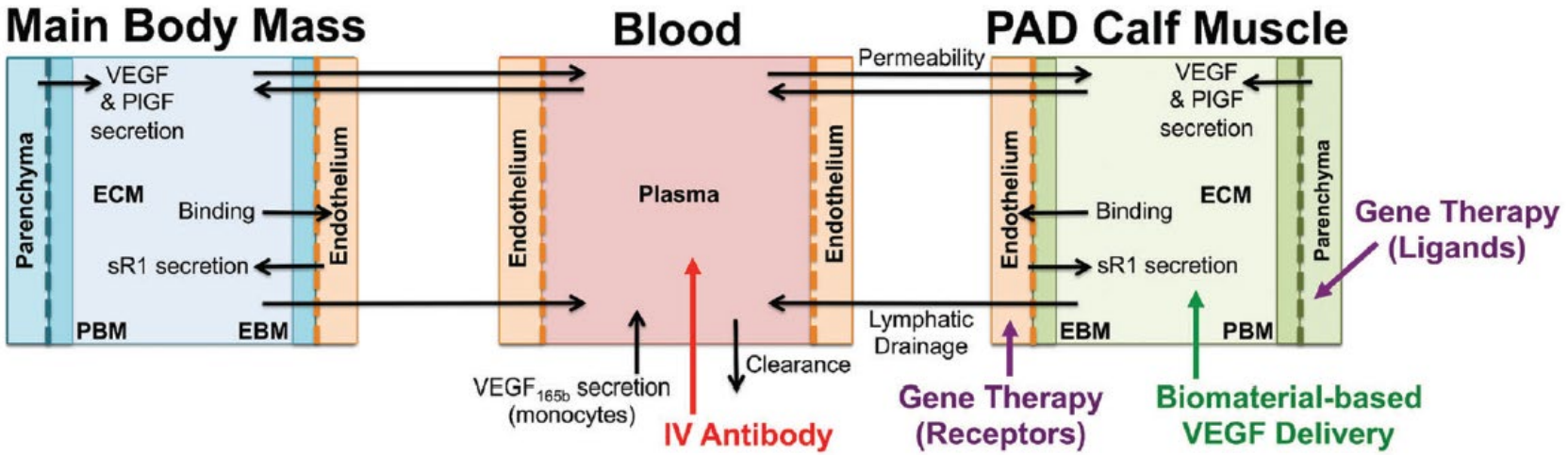
… and mechanistic models can help us identify variability in compensatory or off-target effects too

Increase in the formation of PlGF-VEGFR1 complexes in the tumor following anti-VEGF treatment (RCC)



Bender and Mac Gabhann

Multiscale mechanistic models combine **physiology** with detailed **molecular and cellular biology**



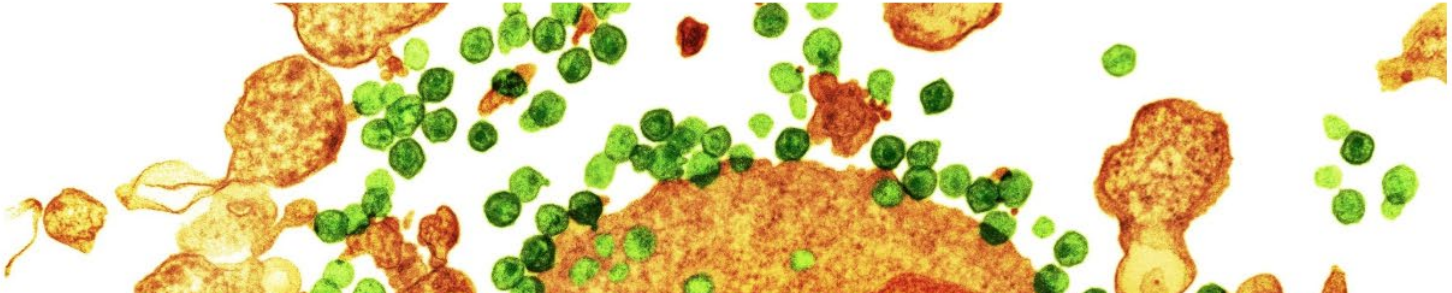
This enables us to simulate a wide range of interventions –
including **drugs** like small molecules and biologics;
but also **non-drugs** like gene therapy, biomaterials… even exercise.

Clegg & Mac Gabhann, Integr Biol 2018

The New York Times

H.I.V. Is Reported Cured in a Second Patient, a Milestone in the Global AIDS Epidemic

Scientists have long tried to duplicate the procedure that led to the first long-term remission 12 years ago. With the so-called London patient, they seem to have succeeded.



The London patient

LETTER
doi:10.1038/s41586-019-1027-4

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

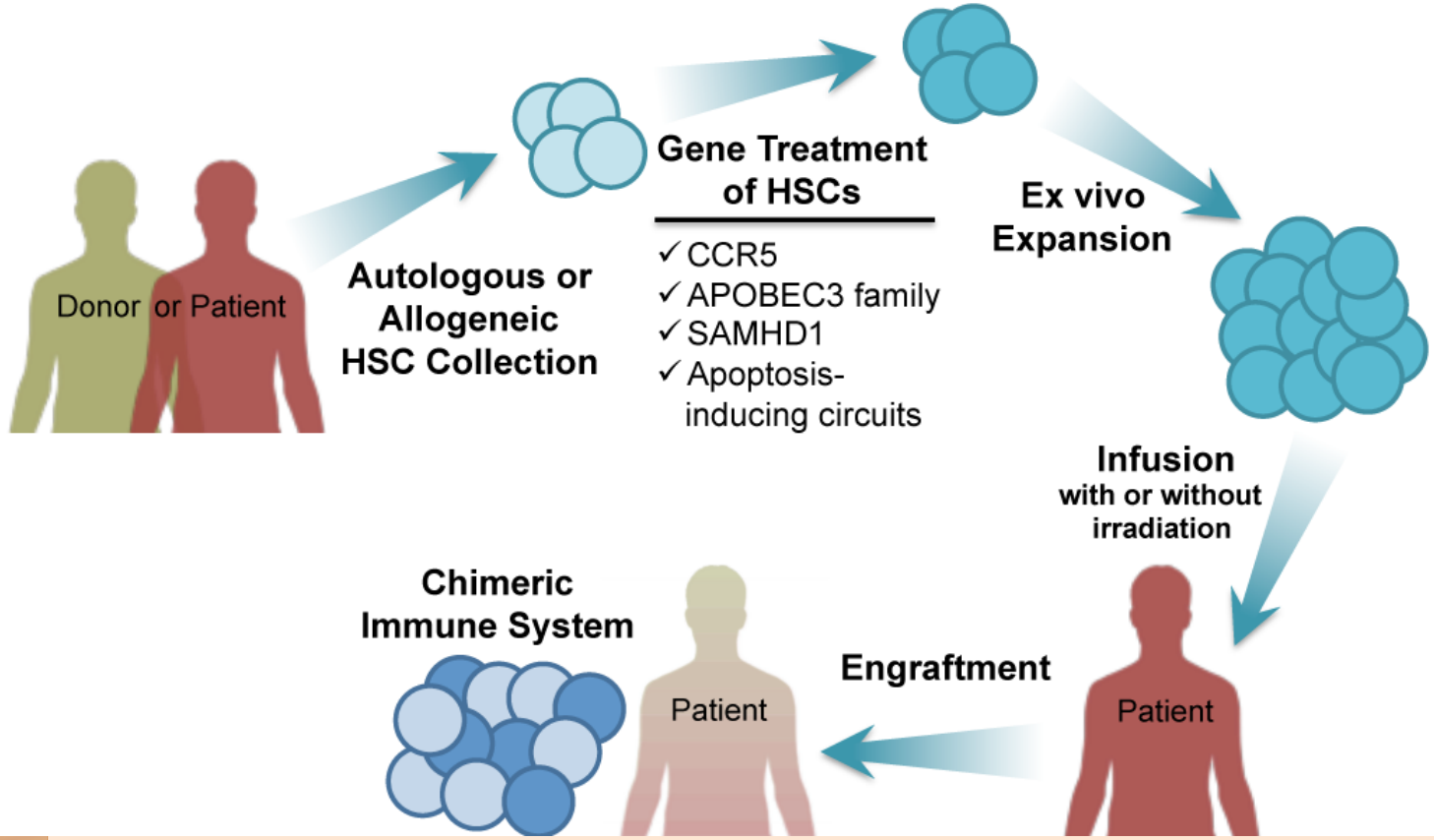
Ravindra K Gupta, Sultan Abdul-jawad, Laura E McCoy, Hoi Ping Mok, Dimitra Peppa, Maria Salgado, Javier Martinez-Picado, Monique Nijhuis, Annemarie M.J. Wensing, Helen Lee, Paul Grant, Eleni Nastouli, Jonathan Lambert, Matthew Pace, Fanny Salasc, Christopher Monit, Andrew Innes, Luke Muir, Laura Waters, John Frater, Andrew ML Lever, SG Edwards, Ian H Gabriel & Eduardo Olavarria

nature

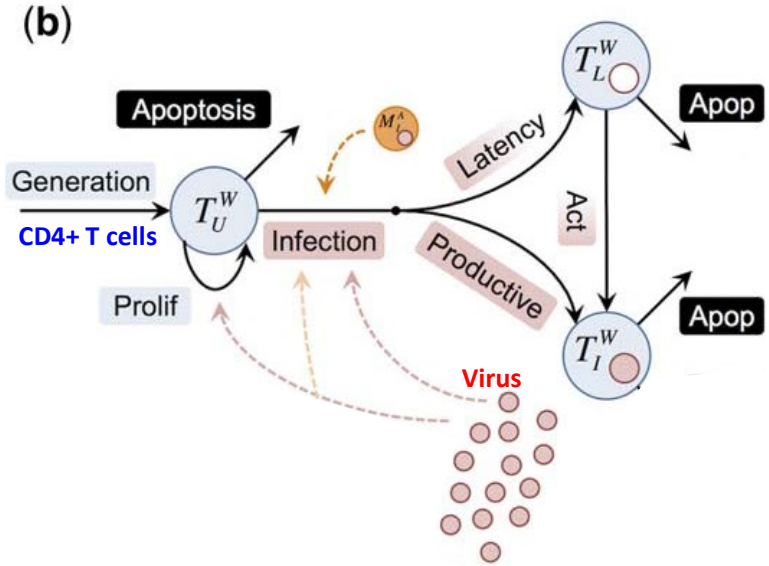
An HIV-1-infected adult underwent allo-HSCT for Hodgkin's lymphoma using cells from a CCR5Δ32/Δ32 donor. He experienced mild gut graft versus host disease.

