QSP for non-drug treatments

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Mechanism, mechanism, mechanism

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)

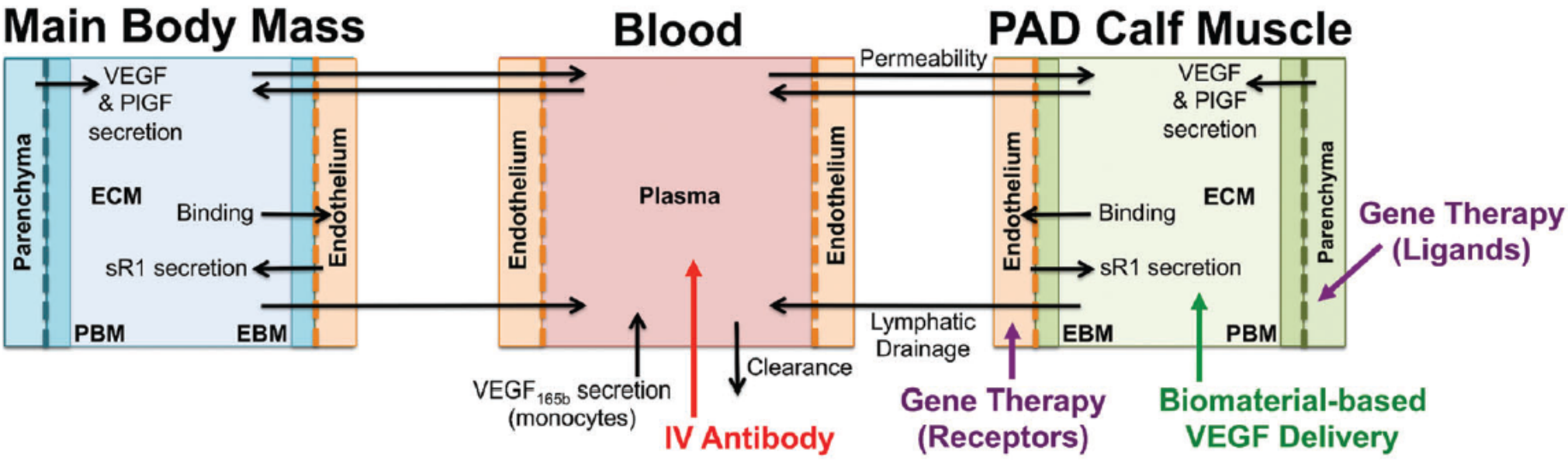
*"We require better quantitative models of pharmacological **mechanism at all scales**, starting with single targets and drugs and scaling to vertically and horizontally integrated **multi-scale models**."*

QSP includes a move from drug-centered modeling to target-centered modeling

The field is moving from a focus on "drug and target" only, to inclusion of the target's complex and dynamic environment, including networks of interactions with other molecules.

This change in 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**



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.

