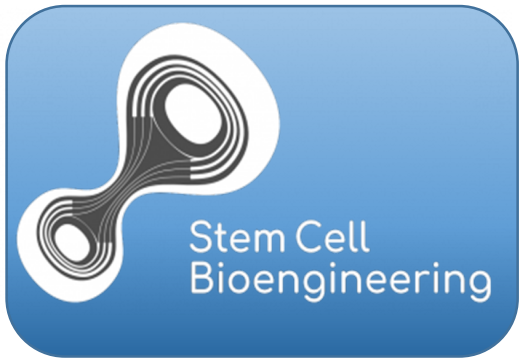
# APPLYING SYSTEMS THINKING TO REGENERATIVE MEDICINE

## National Academies of Sciences, Engineering, and Medicine's Workshop

**October 22nd, 2020**




Peter Zandstra
@pzandstra

# DISCLOSURE

Peter Zandstra has a financial relationship with Excellthera and Notch Therapeutics, in each case, as an equity holder and consultant/advisor.

Dr. Zandstra also has a financial interest in certain patent licenses granted to either Excellthera or Notch Therapeutics concerning technology generated in his laboratory.

# **EXAMPLE 1:** GROWING BLOOD STEM CELLS AS THERAPIES FOR LEUKEMIA

# WHY IS IT SO DIFFICULT TO GROW BLOOD STEM CELLS?

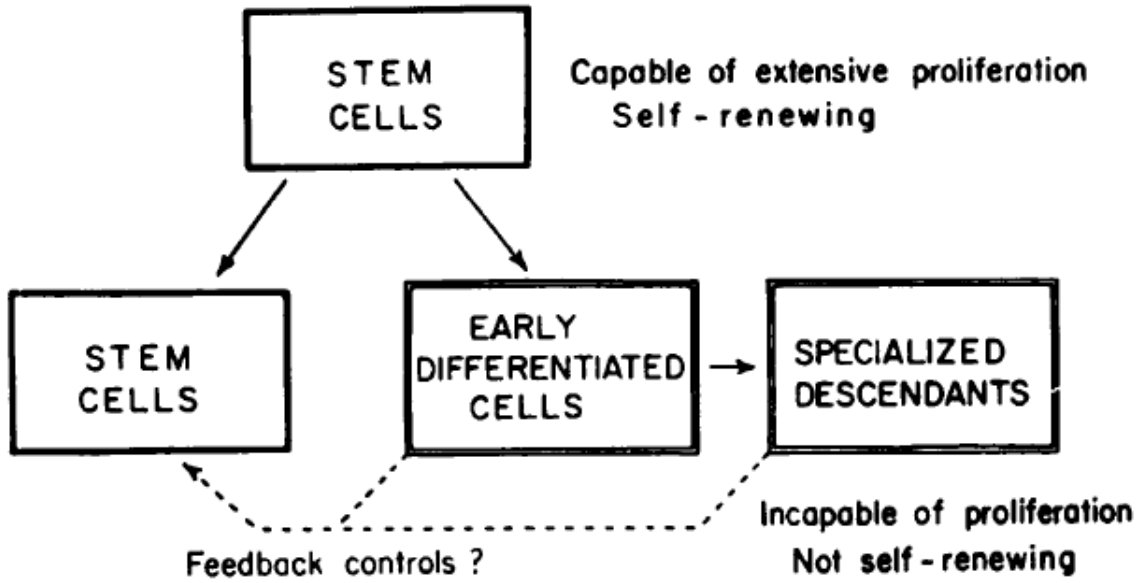


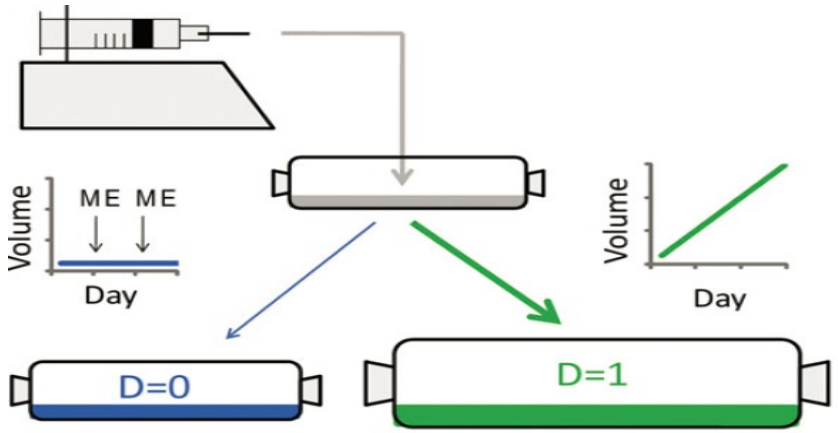

FIG. 1.—A diagrammatic representation of the principal modes of proliferation of blood-forming cells.

