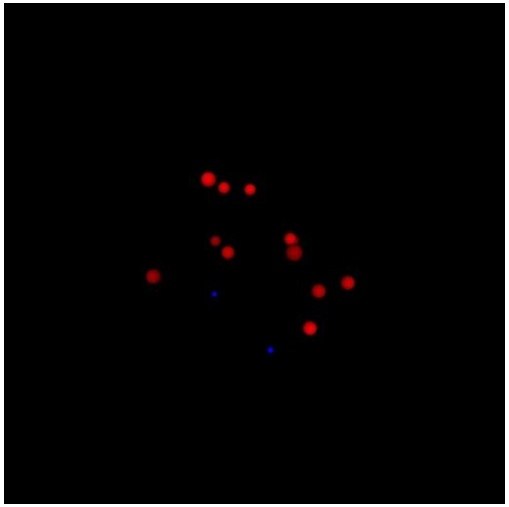
Agent-based model concepts

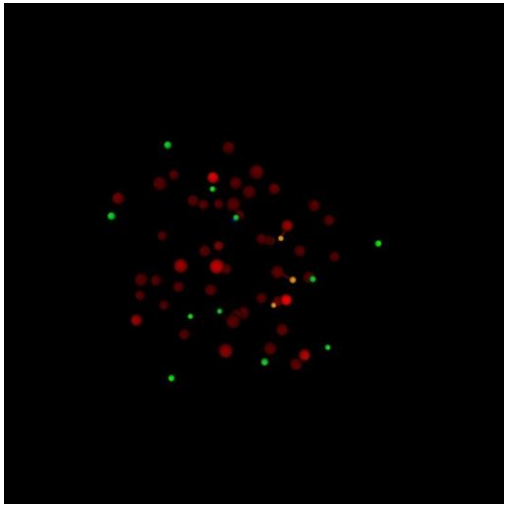
Agent-based models are simulations to determine the global consequences of local interactions of members of a population.

- An agent may be mobile
  - motion could be discrete (on a lattice) or continuous
- Agent state changes with time (evolves) according to the individual experience of the agent, and a set of rules
  - state vector components may take discrete or continuous values
  - interactions take place between nearby agents and/or between agent and environment
- Atomistic approach
  - deals directly with discrete, autonomous entities/individuals/agents rather than with averages or concentrations
  - net result determined by summing over the population, rather than by solving DEs
- Stochastic effects are often important
  - e.g. random walk motility of lymphocytes
  - results are in the form of probability distributions

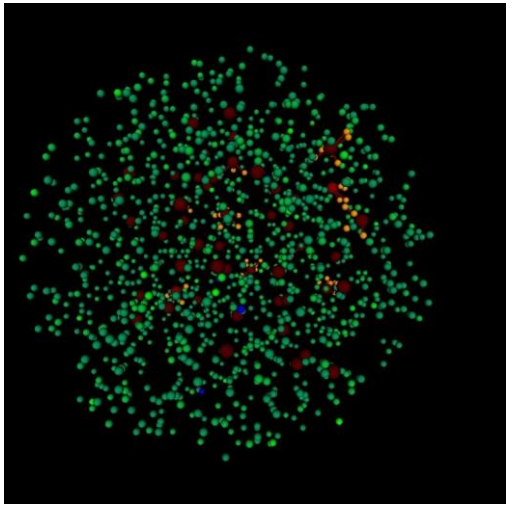
Typical simulated response progression



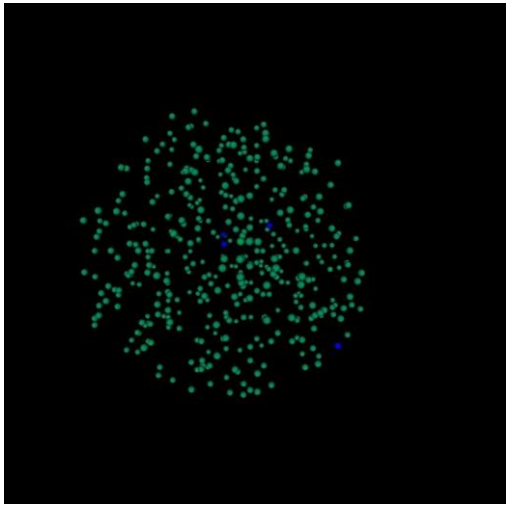
Day 0



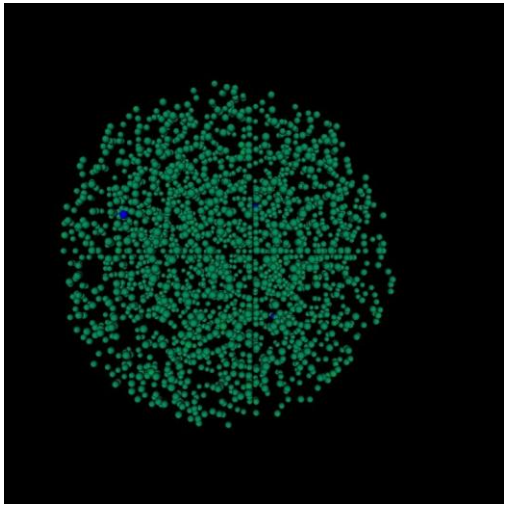
Day 2



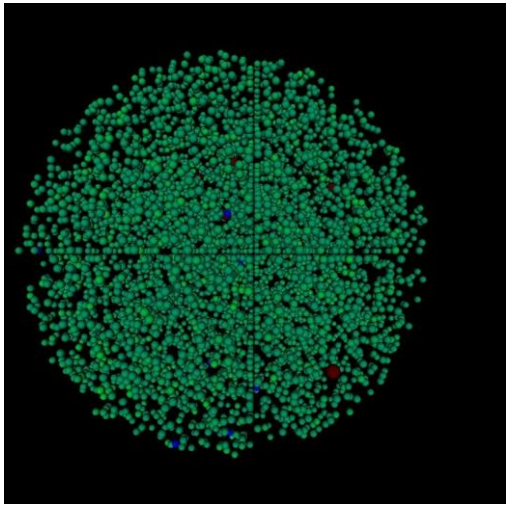
Day 4



Day 10



Day 8



Day 6

B cell rules:

Progression through division changes probability of switching

Cytokines/signals change relation with division

Rules can be found for combinations of signals - indicating cross talk or independence

Key experimental observations -

1. Lognormal times to divide
2. Resetting of times after division - lack of inheritance
3- Division 'counting' can alter parameters
   eg. division progression

4 - Independent regulation of division and death

- Hallmarks of competition for fates apparent
- Asymmetric fates observed but conform to statistical likelihood

Activation-Induced B Cell Fates Are Selected by Intracellular Stochastic Competition

Ken R. Duffy,[1] Cameron J. Wellard,[2,3] John F. Markham,[4] Jie H. S. Zhou,[2,3] Ross Holmberg,[2] Edwin D. Hawkins,[5] Jhagvaral Hasbold,[2,3] Mark R. Dowling,[2,3]* Philip D. Hodgkin[2,3]*†

20 JANUARY 2012 VOL 335 SCIENCE

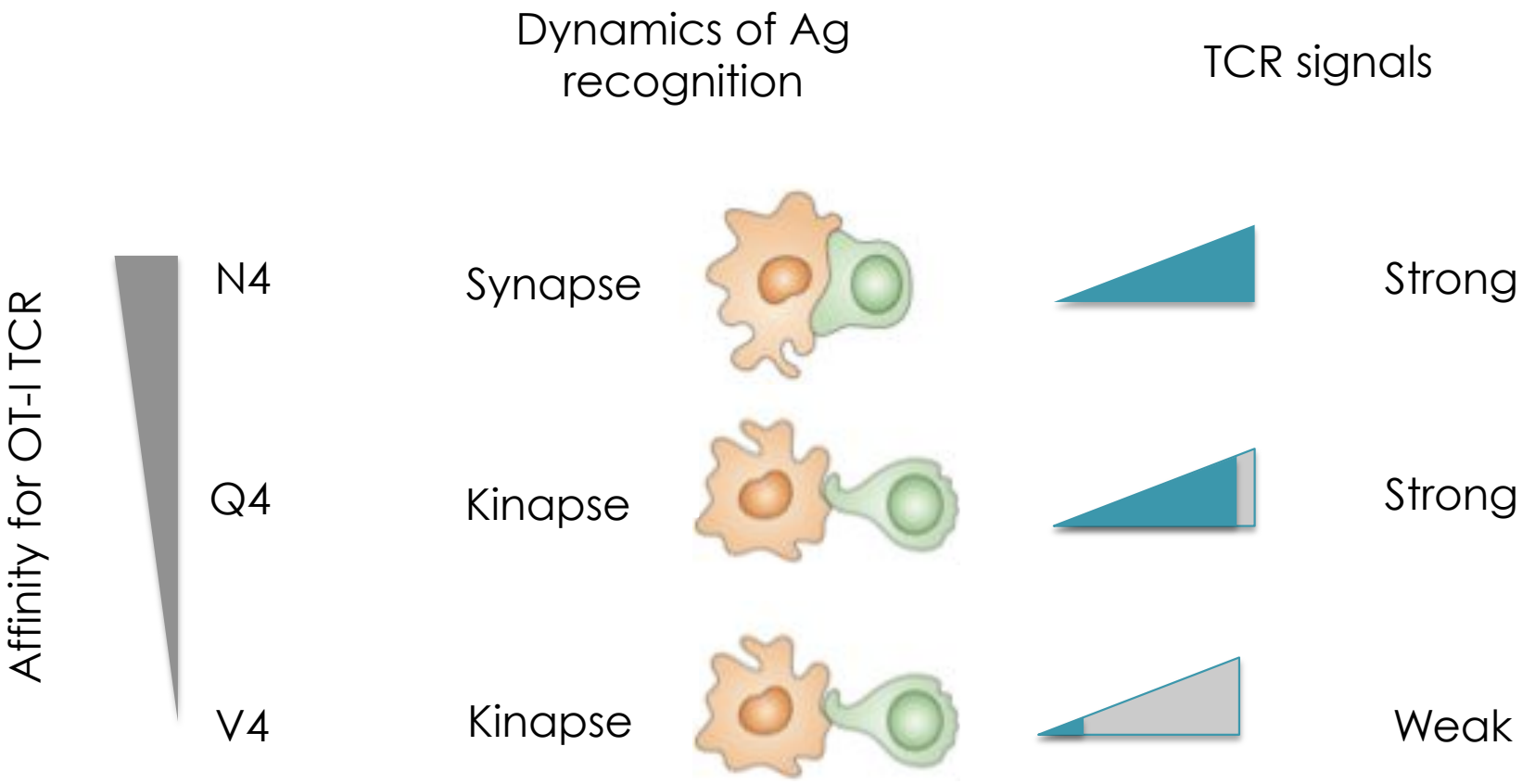
Conclusions

Complex features of lymphocyte control result from a form of modulated 'randomness' of times to different fates set in competition in each cell