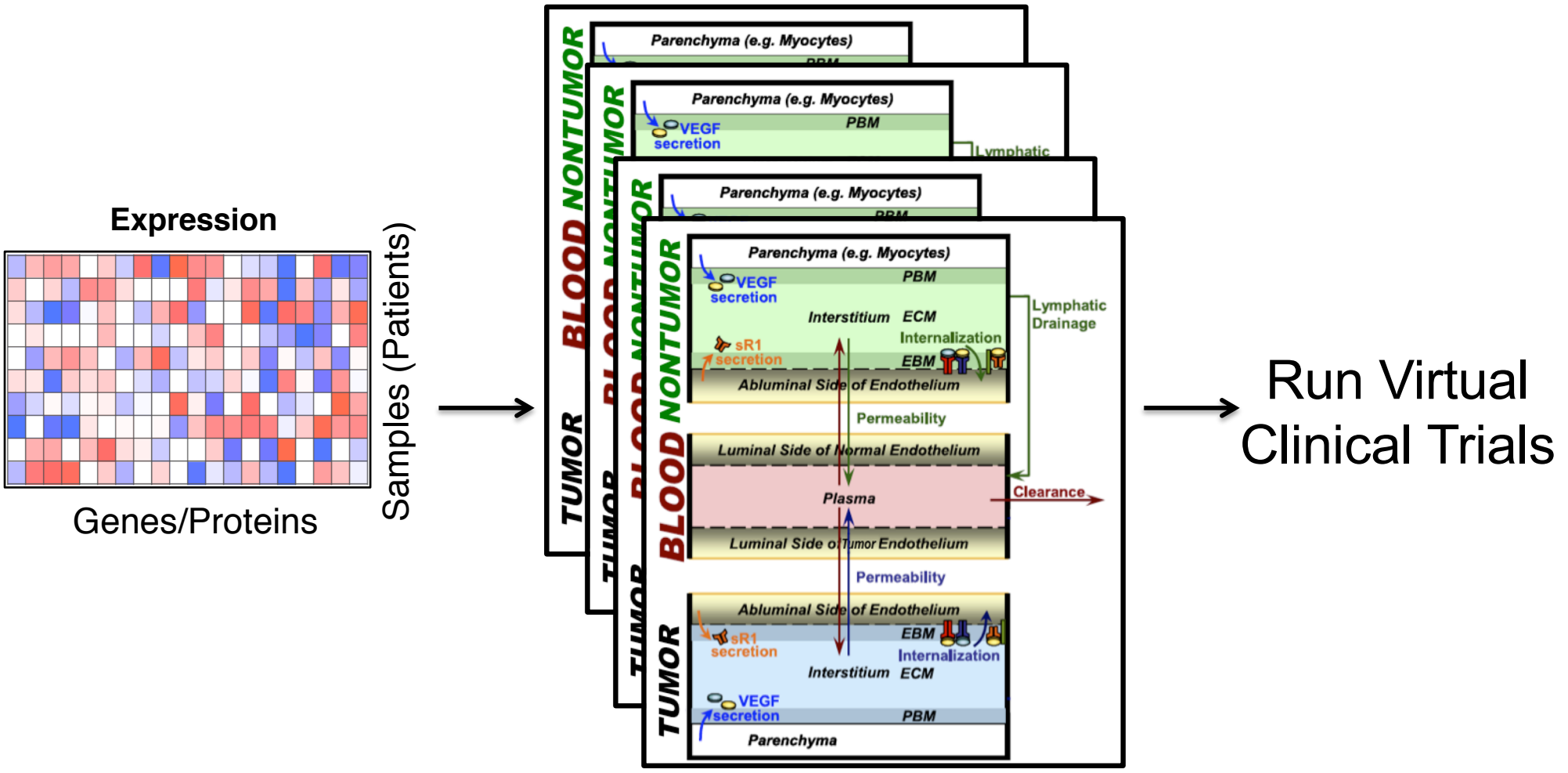
Clegg & Mac Gabhann, Integr Biol 2018

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

Focus in the past has been on
population pharmacokinetics (PopPK),
largely due to availability of measurements.
The goal is to decrease variability in drug exposure
(typically by informing dosings and scheduling)

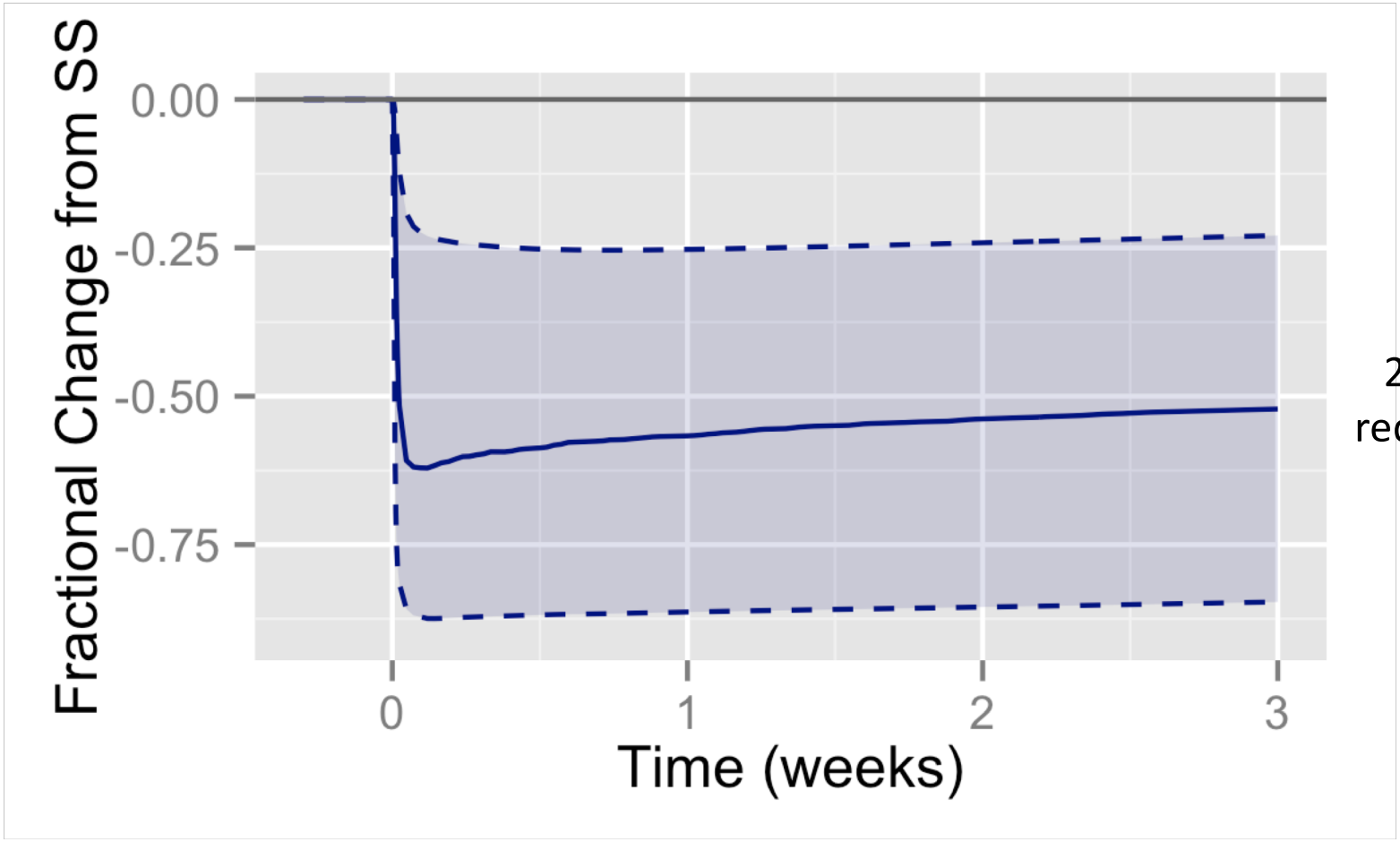
With detailed multiscale modeling of therapy
mechanism of action, we can now consider
population pharmacodynamics (PopPD),
which may be responsible for more
of the variability from person to person.