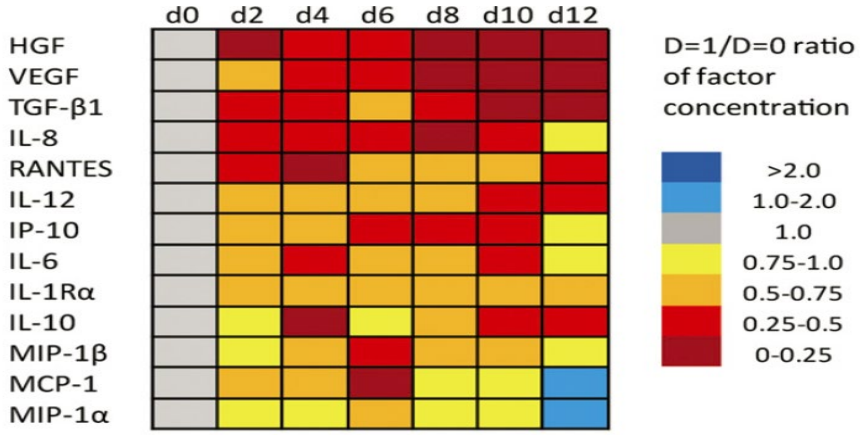
TILL JE, MCCULLOCH EA, SIMINOVITCH L.

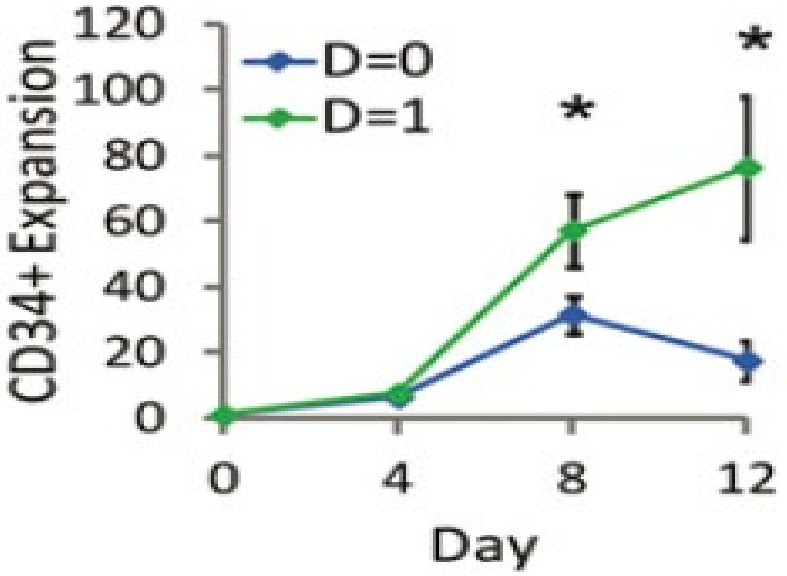
Proc Natl Acad Sci U S A. 1964

A STOCHASTIC MODEL OF STEM CELL PROLIFERATION, BASED ON THE GROWTH OF SPLEEN COLONY-FORMING CELLS.