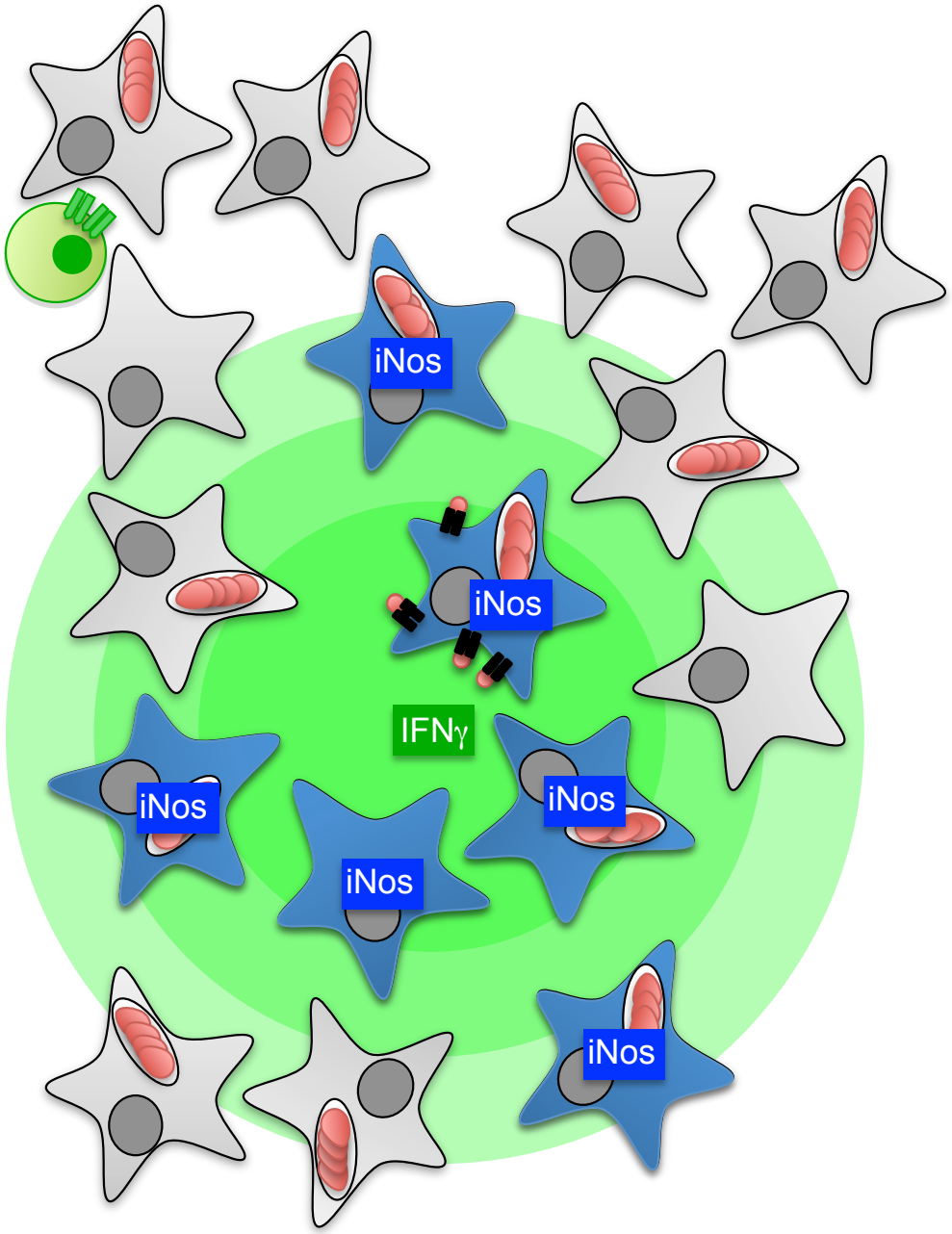
By manipulating the frequencies and times to change, by signals and cell division, a robust system for allocating different cells to large number of different fates is created

Combinatorially for example - just 20 independent surface marker 'machines' - gives one million possible 'phenotypes'

pMHC affinity: dual role with distinct thresholds



DISC: An approach to simultaneously assess cell dynamics and phenotype
A tool for quantifying imaging data
DISCit software freely available upon request



Antigen-specific CD4 T cells form limited number of stable contacts with infected cells (presumably due to limited antigen presentation)