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



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

Decrease in predicted tumor VEGF levels following anti-VEGF treatment (renal cell carcinoma)



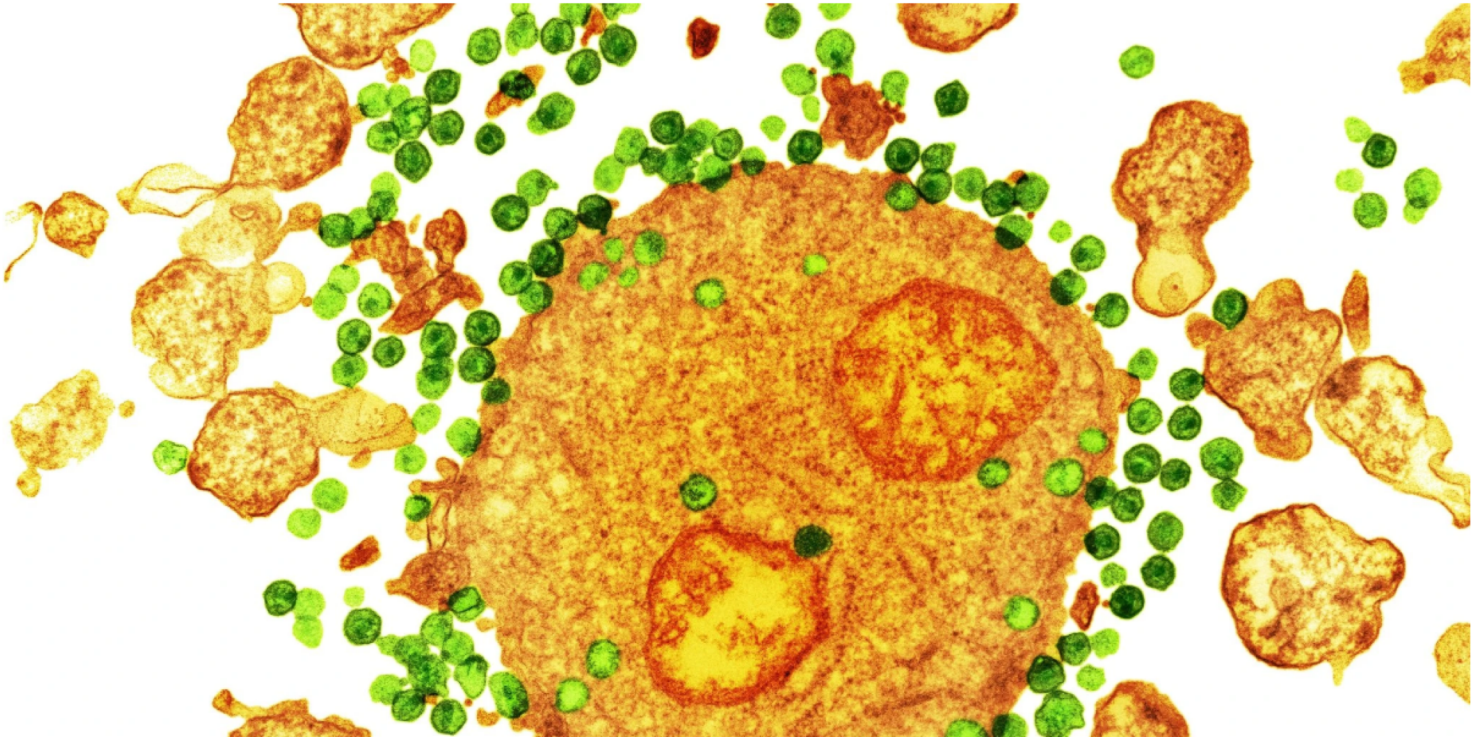
25-80% reductions

Bender and Mac Gabhann

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

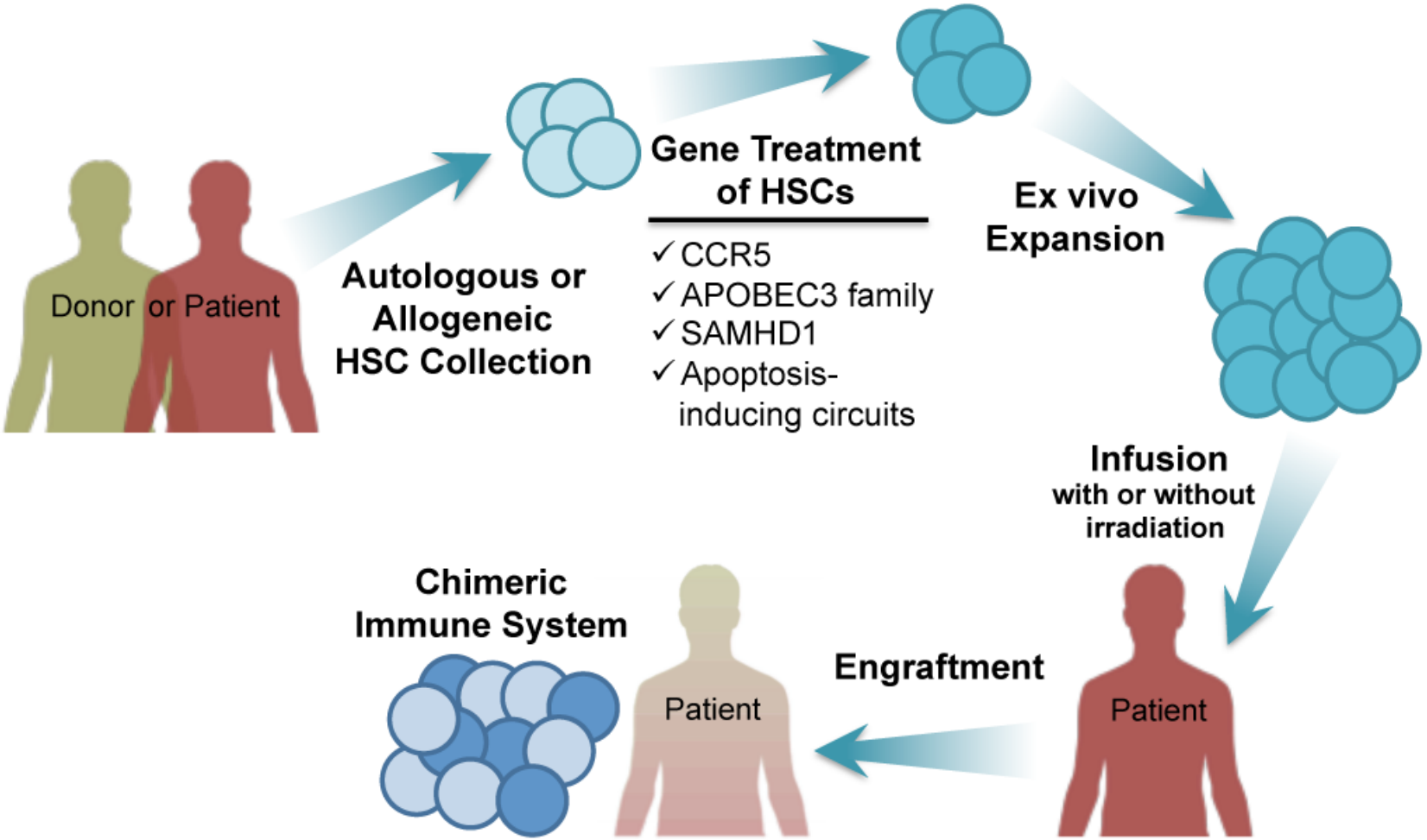
Ravindra K Gupta, Sultan Abdul-jawad, Laura E McCoy, Hoi Ping Mok, Dimitra Peppa, Maria Salgado, Javier