# AN AUTOMATED "FED-BATCH" BIOREACTOR TO REDUCE FEEDBACK SIGNALS

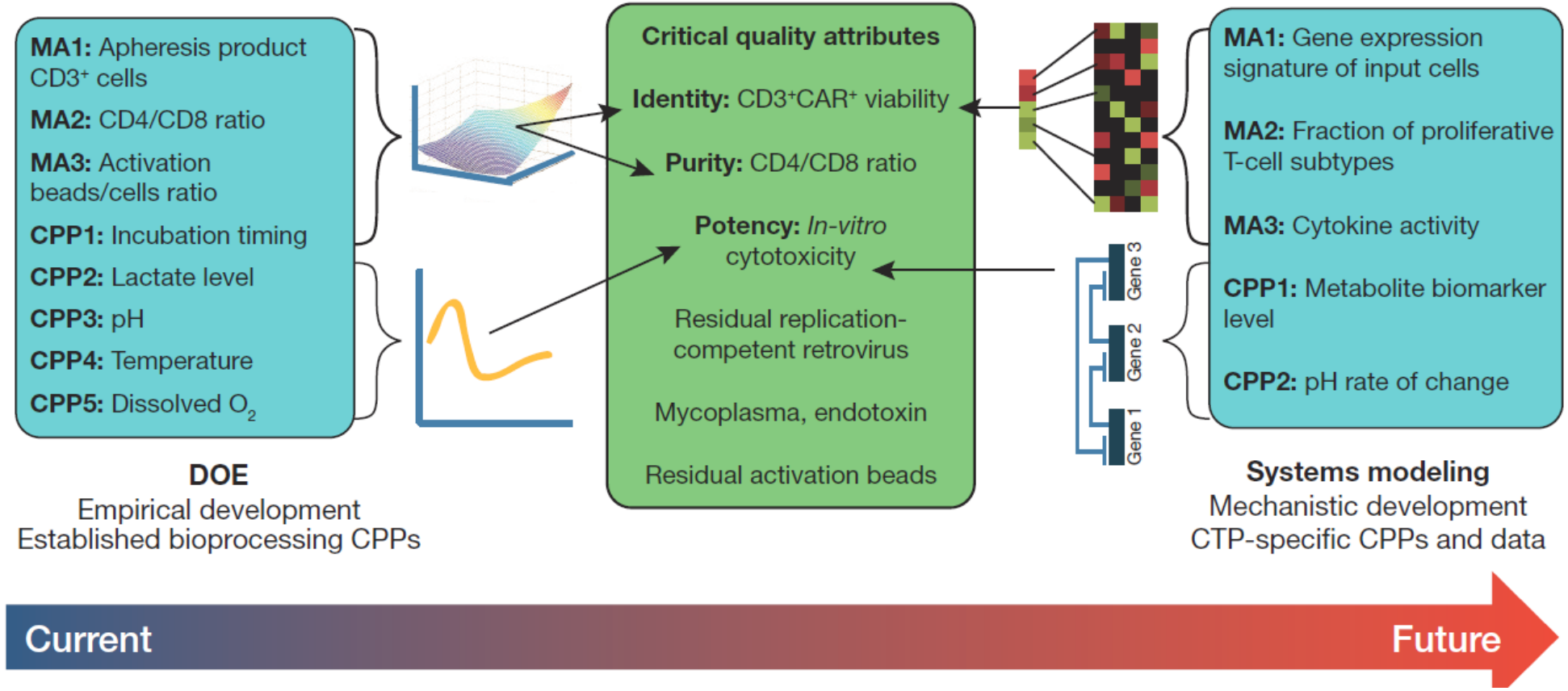


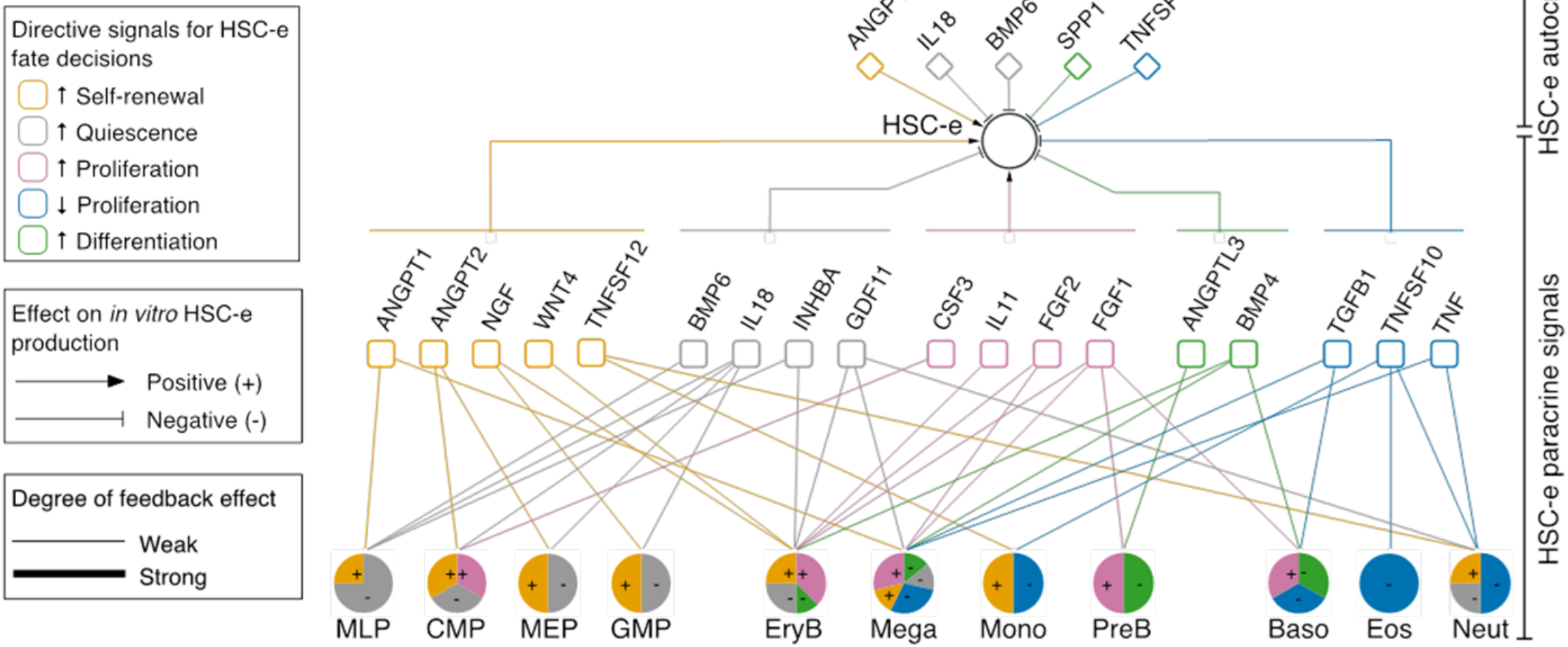

Kirouac et al. Mol Systems Biology (2012)
Csaszar et al. Cell Stem Cell (2013)

# MOVING FROM EMPIRICAL TO MECHANISTIC MODELING IN CELL THERAPY PROCESS DEVELOPMENT



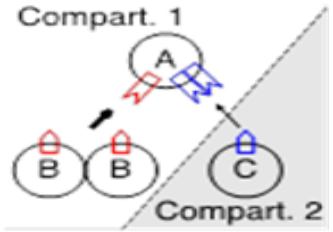

Lipsitz, Timmins & Zandstra, Nature Biotechnology 34, 393-400 (2016)