Antiretroviral therapy was interrupted 16 months after transplantation. HIV-1 remission has been maintained through a further 18 months.

Hematopietic stem cell transplant (HSCT) using modified cells from donor or self

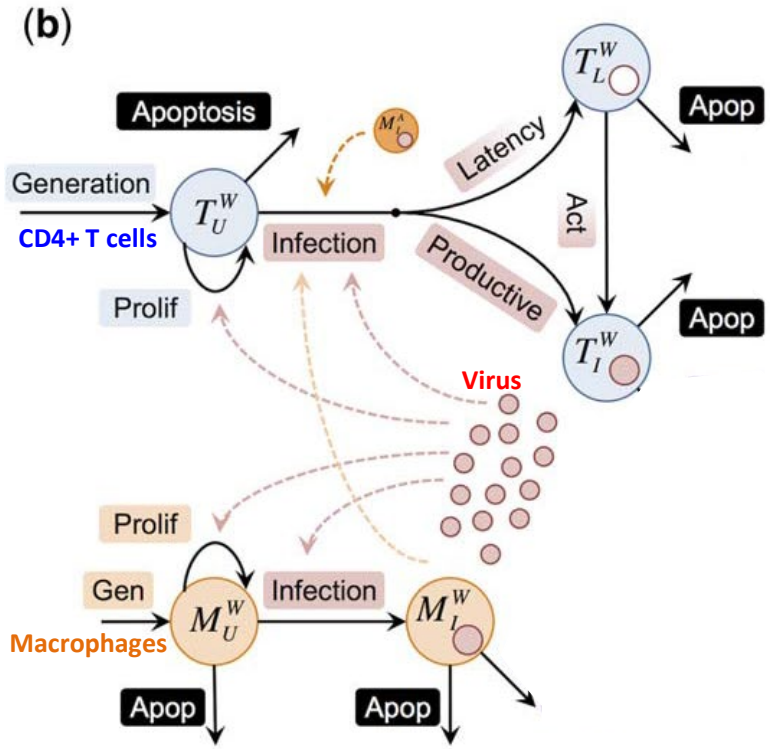


CD4+ & CD8+ T-cells, Macrophages, and virus



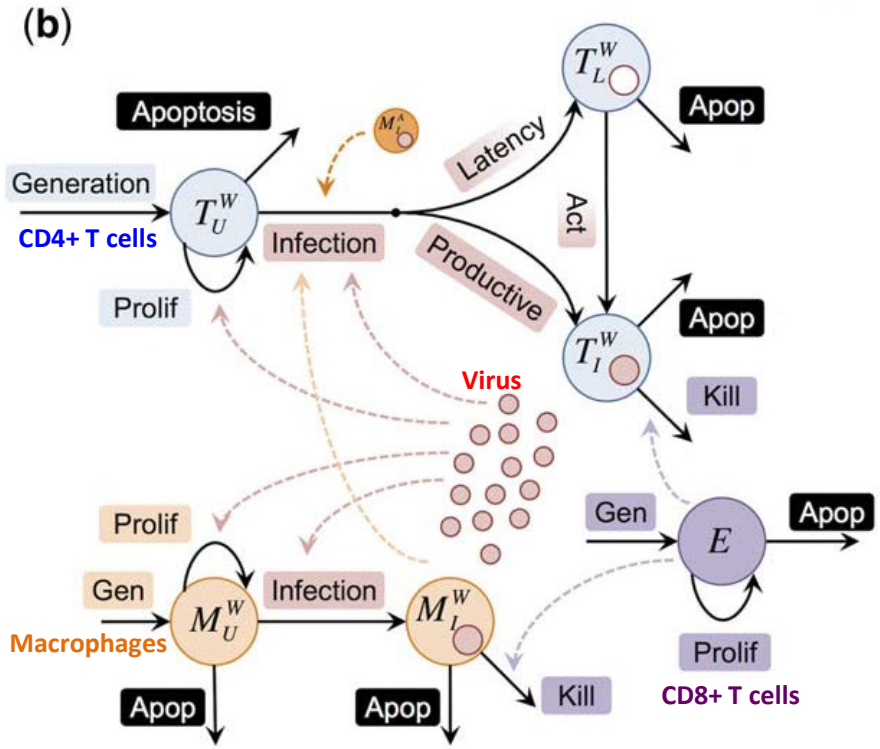
Hosseini and Mac Gabhann, CPT:PSP 2016

CD4+ & CD8+ T-cells, Macrophages, and virus



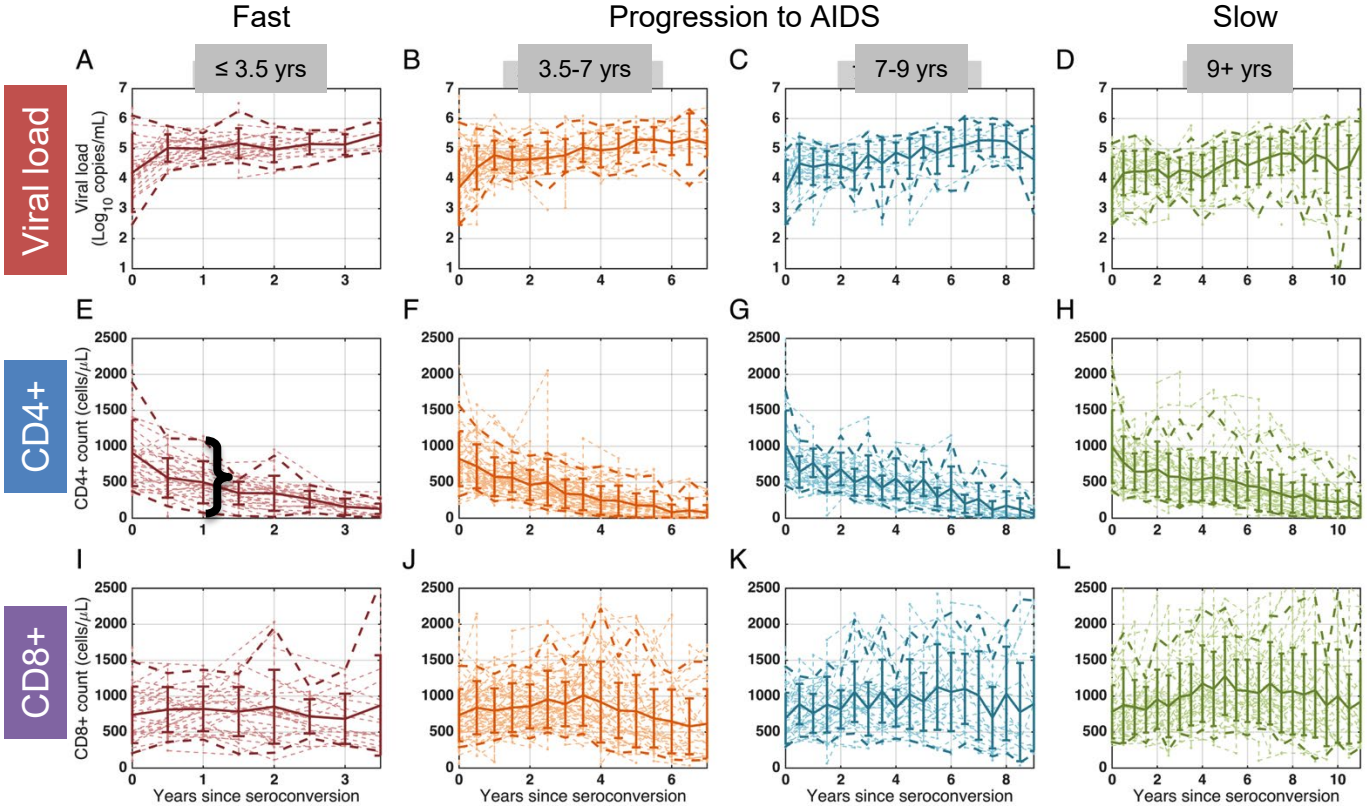
Hosseini and Mac Gabhann, CPT:PSP 2016

CD4+ & CD8+ T-cells, Macrophages, and virus



Hosseini and Mac Gabhann, CPT:PSP 2016

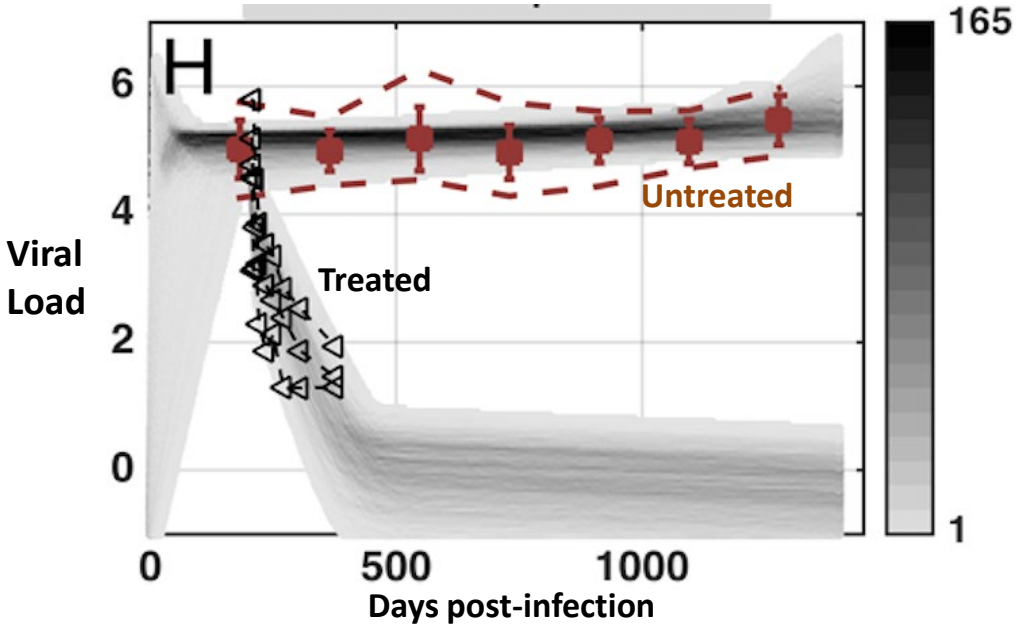
Data from MACS (Multicenter AIDS Cohort Study): Viral load, CD4+ and CD8+ T cell counts