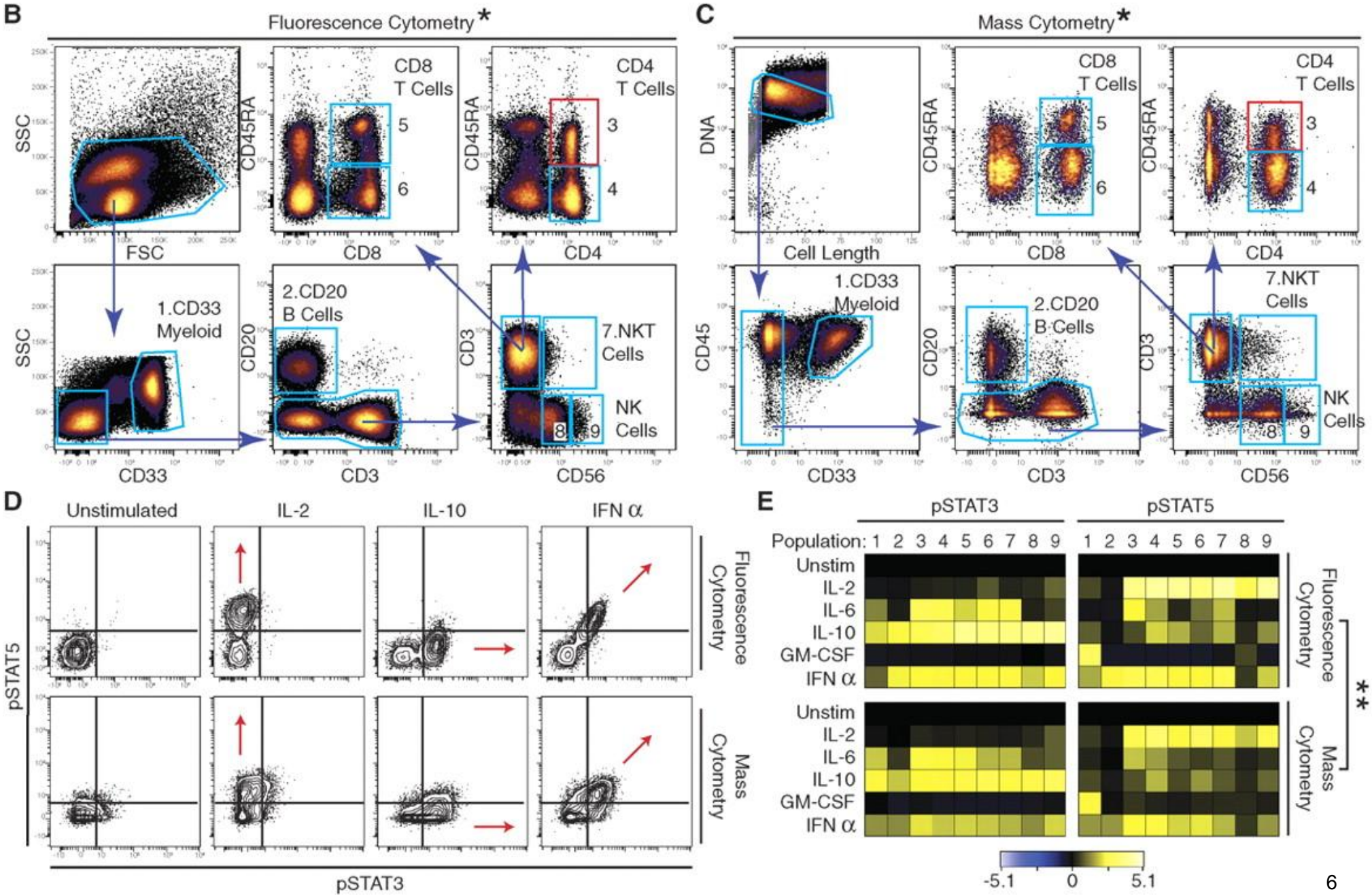
CD4 T cells effector functions occurs beyond the immunoligical synapse, reaching not only the antigen-presenting cell but also non-presenting bystander cells (range >100 µm)

CD4 T cells can control an infection by engaging <10% of infected cells

Single-Cell Mass Cytometry of Differential Immune and Drug Responses Across a Human Hematopoietic Continuum

Sean C. Bendall,[1*] Erin F. Simonds,[1*] Peng Qiu,[2] El-ad D. Amir,[3] Peter O. Krutzik,[1] Rachel Finck,[1] Robert V. Bruggner,[1,7] Rachel Melamed,[3] Angelica Trejo,[1] Olga I. Ornatsky,[4,5] Robert S. Balderas,[6] Sylvia K. Plevritis,[2] Karen Sachs,[1] Dana Pe'er,[3] Scott D. Tanner,[4,5] Garry P. Nolan[1†]

Science vol 332 (6 May 2011) page 687


B
Fluorescence Cytometry*
SSC
FSC
CD45RA
CD8
CD8 T Cells
5
6
CD4
CD4 T Cells
3
4
1.CD33 Myeloid
CD33
2.CD20 B Cells
CD20
CD3
7.NKT Cells
NK Cells
8
9
CD56
C
Mass Cytometry*
DNA
Cell Length
CD45
D
Unstimulated
IL-2
IL-10
IFN α
pSTAT5
pSTAT3
Fluorescence Cytometry
Mass Cytometry
E
pSTAT3
pSTAT5
Population: 1 2 3 4 5 6 7 8 9
Unstim
IL-2
IL-6
IL-10
GM-CSF
IFN α
**
-5.1
0
5.1

- “A central dogma of immunology is that cells at different stages of maturation can be characterized by the expression of unique sets of proteins on the cell surface.”
- “The number of nodes and ultimately their boundaries is driven by a user-definable value (21).”