# AN HSC-CENTRIC CELL-CELL COMMUNICATION NETWORK

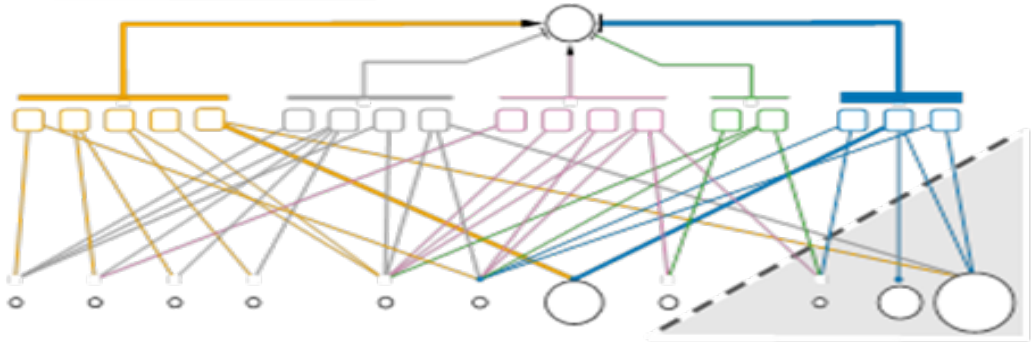



**Qiao et al. Molecular Systems Biology 2014**

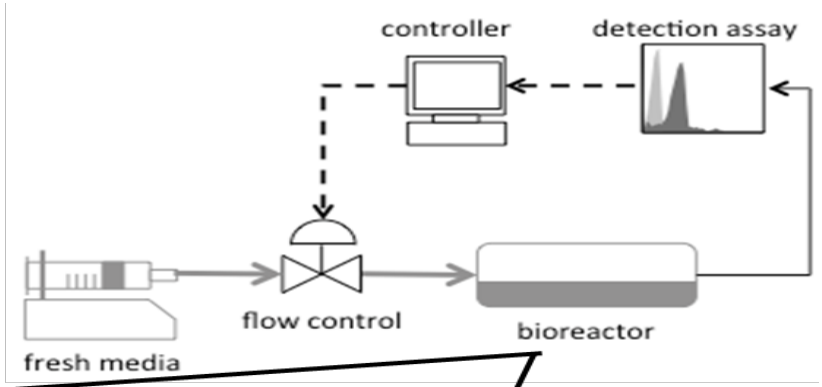
# Next generation “personalized” bioreactors