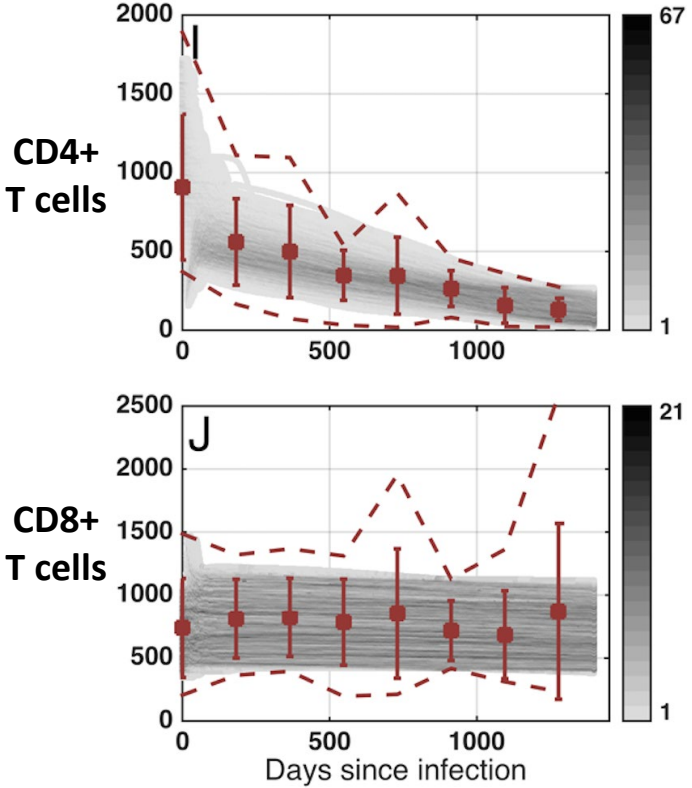


High inter-individual variability within the patient subpopulations

Individual timecourses can be noisy, making them difficult to model explicitly

Create virtual population to capture variability; Validate population model against treatment data

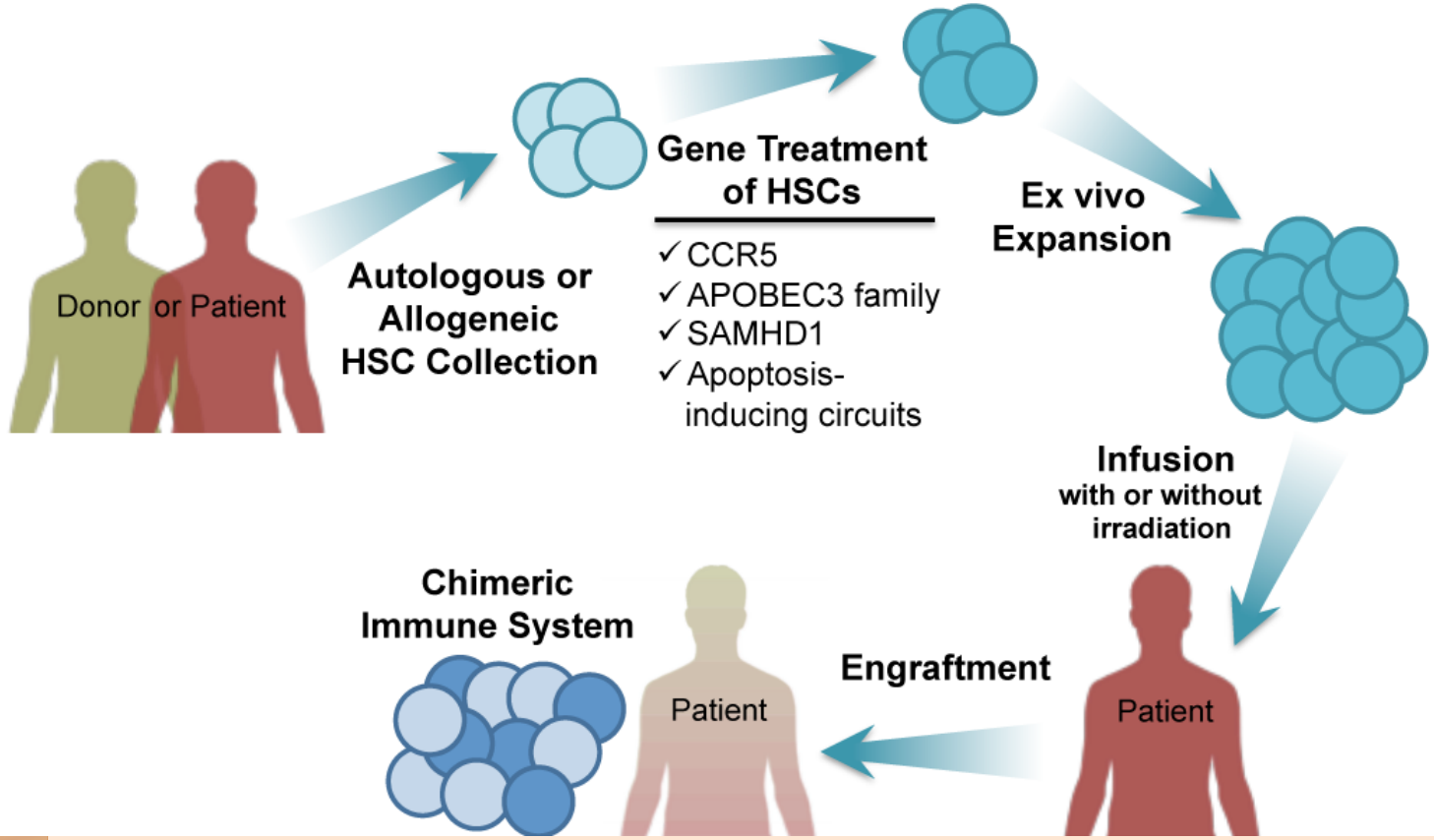




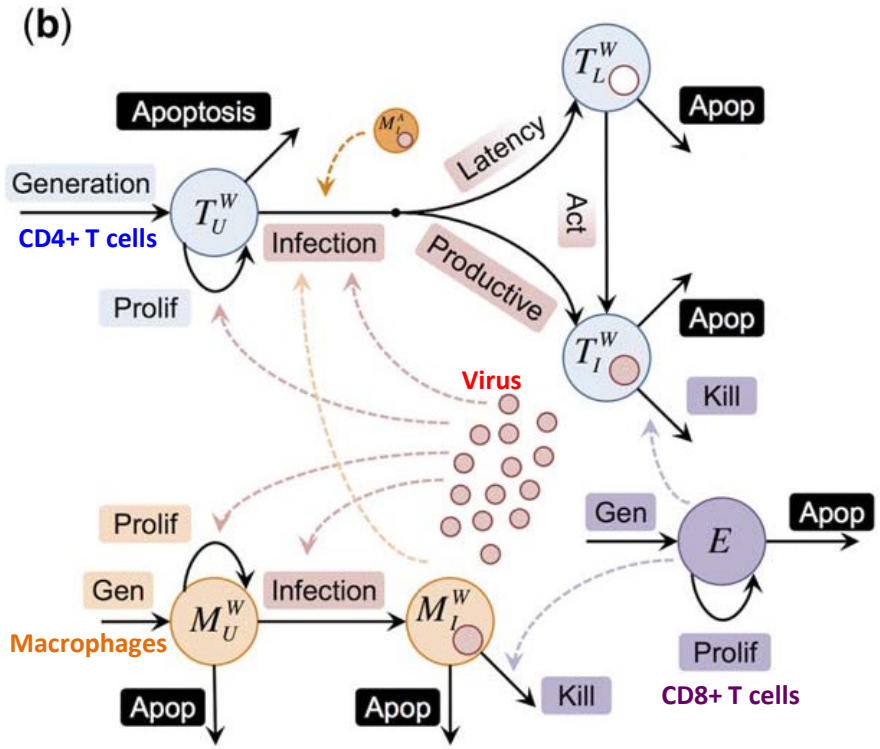
Treatment Data: Keppler et al. *Cell Stem Cell,* 2012