Martinez-Picado, Monique Nijhuis, Annemarie M.J. Wensing, Helen Lee, Paul Grant, Eleni Nastouli, Jonathan Lambert, Matthew Pace, Fanny Salasc, Christopher Monit, Andrew Innes, Luke Muir, Laura Waters,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

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.

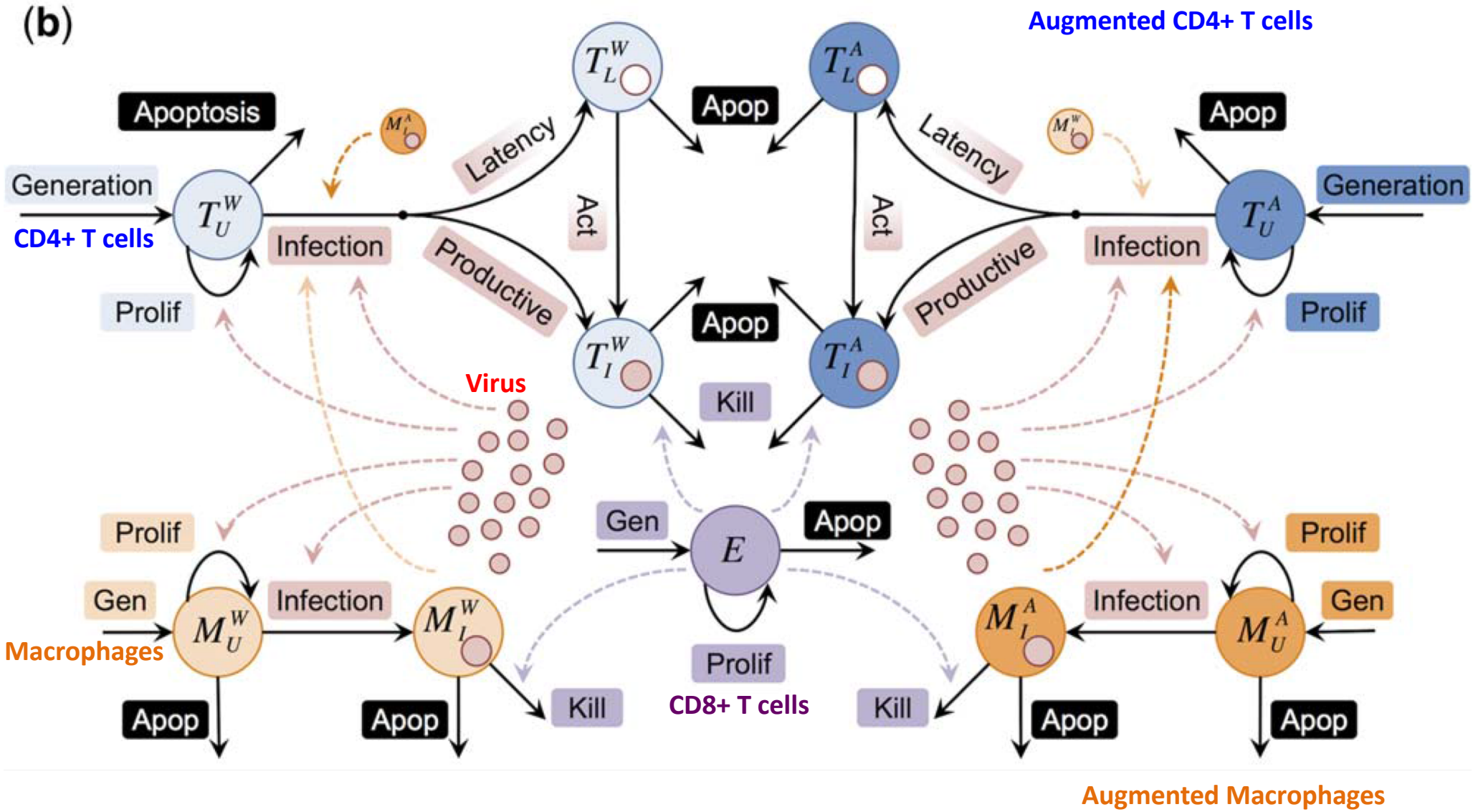
Antiretroviral therapy was interrupted 16 months after transplantation. HIV-1 remission has been maintained through a further 18 months.