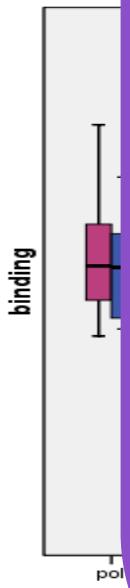
Imperial College London

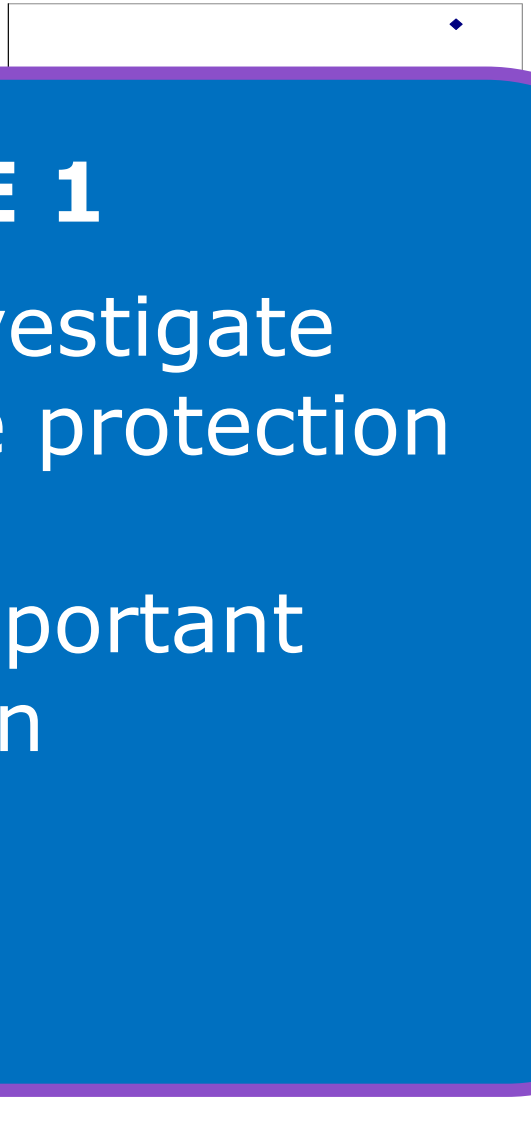
Summary: Determinants of efficiency I

Used epitope prediction software to i… pr… d

TAKE HOME 1

- General approach to investigate determinants of immune protection
- Protein specificity an important determinant of protection
- Immunogenicity is not