Simulations: Hosseini and Mac Gabhann, CPT:PSP 2016

Hematopietic stem cell transplant (HSCT) using modified cells from donor or self



HSCT augmented with genetic modification



Hosseini and Mac Gabhann, CPT:PSP 2016

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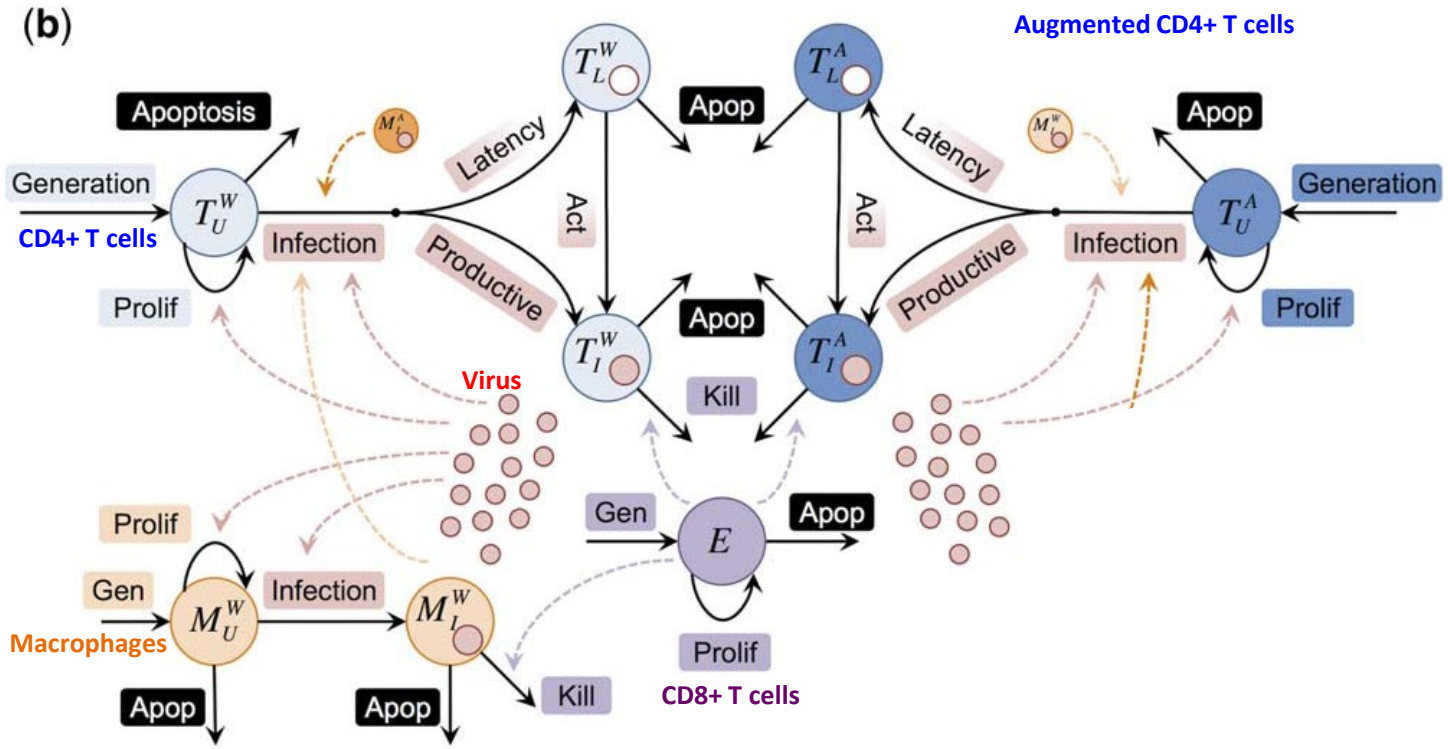
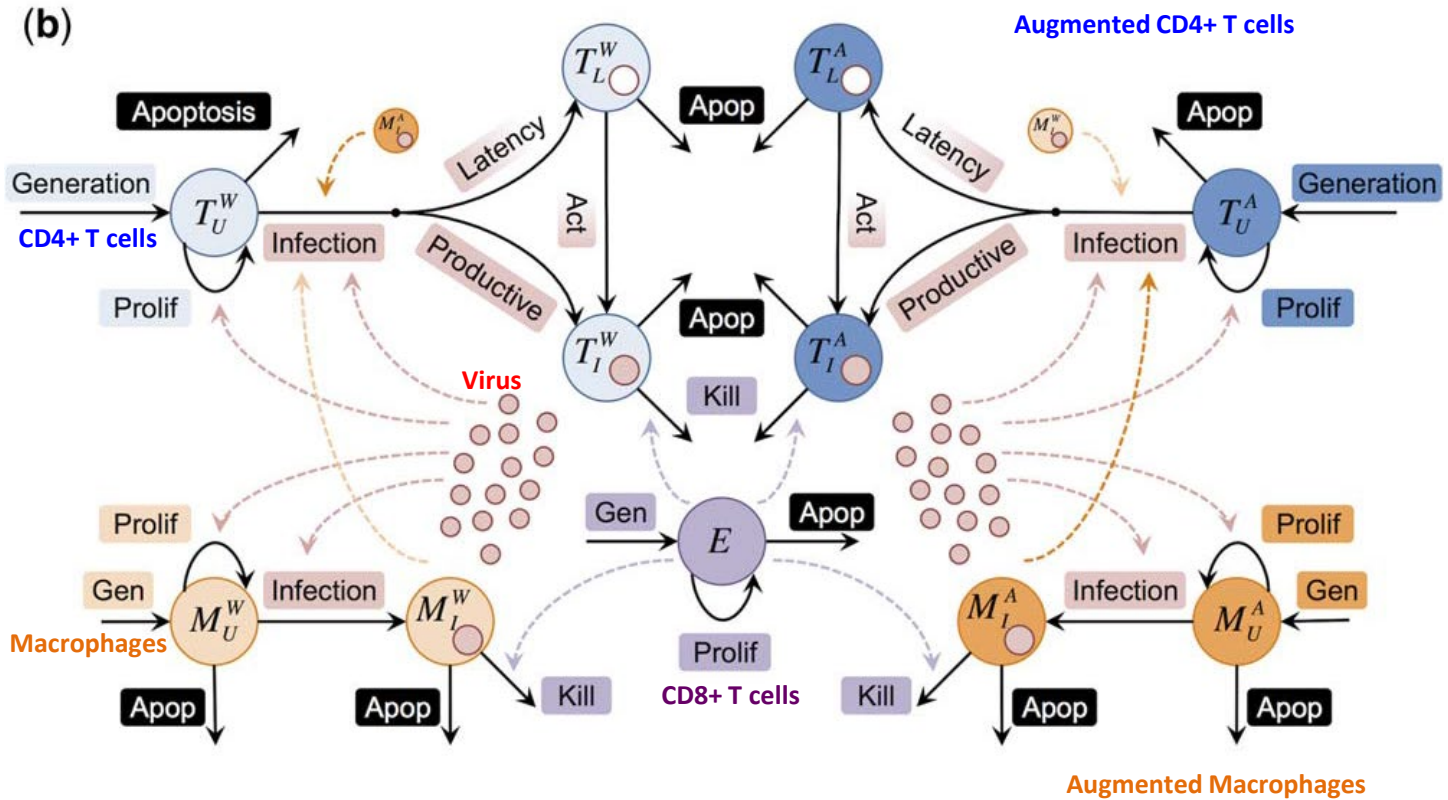


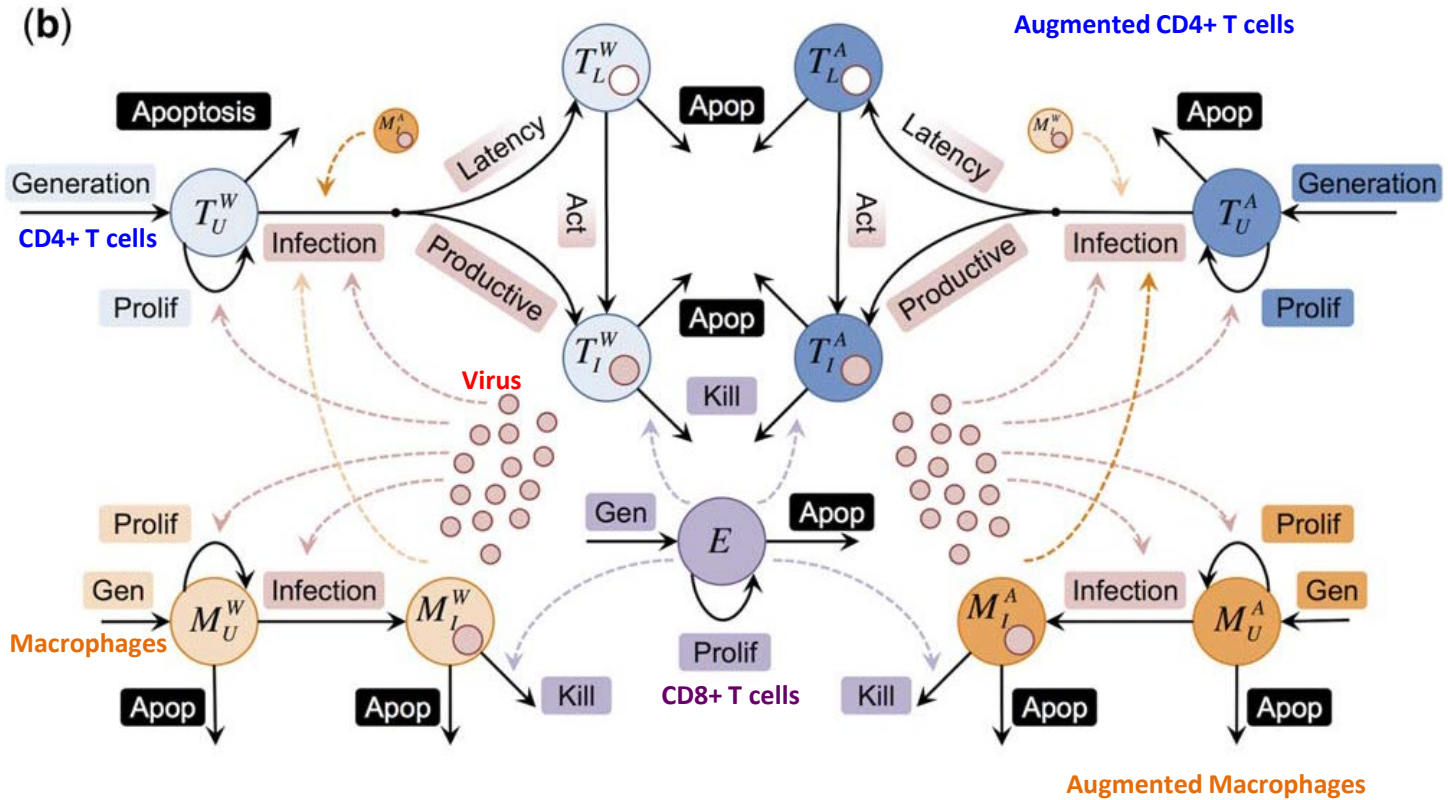
Hosseini and Mac Gabhann, CPT:PSP 2016

HSCT augmented with genetic modification



Hosseini and Mac Gabhann, CPT:PSP 2016

HSCT augmented with genetic modification (results in chimerism – donor and recipient cells)