nature

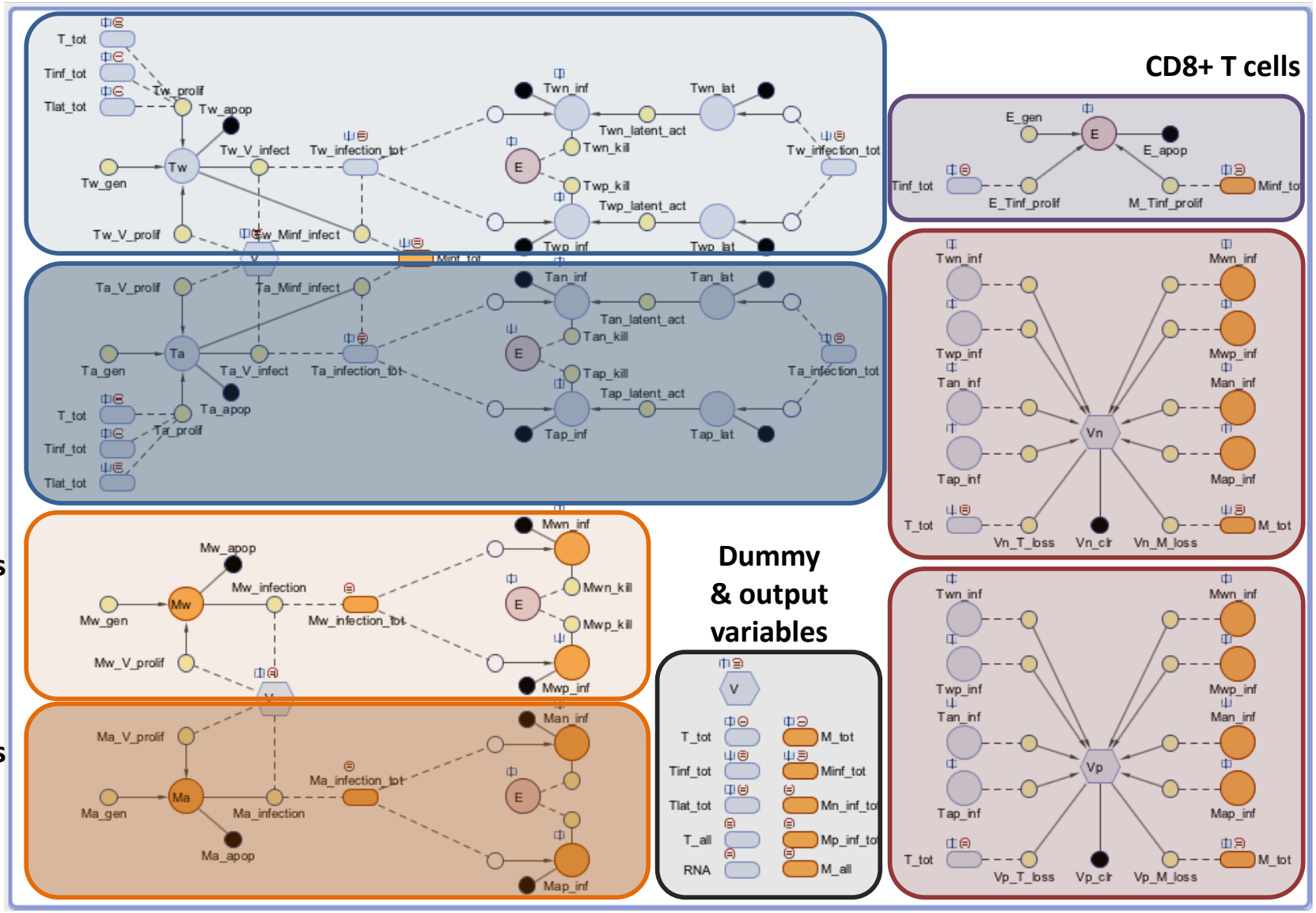
Hematopietic stem cell transplant (HSCT) using modified cells from donor or self