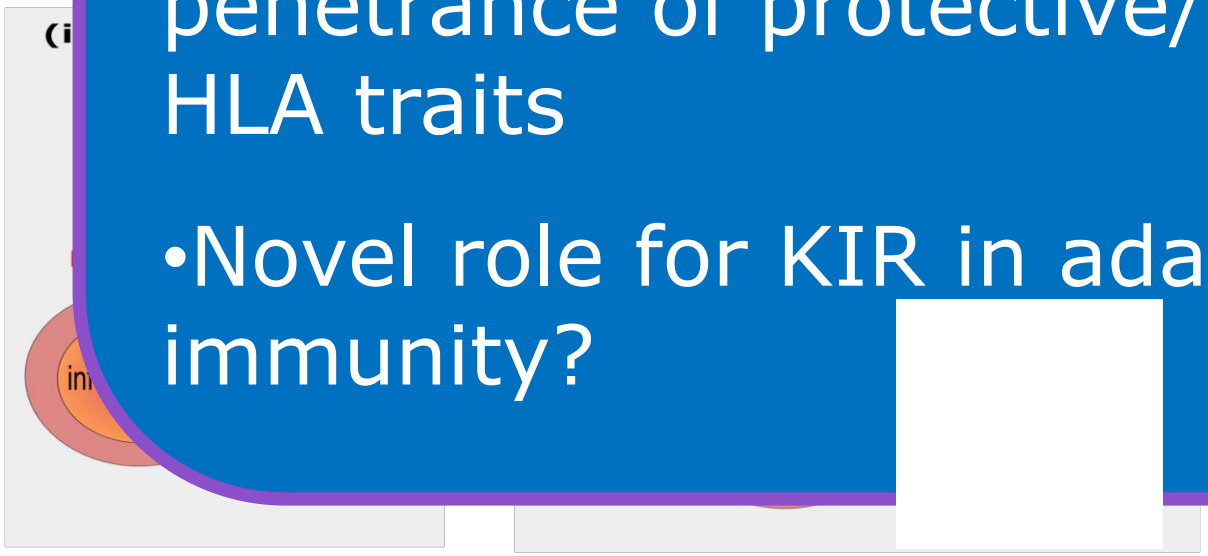


Imperial College London

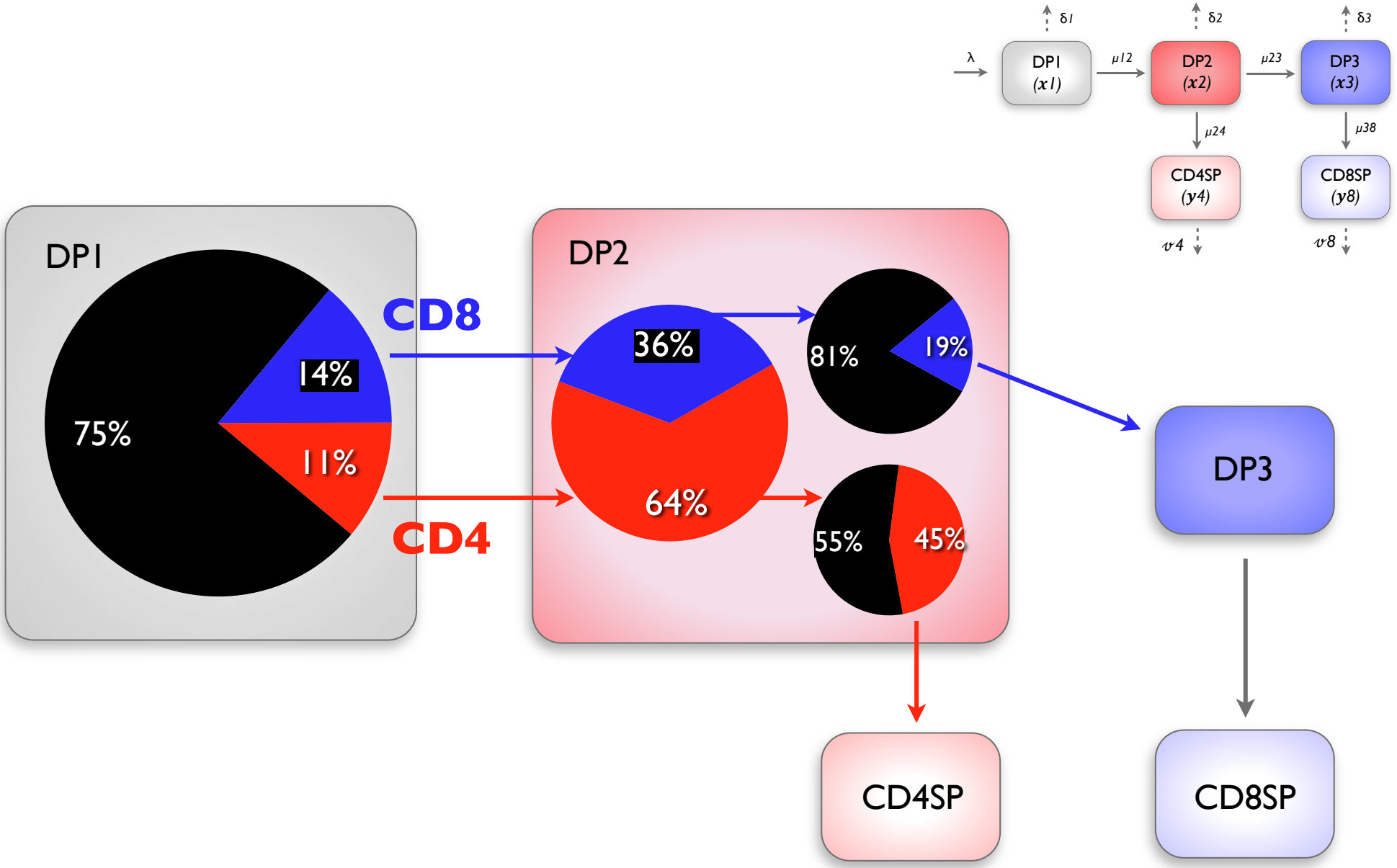
Summary: Determinants of efficiency II

TAKE HOME 2

- An "innate" receptor is enhancing HLA class I associations
- Potential explanation for incomplete penetrance of protective/ detrimental HLA traits
- Novel role for KIR in adaptive immunity?



Modeling reveals unexpectedly high CD8 lineage biased death in selection



Conclusions on T cell kinetics in mice

Life span	Range		T cell type	Method	Model	Ref.	Remarks
mouse							
68 d	65–71 d	CI	naive $CD8^+$	BrdU	Eq. (13)	Parretta *et al.* [172]	thymectomized mice
47 d	41–54 d	CI	naive $CD4^+$	^2H_2O	Eq. (23)	Den Braber *et al.* [56]	young adult mice
80 d	67–92 d	CI	naive $CD8^+$	^2H_2O	Eq. (23)	Den Braber *et al.* [56]	young adult mice
41 d	36–47 d	CI	naive $CD4^+$	^2H_2O	Eq. (23)	Den Braber *et al.* [56]	old mice
116 d	94–139 d	CI	naive $CD8^+$	^2H_2O	Eq. (23)	Den Braber *et al.* [56]	old mice
90 d	64-133 d	CI	memory $CD8^+$	BrdU	Eq. (18)	Parretta *et al.* [172]	no source: $\sigma = 0$, no de-labeling
50 d	—		memory $CD8^+$	CFSE	Eq. (15)	Choo *et al.* [35]	LCMV specific memory cells
14–22 d	—		memory $CD4^+$	BrdU	*	Younes *et al.* [238]	memory phenotype cells
50 d	—		memory $CD4^+$	Ki67	—	Younes *et al.* [238]	LCMV specific memory cells
15 d	11–15 d	CI	memory $CD4^+$	^2H_2O	Eq. (26)	Westera *et al.* [226]	3 different labeling periods
20 d	12–22 d	CI	memory $CD8^+$	^2H_2O	Eq. (26)	Westera *et al.* [226]	3 different labeling periods

Memory phenotype cells turn over faster
than "true" memory T cells?
Naive T cells live longer than memory T cells.
$CD8^+$ naive T cells live longer than $CD4^+$ naive T cells.

Review: De Boer & Perelson (JTB, submitted)

Conclusions from 5 human volunteers labeled with D-water

Expected life spans (medians)

Naive $CD4^+$ T cells: 2000 days (5.5 years)

Naive $CD8^+$ T cells: 3300 days (9.1 years)

Effector/memory $CD4^+$ T cells: 160 days (0.45 years)

Effector/memory $CD8^+$ T cells: 160 days (0.45 years)

Compartments:

Naive T cell data typically requires only one exponent

Memory data do require 2 compartments: heterogeneity

Immunological memory is maintained by short-lived cells

Vrisekoop et al PNAS 2008
Westera et al Submitted

Conclusions on using labeling to infer T cell population dynamics

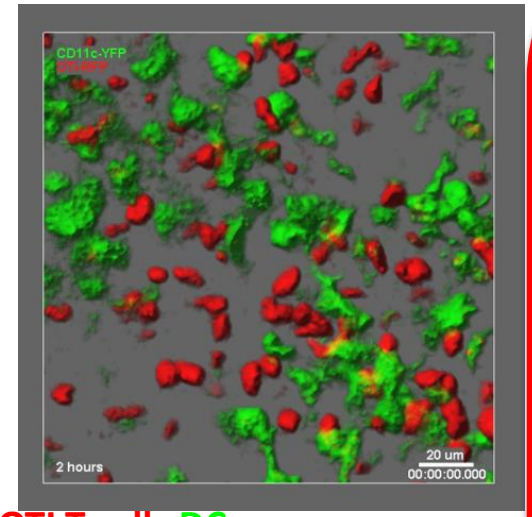
Interpretation of deuterium data seemed so simple:
no toxic effects, no dilution, loss by death only.
Nevertheless very contradictory estimates.