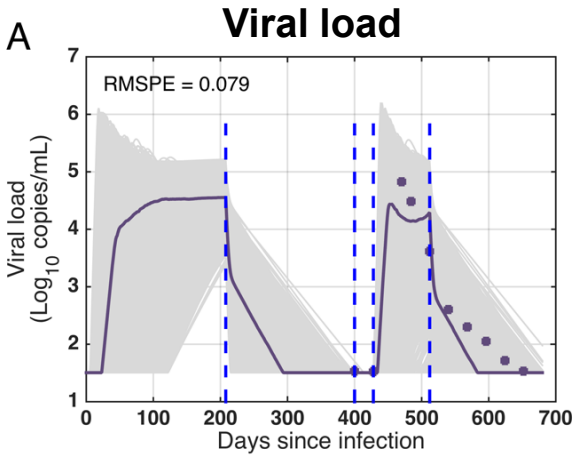


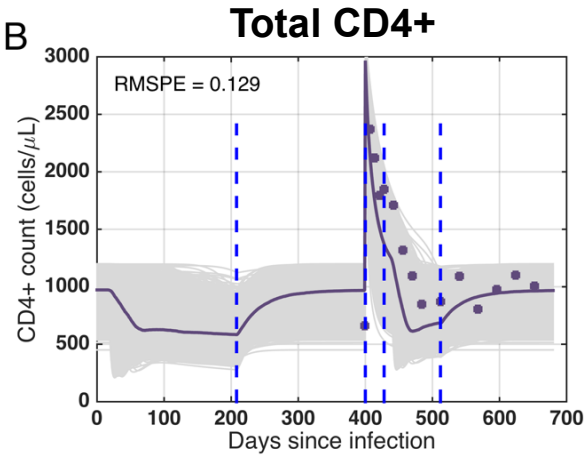
Hosseini and Mac Gabhann, CPT:PSP 2016

This multiscale mechanistic model can simulate complex, multistep clinical trial protocols over long times

Virtual clinical trial,
patients receiving infusion of 10 billion **autologous CD4+ T cells (20% CCR5-modified)**

Multistep protocol/simulation:
pre-treatment infected,
drug treatment,
infusion of cells,
cessation of drug treatment



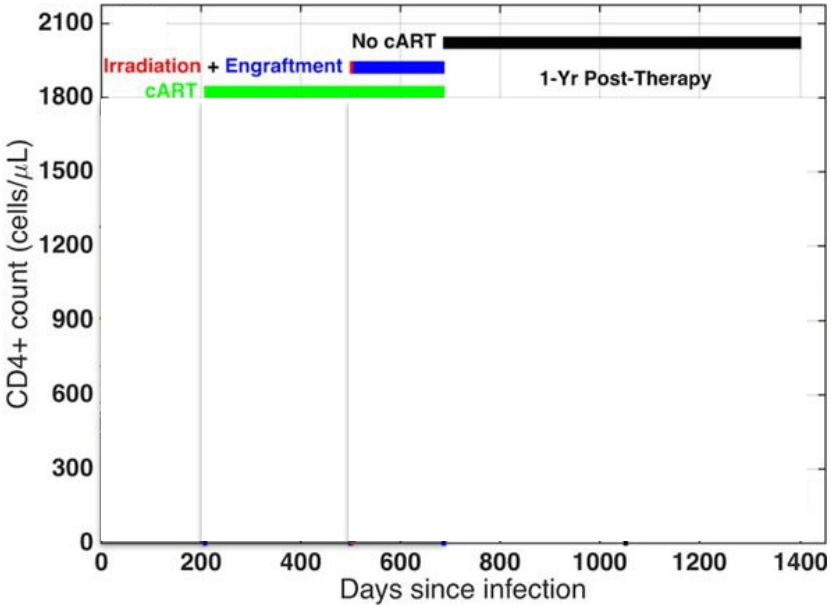


Hosseini and Mac Gabhann, CPT:PSP 2016

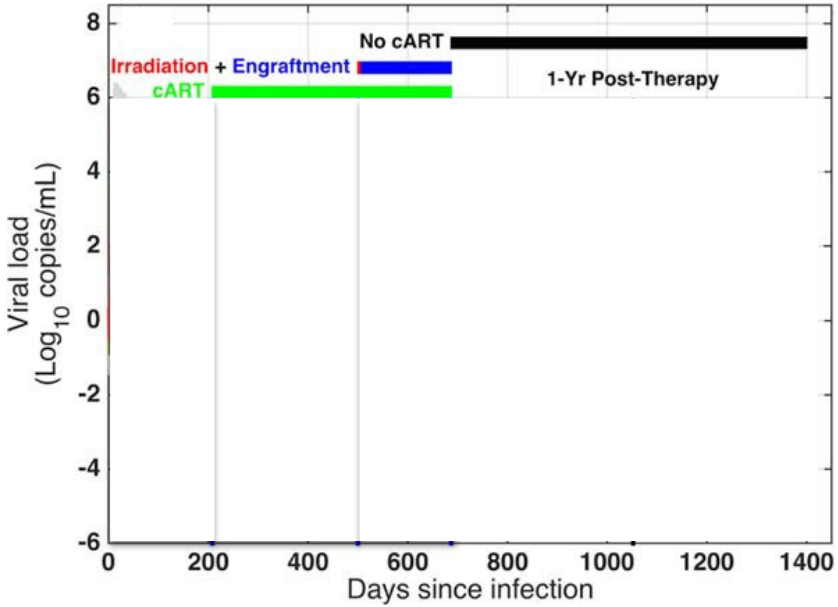
Experimental data: Tebas et al. *New England Journal of Medicine,* 2014

Virtual clinical trial: CCR5-HSCT therapy is predicted to be successful at stopping HIV infection in some patients

CD4+ T Cells



Viral load



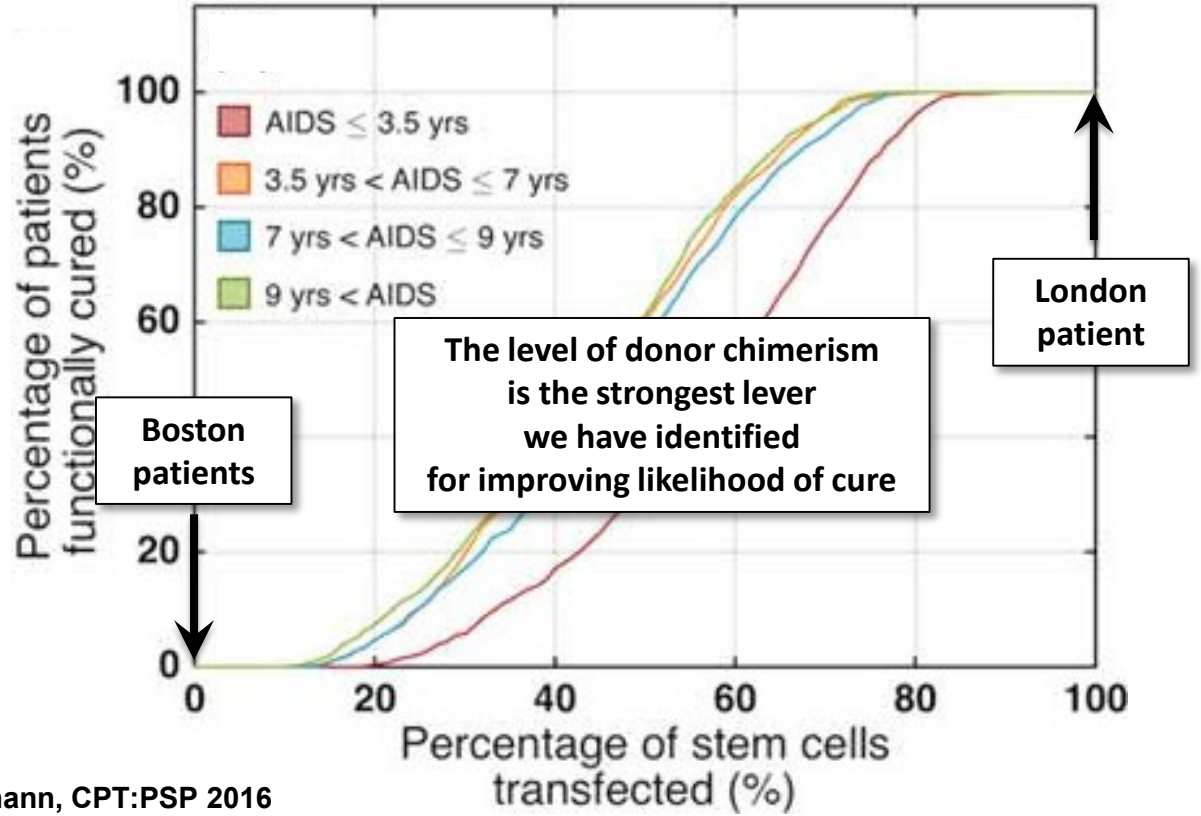
Each line = a virtual patient

f_T **= donor chimerism =** percentage of stem cells transfected **= 50%**

AIDS ≤ 3.5

Hosseini and Mac Gabhann, CPT:PSP 2016

Probability of cure for CCR5-HSCT therapy depends on the level of immune donor chimerism



Hosseini and Mac Gabhann, CPT:PSP 2016

Summary

Mechanistic models can serve as platforms
to simulate and compare therapies and combinations,
including complex multi-modal clinical protocols

Mechanistic models developed to simulate drug treatment
can be repurposed to simulate non-drug treatment,
including cell therapy and biomaterials

Population differences in ‘mechanism-of-action’ components
demonstrates a high level of variability in pharmacodynamics
that rivals or exceeds that in pharmacokinetics

Acknowledgments

Lab Members
Inez Lam
Sarvenaz Sarabipour
Wangui Mbuguiro
Christy Pickering
Adriana Gonzalez
Linh Tran

Recent Alumni
Lindsay Clegg
Yasmin Hashambhoy
R. Joseph Bender
Iraj Hosseini

NIH National Heart, Lung, and Blood Institute
NIH National Institute of Allergy and Infectious Diseases
NIH NIGMS
CDMRP
GRFP
NDSEG NATIONAL DEFENSE SCIENCE & ENGINEERING GRADUATE FELLOWSHIP
American Heart Association®
Alfred P. Sloan FOUNDATION
WILLOWCROFT FOUNDATION

Mechanism-based modeling is not antagonistic to data-driven approaches we've seen at this meeting

There is potential for Deep Learning and other data-driven strategies to give mechanistic insights.

We also have other sources of mechanistic insights, including decades of detailed & quantitative biophysical, biochemical, and physiological experiments.