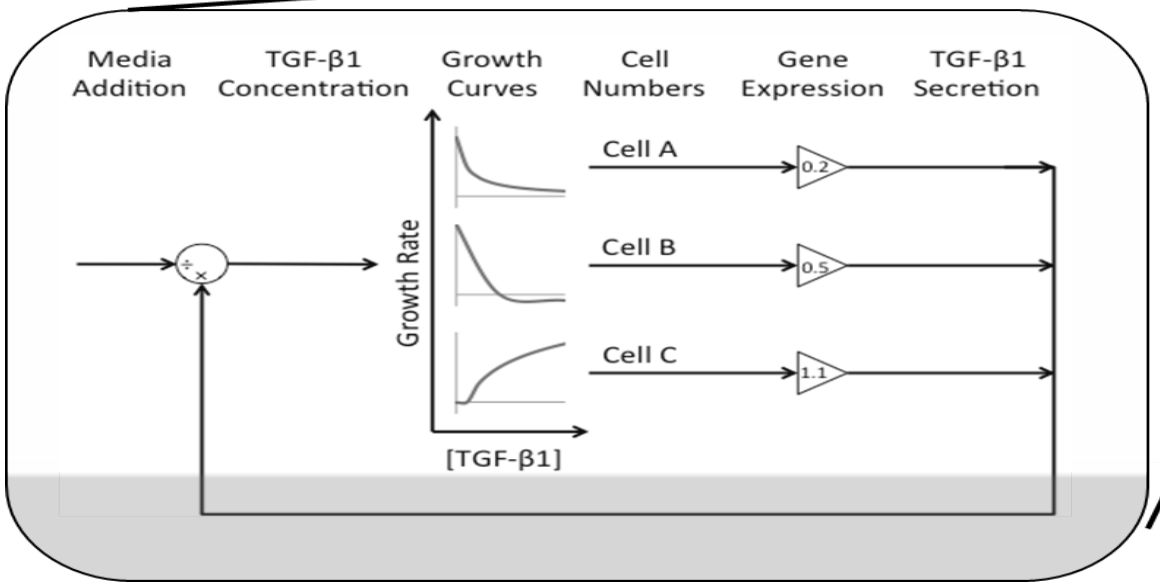


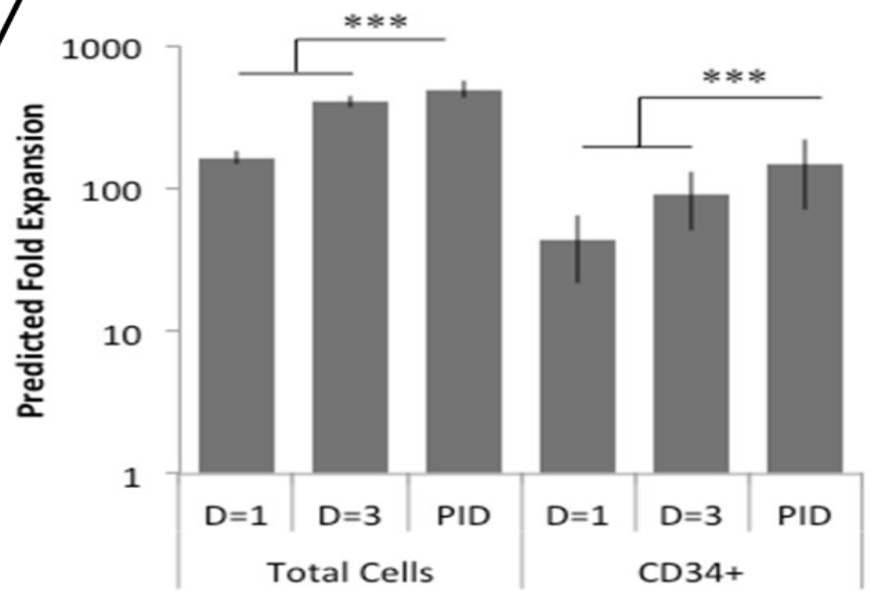

Cell frequency and compartmentalization overlaid network



Qiao et al. Molecular Systems Biology 2014



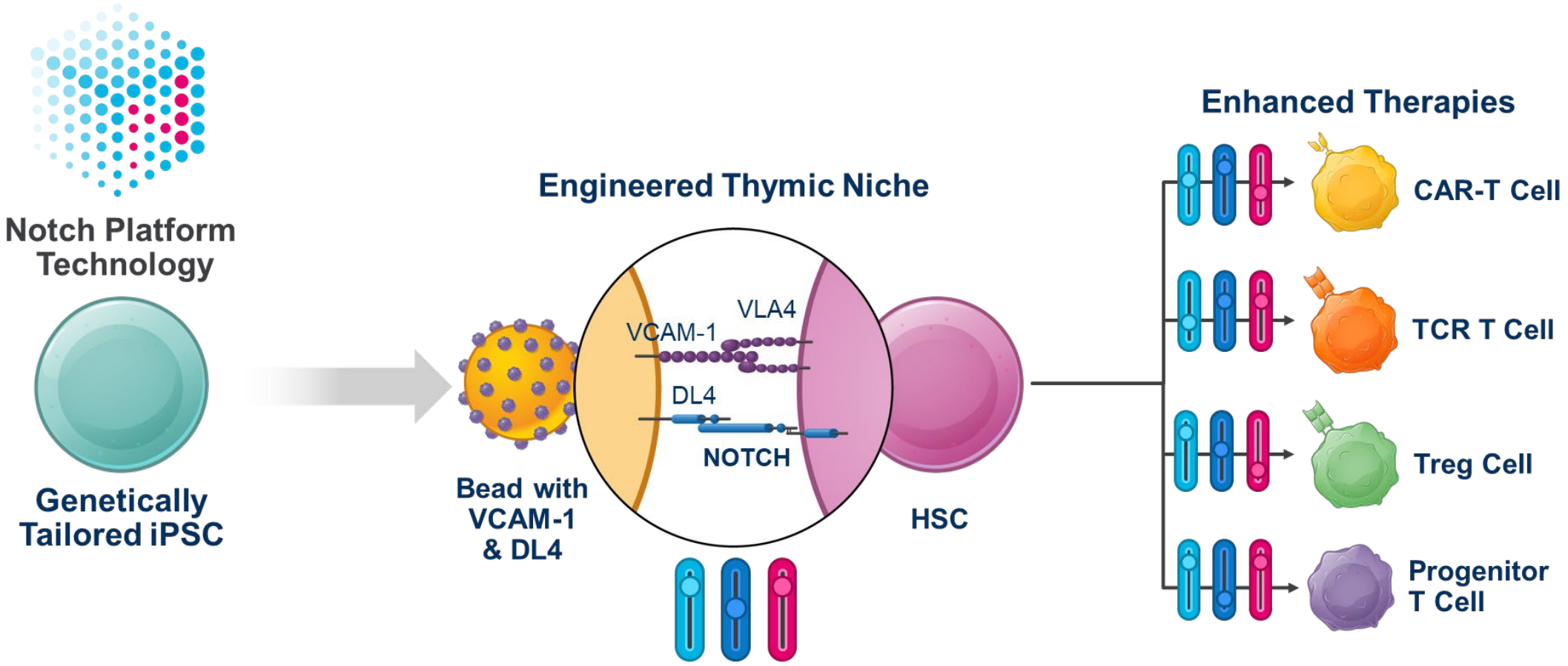




Csaszar et al. Biotechnology and Bioengineering 2014
Caldwell et al. Biotechnology and Bioengineering 2015