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

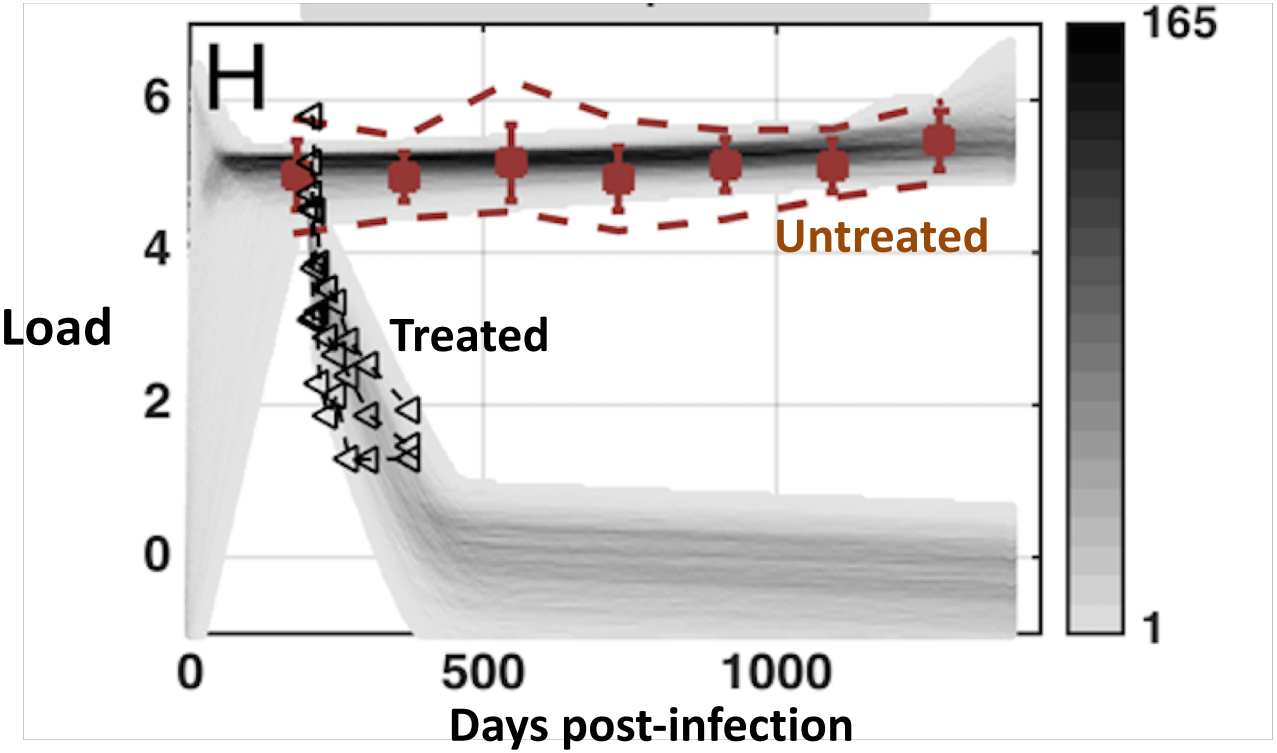


HSCT augmented with genetic modification: multiscale mechanistic model of immune cells & virus