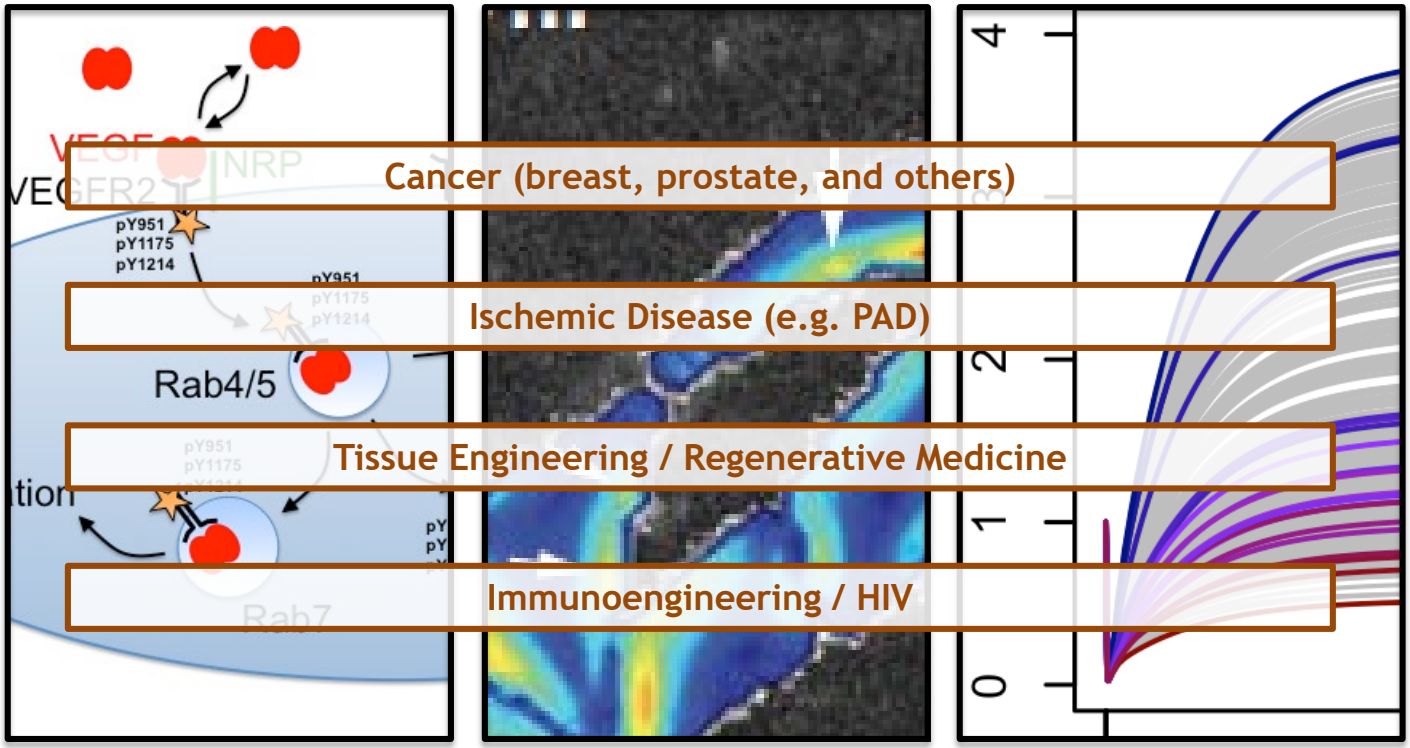
In summary.. we are not in the dark when it comes to mechanistic models.

Computational Design of Therapeutics

Improve understanding of molecular mechanism

High-resolution simulation of tissue

PK/PD models and Personalized Medicine



Cancer (breast, prostate, and others)

Ischemic Disease (e.g. PAD)

Tissue Engineering / Regenerative Medicine

Immunoengineering / HIV

For how many people does a drug work?

bevacizumab (anti-VEGF mAb) Clinical Trials

Cancer Type	Response Rate		Median Overall Survival (months)	
	Treatment	Control	Treatment	Control
Colorectal	**44.8%**	34.8%	**20.3**	15.6
Non-small cell lung cancer	**35%**	15%	**12.3**	10.3
Renal cell carcinoma	**31%**	13%	23.3	21.3
Cervical	**48%**	36%	**17.0**	13.3
Gastric	**46%**	37%	12.1	10.1
Pancreatic	13%	10%	5.8	5.9
Breast	**36.9%**	21.2%	26.7	25.2
Prostate	**49.4%**	35.5%	22.6	21.5

Red indicates treatment has statistically significant difference from control

Bender and Mac Gabhann, *Unpublished*

Bone marrow transplant (HSCT) in HIV patients

Berlin patient

1995: Diagnosed with HIV & began cART

2007: **allogeneic HSCT for AML from a donor with homozygous CCR5Δ32**

Since cART discontinued, the patient has been **HIV-free**

Boston patients

allogeneic HSCT from donors with wildtype CCR5

7 to 15 weeks after cART cessation, **HIV rebounded**

HSCT is not enough; the cells need anti-HIV functionality

If they don't have it, we can add it (gene therapy)

Identify parameter values using data from long-term HIV cohorts

MACS: Multicenter AIDS Cohort Study dataset (n = 6972)

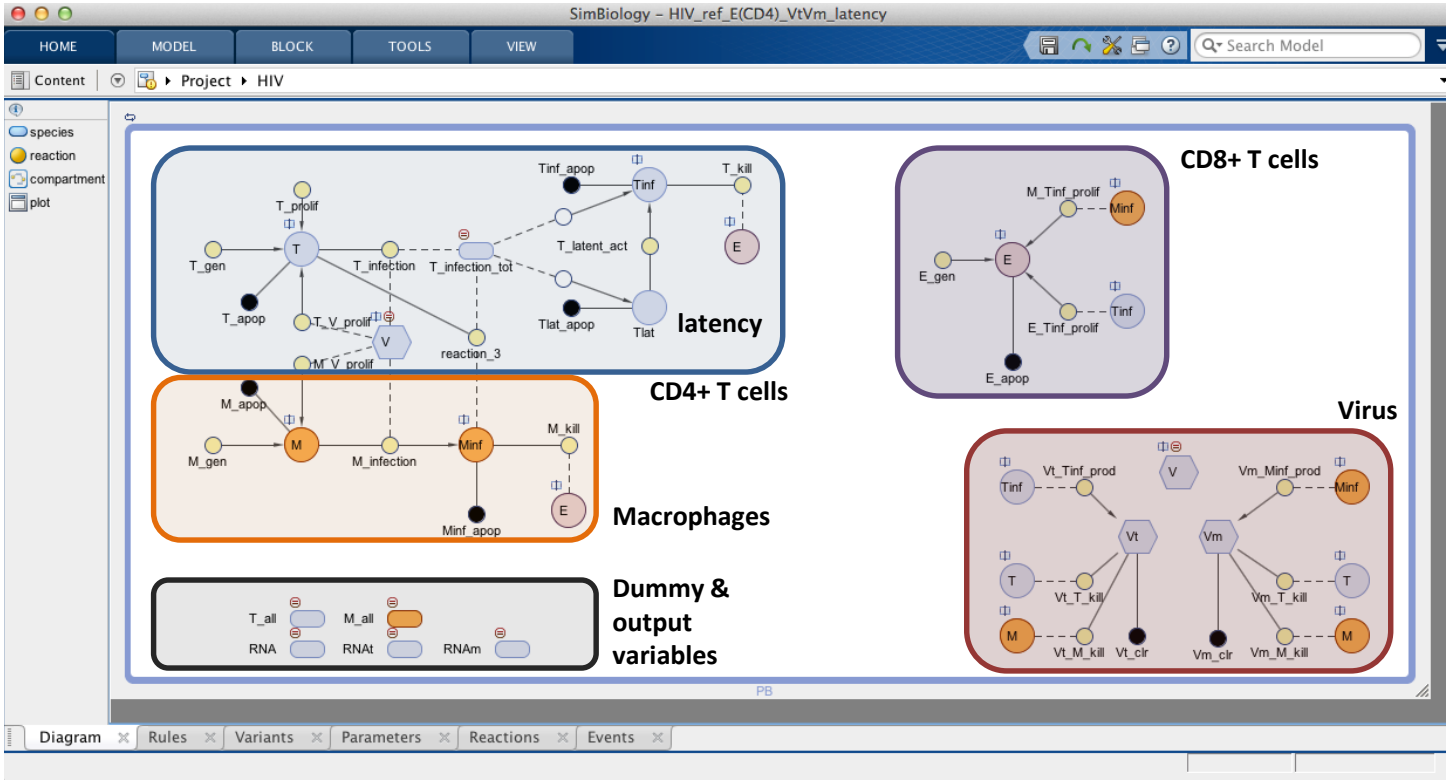
Target patients: **cART-naïve** HIV-infected patients with (approx.) known date of **seroconversion** and date of **AIDS diagnosis**

- **cART-naïve:** filtered if seroconv. date > 1996 or AIDS > 1996
- **Seroconv. date:** filtered if seropos. date – seroneg. date > 1 yr
  - **AIDS date:** filtered if no AIDS date