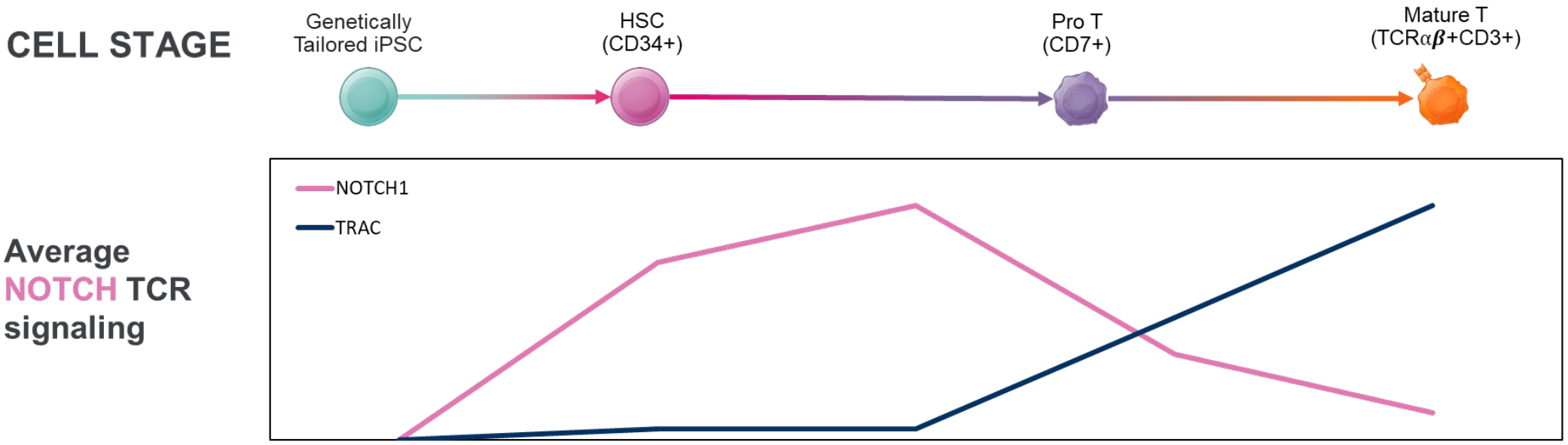
# **EXAMPLE 2:** GENERATING IMMUNOTHERAPIES FROM PLURIPOTENT STEM CELLS

# Stem cell derived manufacturing of immunotherapies: Towards a universal, homogenous and scalable off-the-shelf product

# Notch Platform Technology- Tuning Signaling Context for a Range of Targeted Therapeutics



# ETN Allows for Engineered Modulation of Notch Signalling to Control Cell Fate




How to quantitatively modulate Notch & TCR signaling to match in vivo thympopoiesis?

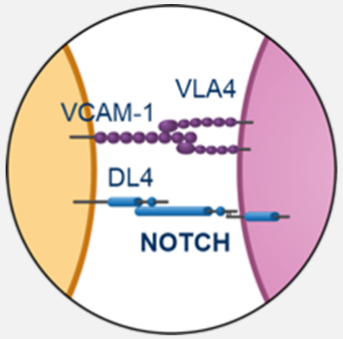
# Computational systems modelling for the predictive design of PSC derived T-cell therapies

How do we quantitatively control biochemical pathways driving T-cell fate?

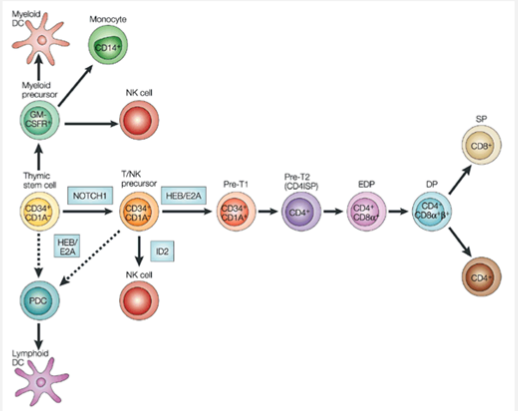
How do culture parameters modulate cell T-cell differentiation and kinetics

How do culture-generated T-cell populations interact with human (patho)-physiology?

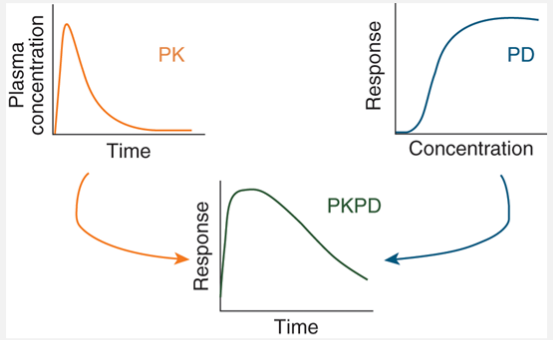
## Mass-action kinetics-based model of Notch-DLL4 signaling




## Cell population model of thymopoiesis



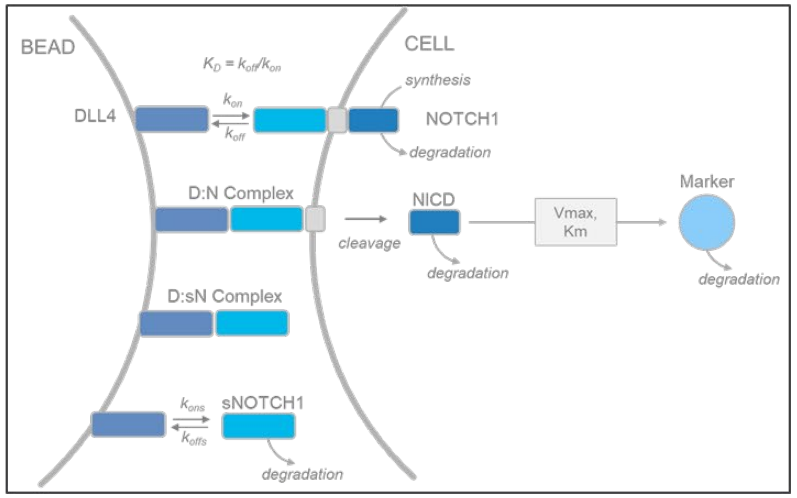

## Cellular kinetic PK/PD model




Notch THERAPEUTICS

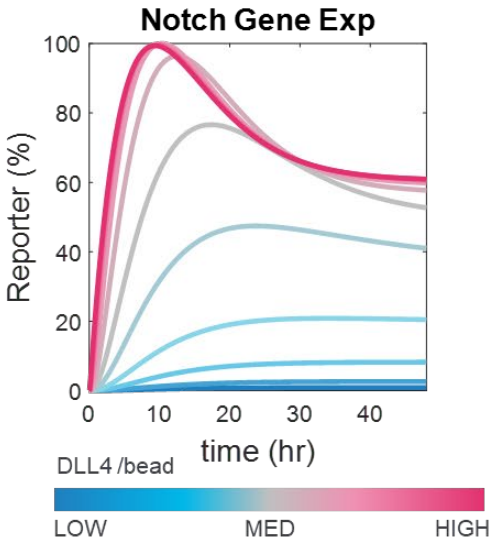
# Notch and TCR signaling models used for *in silico* bead design & optimization