Important to gather dense data having several points during early up and down-slope and fit these with an appropriate model

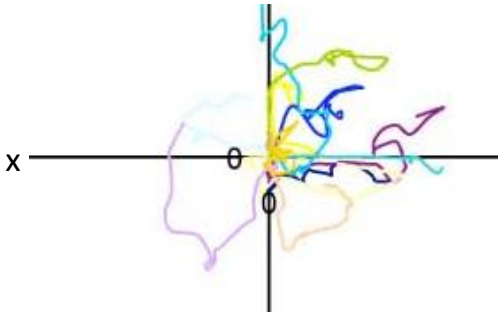
Naive T cells have life spans of
several years in humans and several weeks in mice.
Memory T cells live shorter than naive T cells.

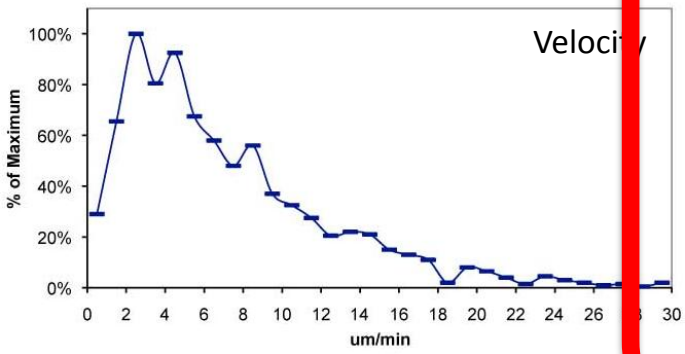
T-cell dynamics during the immune response