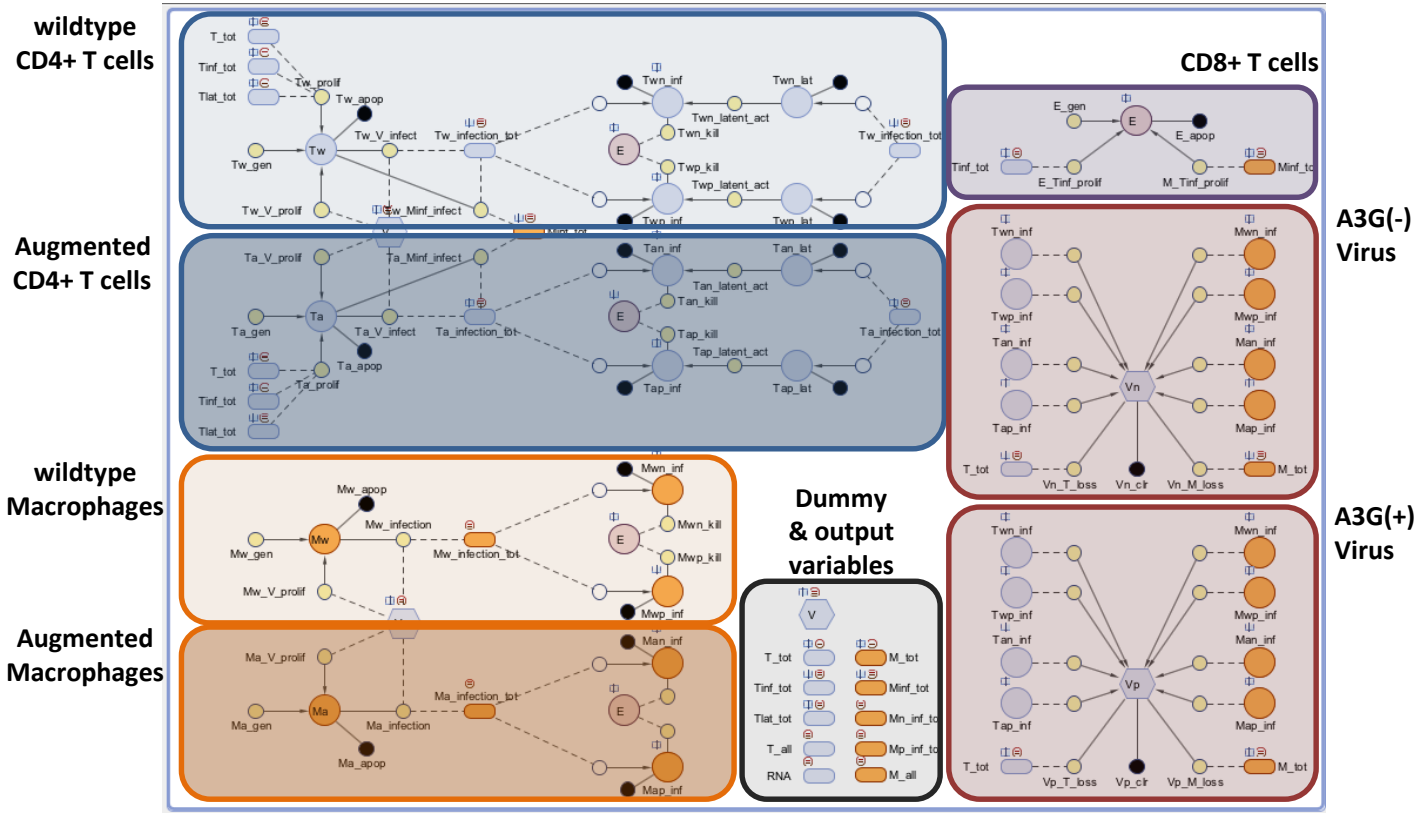
categorized in 4 groups (n = 172)

- **AIDS ≤ 3.5** (n = 32), **3.5 < AIDS ≤ 7** (n = 61), **7 < AIDS ≤ 9** (n = 39), **9 < AIDS** (n = 40)

Multiscale mechanistic model of immune cells & virus



HSCT augmented with genetic modification: multiscale mechanistic model of immune cells & virus

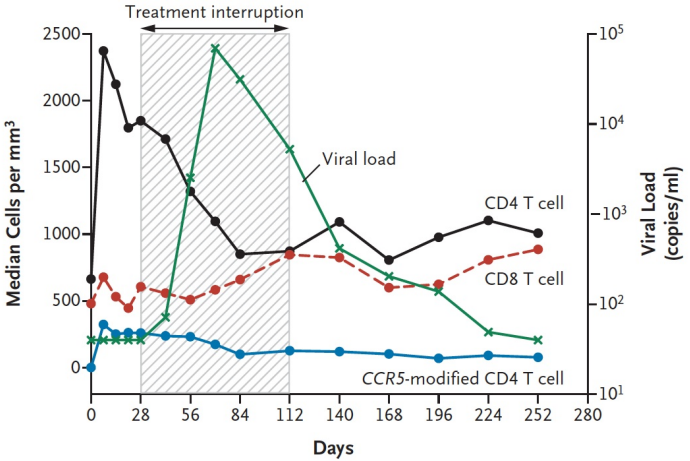


Hosseini and Mac Gabhann, CPT:PSP 2016

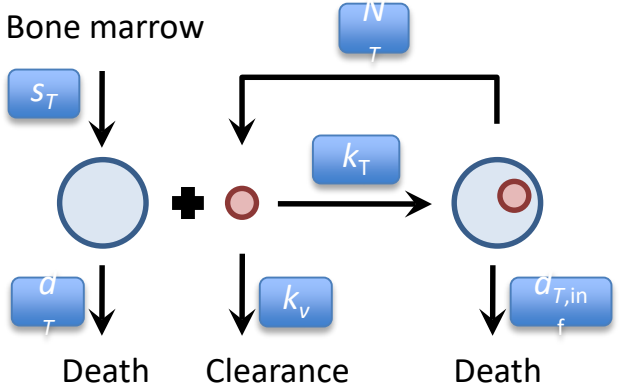
Validation: prediction of results in clinical studies

Infusion of **10 Billion autologous CD4+ T cells**, of which 20% are CCR5-modified

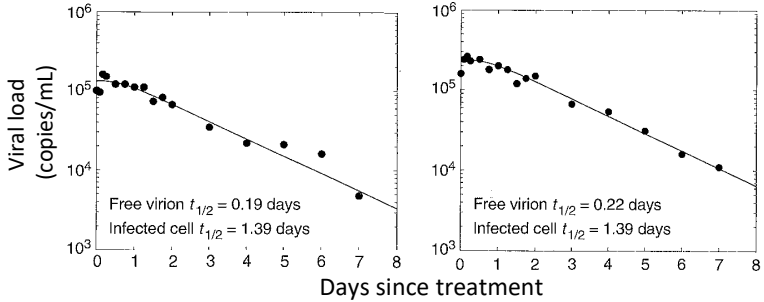
- Patients had chronic aviremic HIV infection and were receiving cART
- Patients had a range of **CD4+ T cell counts: 546-1123 cells/μL**
- 12-week cART interruption 4 weeks after T cell infusion
- Monitored 36 weeks
  - Plasma viremia
  - CCR5-modified T cells
  - Total CD4+ T cell counts



Basic model of HIV infection: three components can capture acute response to treatment …



HIV RNA in plasma after treatment with ritonavir (Perelson et al, Science 1996)



CD4+ T cells

$$\frac{dT}{dt} = s_T - d_T T - k_T VT$$

Virus

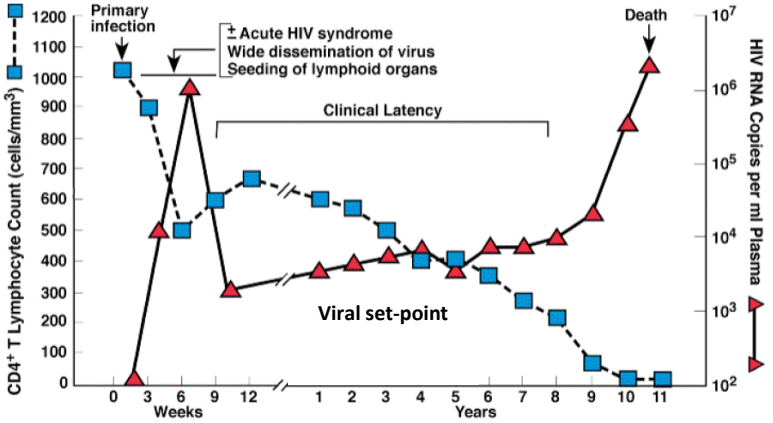
$$\frac{dV}{dt} = N_T I - k_v V$$

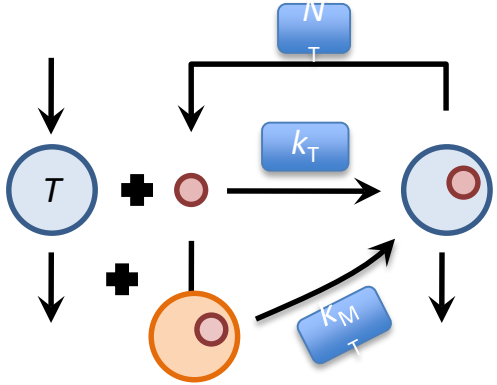
Infected T cells

$$\frac{dI}{dt} = k_T VT - d_I I$$

… but not late-stage viremia; macrophages are required to explain this

Typical course of untreated HIV infection (Fauci et al, Ann Intern Med 1996)



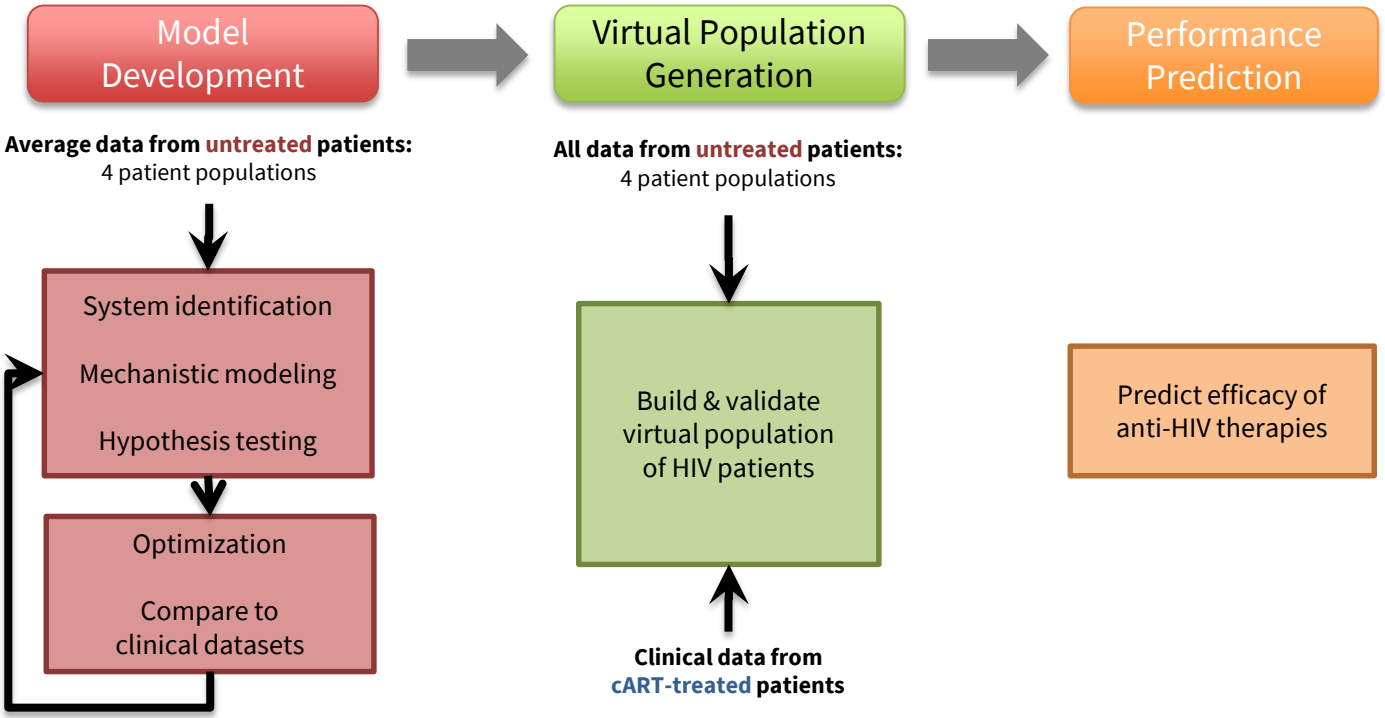


Lesson 1: Where there is controversy, quantitative models can help to identify mechanisms