### Notch signaling diagram

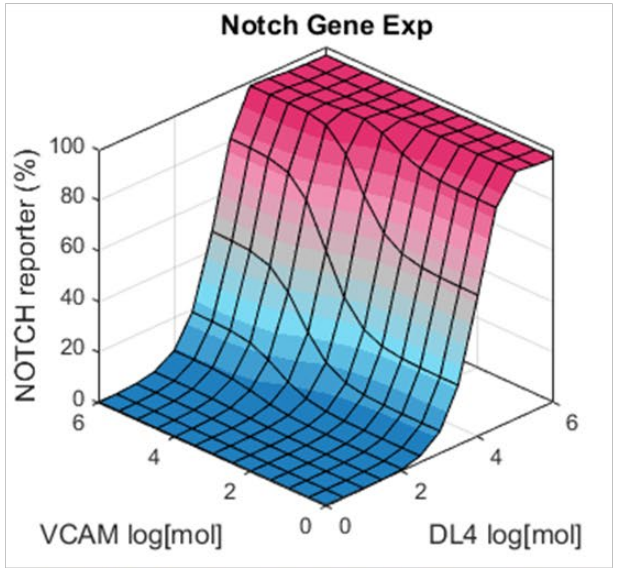



Abbreviations: DL4, delta-like 4; VCAM, vascular cell adhesion molecule

### Dynamic simulations



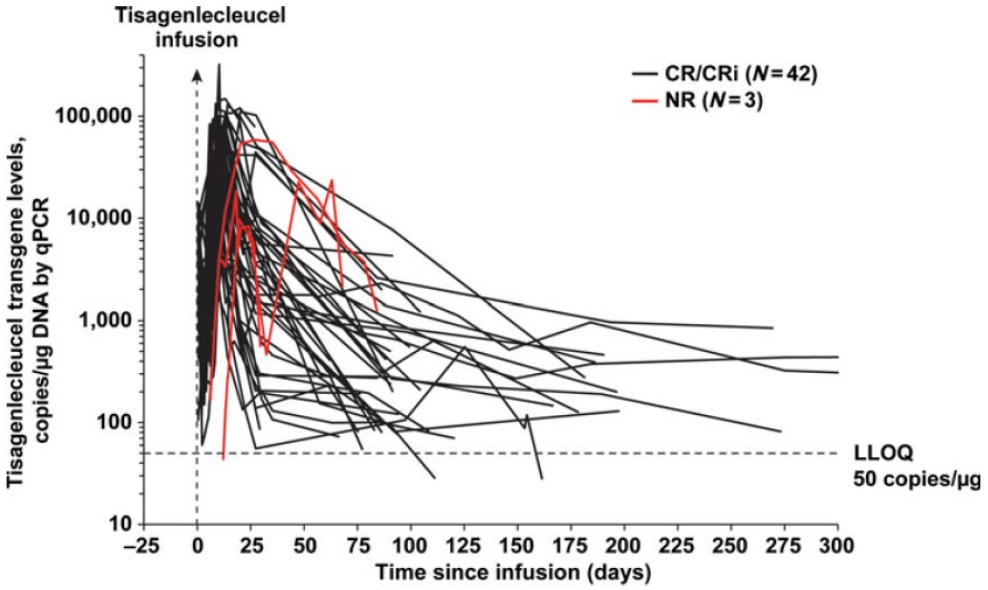

### DLL4 x VCAM surface response




Simulated Notch gene expression in response to graded DL4 and VCAM surface density

# Cell kinetic PK/PD modelling used to understand cellular properties underlying clinical response

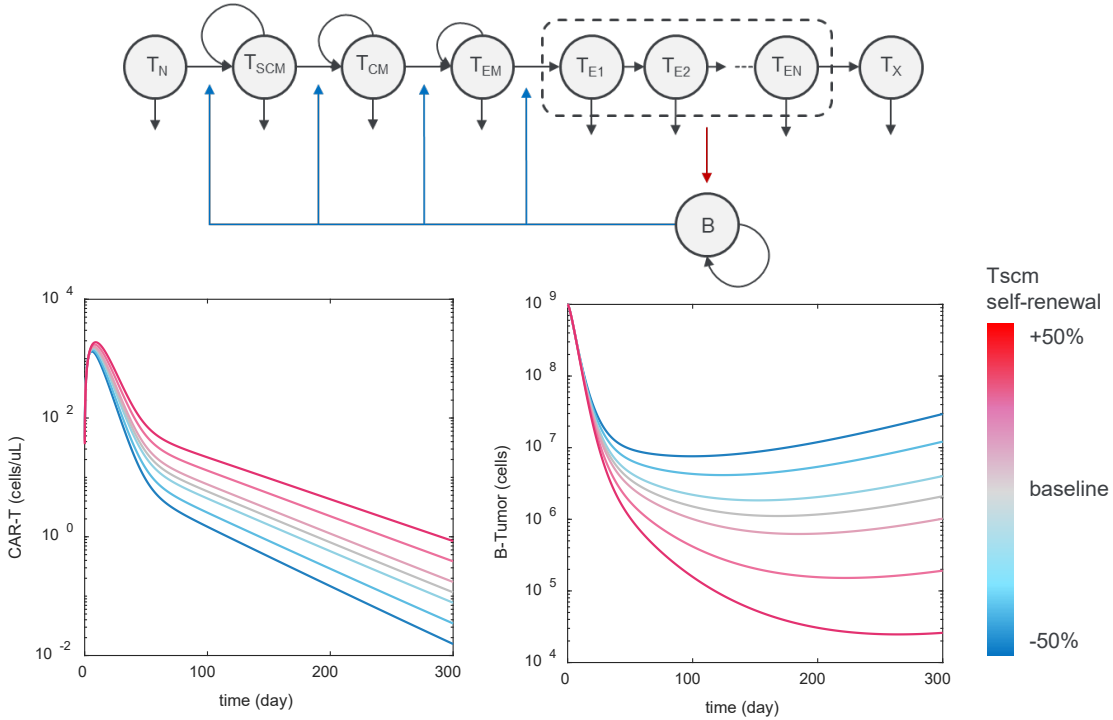
**Problem:** Clinical CAR-T pharmacokinetic and exposure-response relationships are highly variable