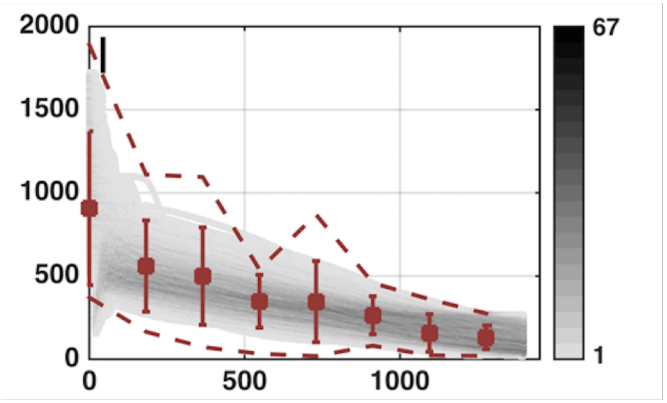


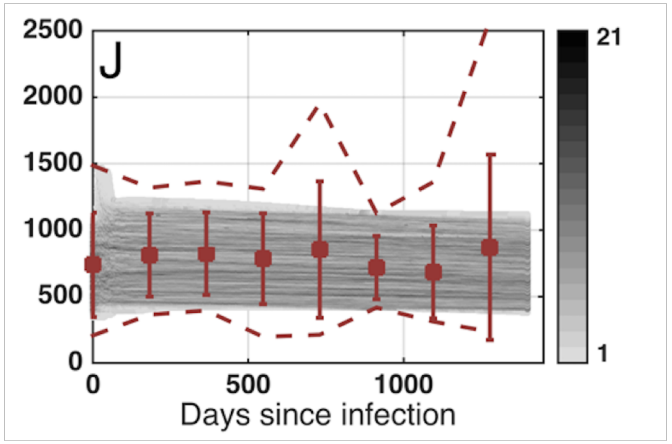
Hosseini and Mac Gabhann, CPT:PSP 2016

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



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





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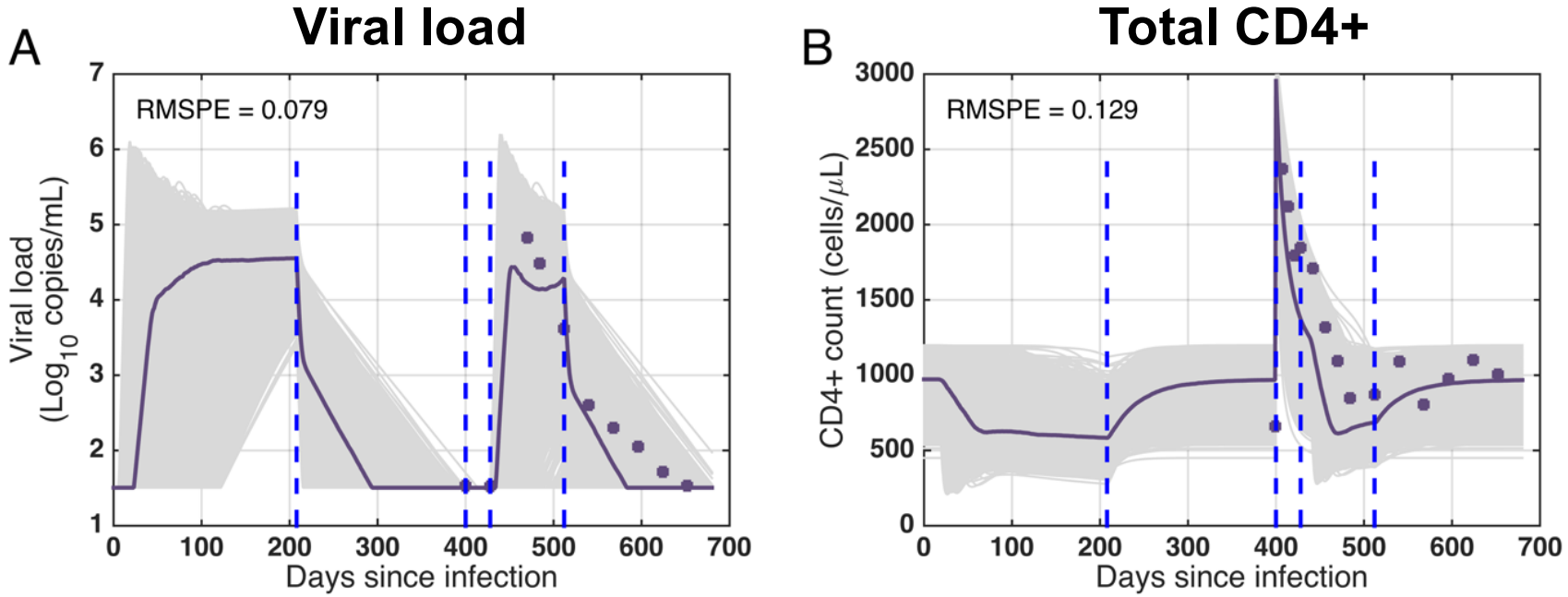
Multiscale mechanistic models can simulate complex, multistep clinical trial protocols over long times

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

Multistep simulation – infection, drug treatment, infusion of cells, cessation of drug treatment



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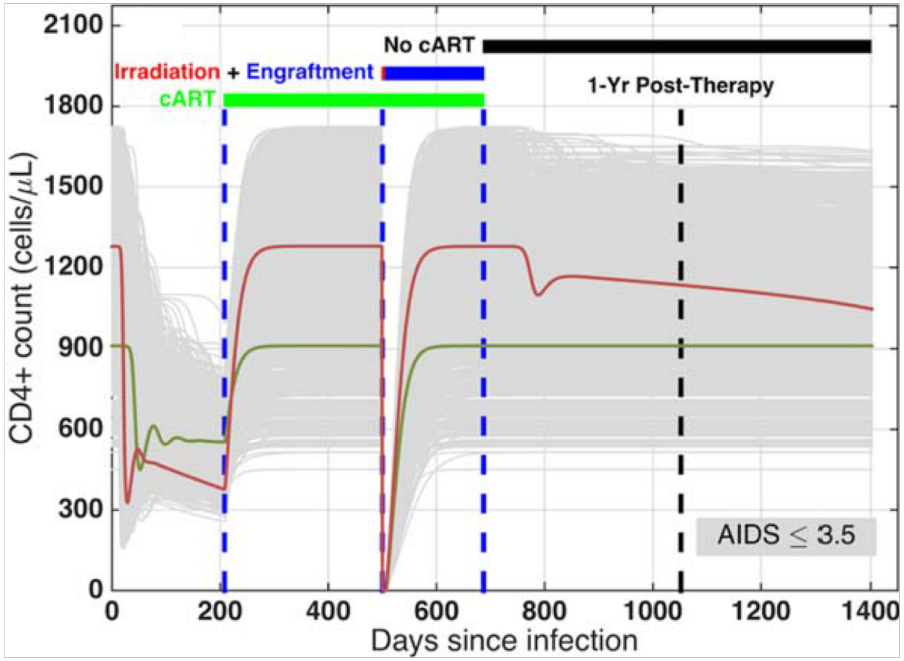
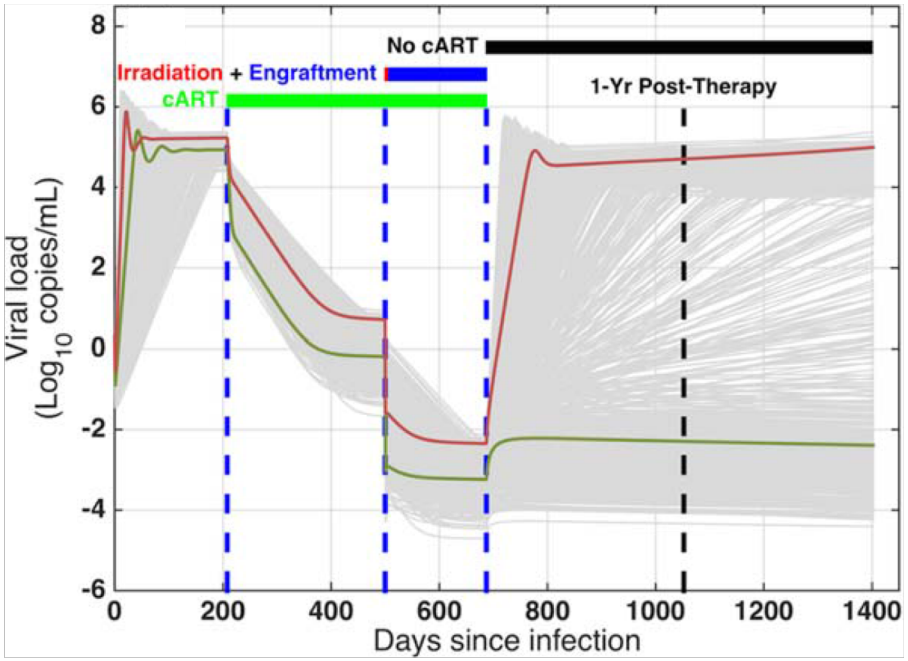
Experimental data: Tebas et al. *New England Journal of Medicine,* 2014