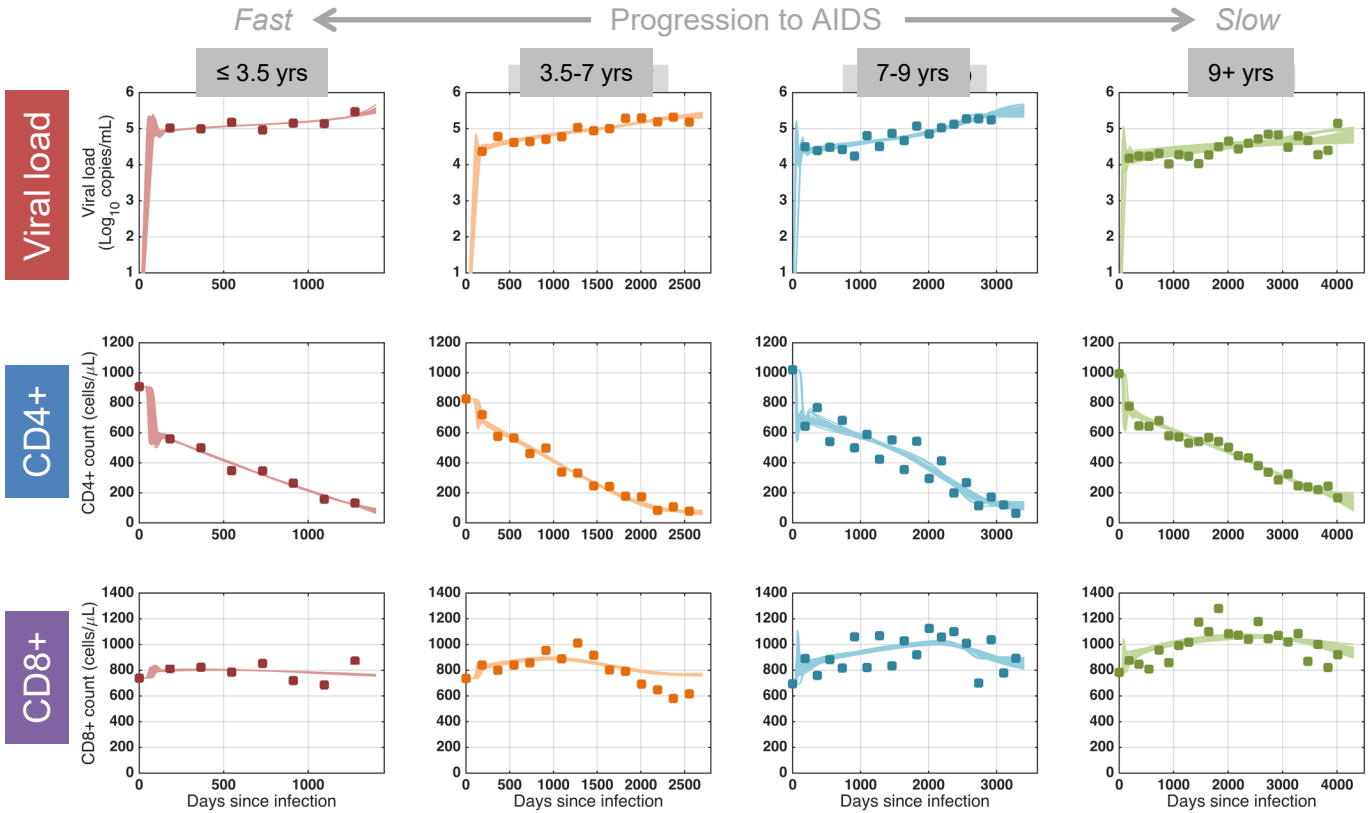
Public datasets

- Proposals submitted to all three cohorts
  - Amsterdam Cohort public dataset (n = 329 → less than < 126, quantized data, date info = mm/yy)
  - MACS public dataset (n = 6972 → 172, date info = yy)
  - 6 categories of patients
    - Seroconverters (585 patients)
    - SeroPrevalents with known date of seroconversion (59 patients)
  - 0 < Seropos_date – Seroneg_date < 7 years
    - 0 < Seropos_date – Seroneg_date < 1 years (486 patients)
  - These patients sometimes have multiple dates for the initial AIDS diagnosis
    - Seroconv_date > 1996 (filtered)
    - AIDS > 1996 or No AIDS date (filtered)
  - Categorized in 4 groups
    - AIDS < 3.5 (32), 3.5 < AIDS < 7 (61), 7 < AIDS < 9 (39), 9 < AIDS (40)
  - 1 Year resolution was not enough, we needed 6 months at least for optimization

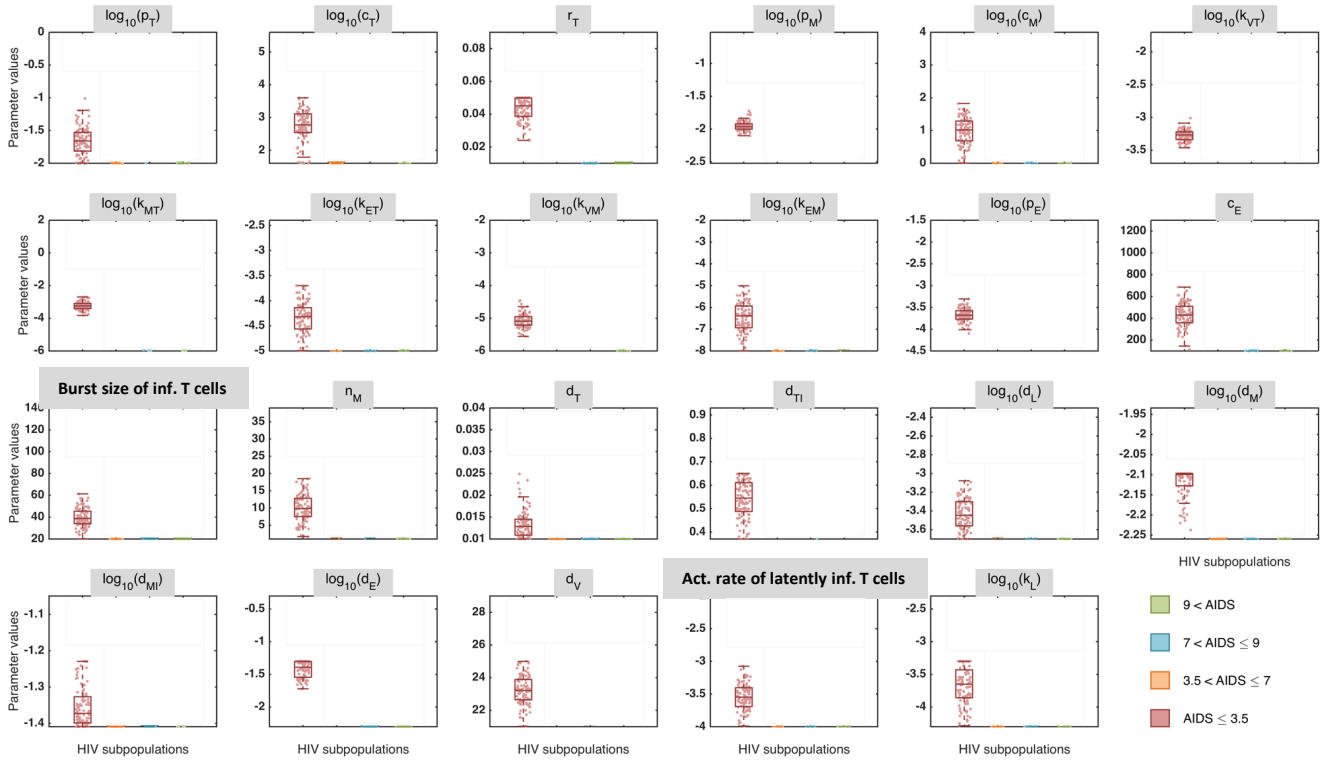
Workflow


Model Development
Virtual Population Generation
Performance Prediction
Average data from untreated patients:
4 patient populations
All data from untreated patients:
4 patient populations
System identification
Mechanistic modeling
Hypothesis testing
Optimization
Compare to clinical datasets
Build & validate virtual population of HIV patients
Clinical data from cART-treated patients
Predict efficacy of anti-HIV therapies

Calibrate model using average subgroup patterns



Parameter values across subpopulations



Multiscale, mechanism-based modeling allows us to simulate non-drug treatments, including engineered materials

Protein	Description	Result in Mice	Reference
VEGF165a 	VEGF165a protein	Poor angiogenic growth, vascular leakage	Martino et al. Science 2014
"Super Affinity" VEGF 	VEGF engineered for increased affinity to ECM	Improved wound healing, decreased leakage	Martino et al. Science 2014
Covalent VEGF w/ proteolysis 	VEGF covalently attached to fibrin matrix with tunable proteolytic release	Improved angiogenesis & wound healing at 1-3 months with low doses	Sacchi et al. PNAS 2014

Clegg & Mac Gabhann, Integr Biol 2018