**Clinical Pharmacology of Tisagenlecleucel in B-cell Acute Lymphoblastic Leukemia**

Mueller KT et al (2018) Clin Cancer Res

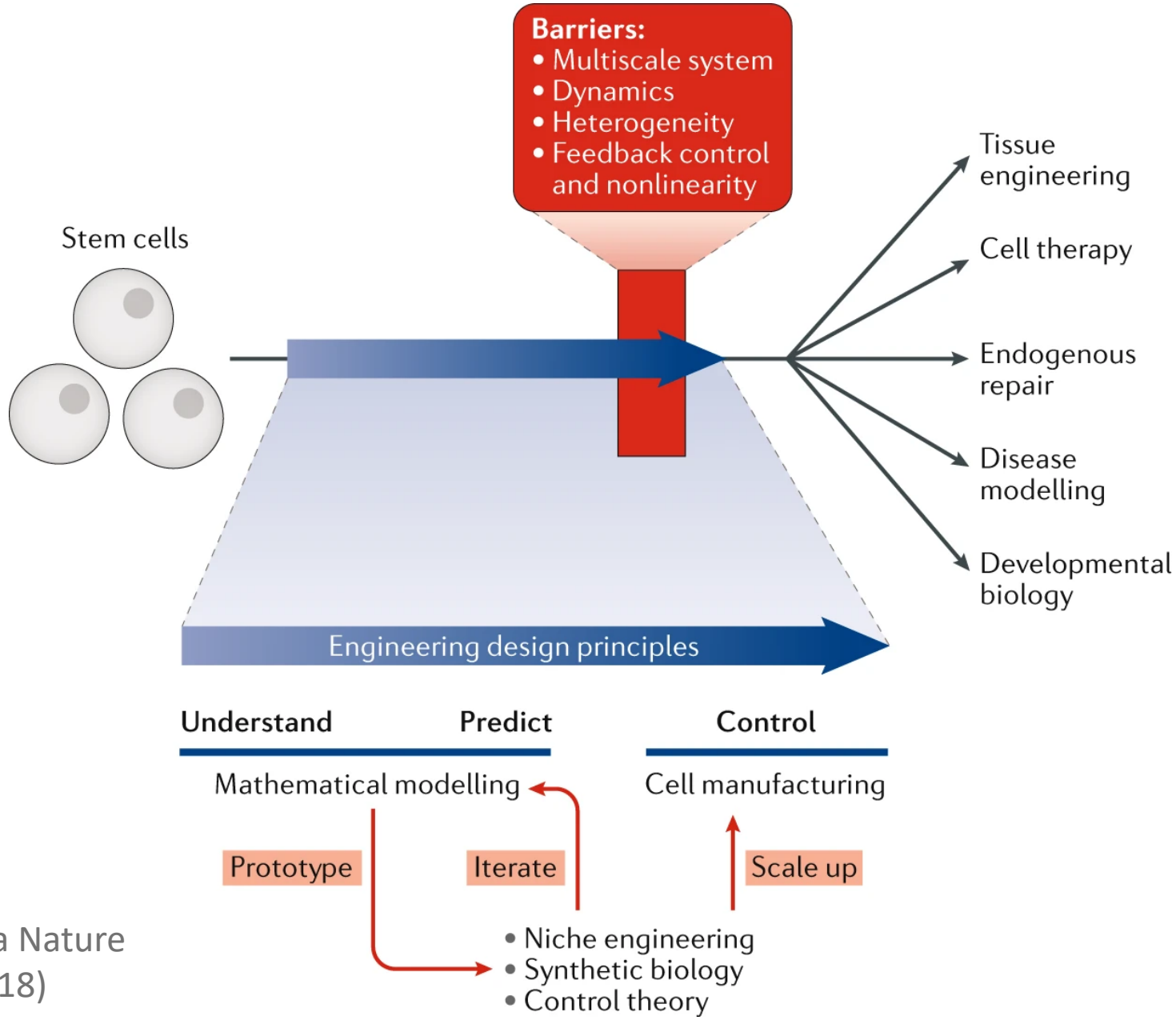
Kinetic model of T-cell maturation and tumor interactions quantifies cellular determinants of clinical activity & variability




Model fit to Phase1B BCMA-CART data [BB2121: Raje N et al (2019) NEJM].
Simulations show effect of varying Tscm self-renewal on PK/PD at 500M cell dose.

Notch THERAPEUTICS

# APPLY ENGINEERING DESIGN PRINCIPLES TO OVERCOME BARRIERS IN CELL THERAPY TRANSLATION




Mukul Tewary, Nika Shakiba & Peter W. Zandstra Nature Reviews Genetics volume 19, pages595–614(2018)