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

CD4+



Viral load



Each line = a virtual patient

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

AIDS ≤ 3.5

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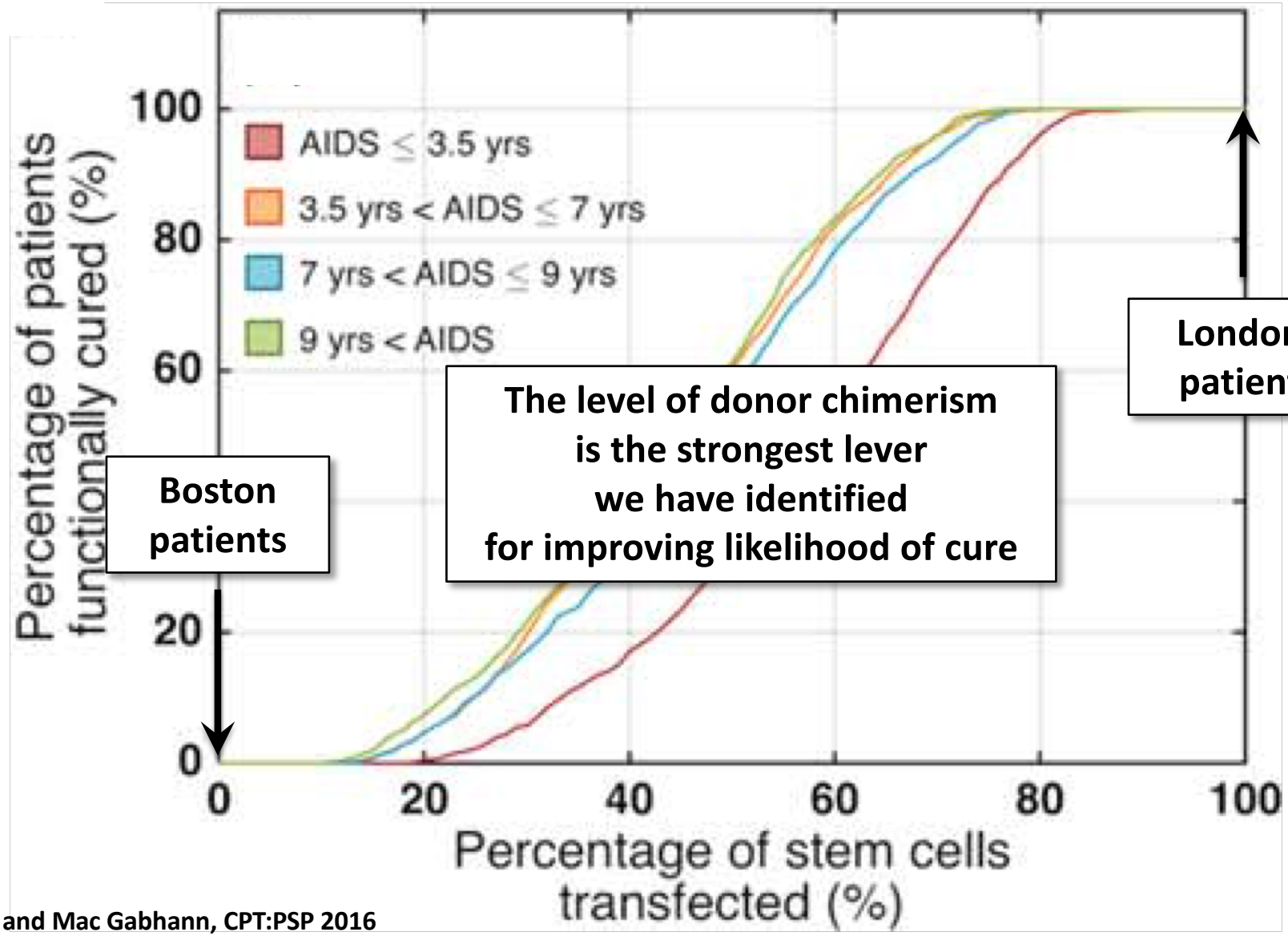
Probability of cure for CCR5-HSCT therapy depends on the level of immune donor chimerism



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Acknowledgments

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