Phase 1: Transient contacts

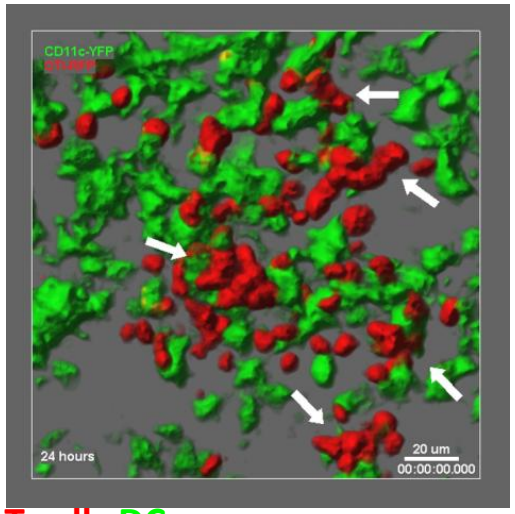


OTI T cells DCs

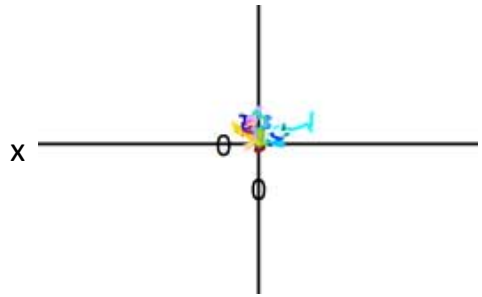


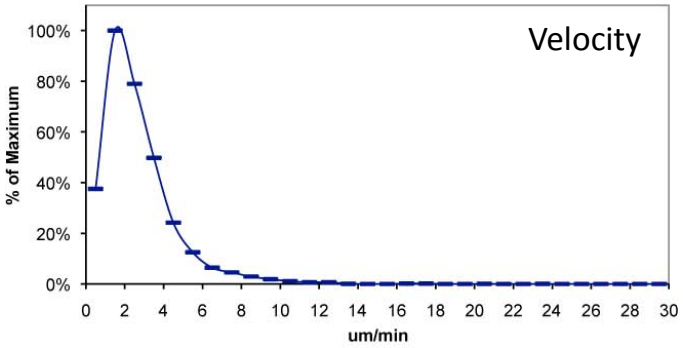


Phase 2: Arrest phase

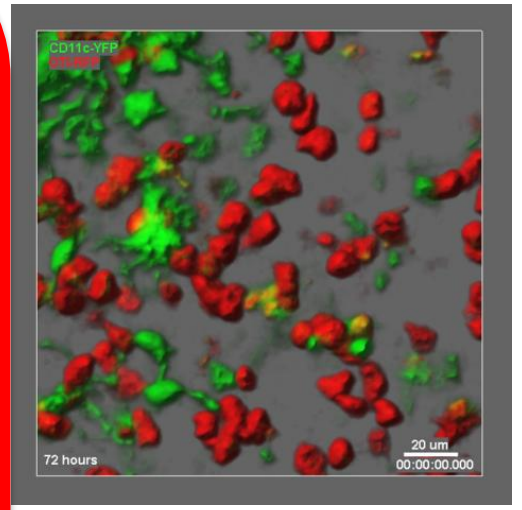


OTI T cells DCs

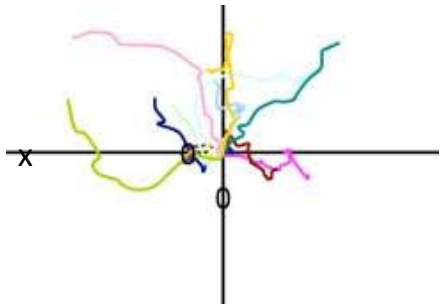


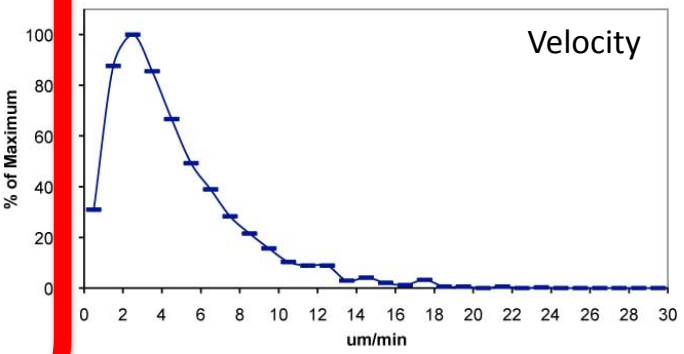


Phase 3: Swarming



OT T cells DCs



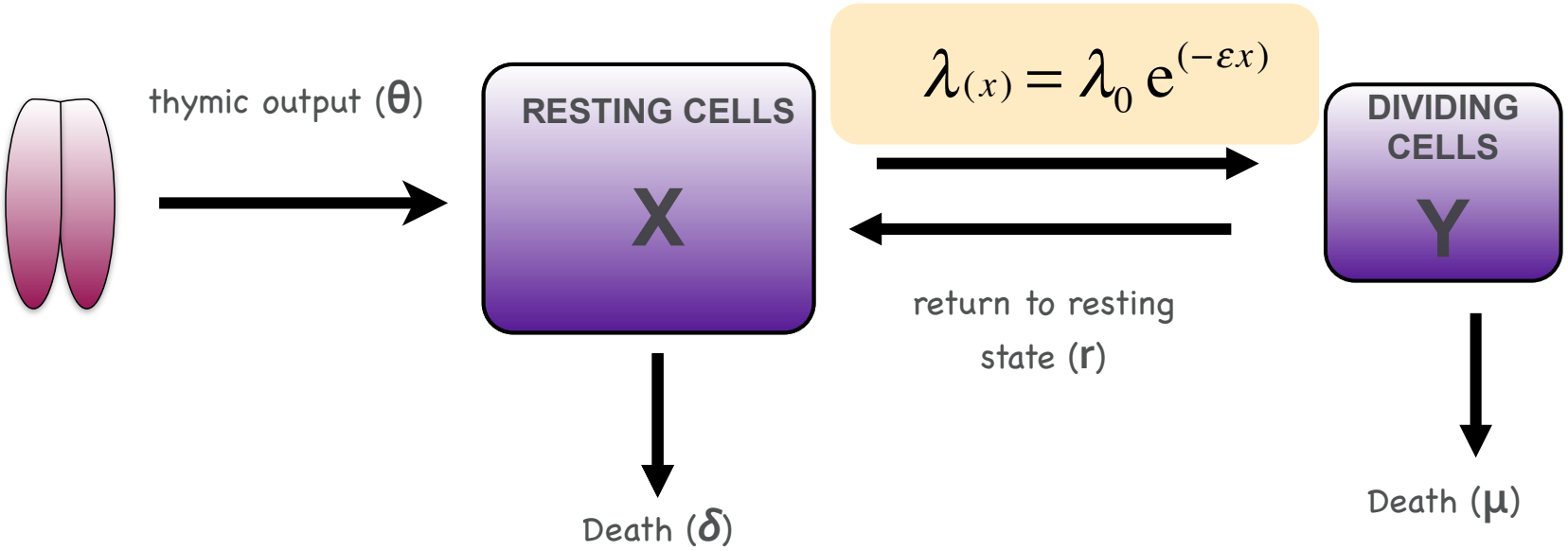


DEC-OVA + CD40 Ab

2h **24h** **48h**

Time

Dependence on Resource



λ_0 → sensitivity of individual clone to homeostatic growth signal

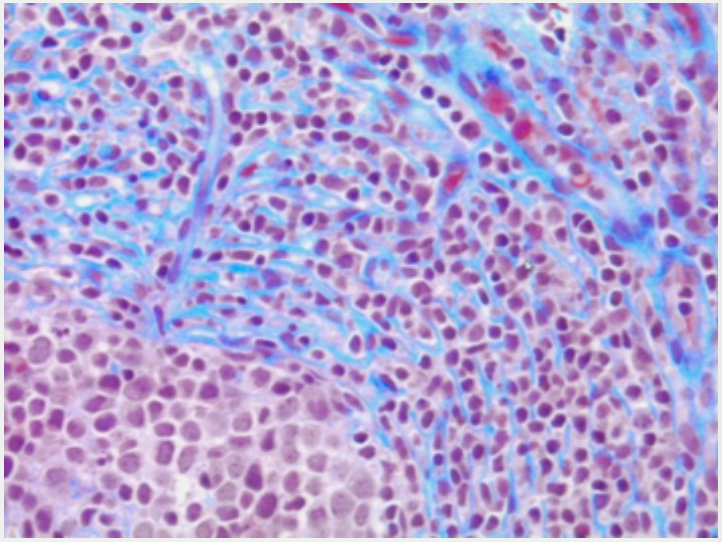
$1/\varepsilon \propto$ resource (e.g. IL7)

Collagen deposition in HIV-1 infected lymphatic tissues and T cell homeostasis

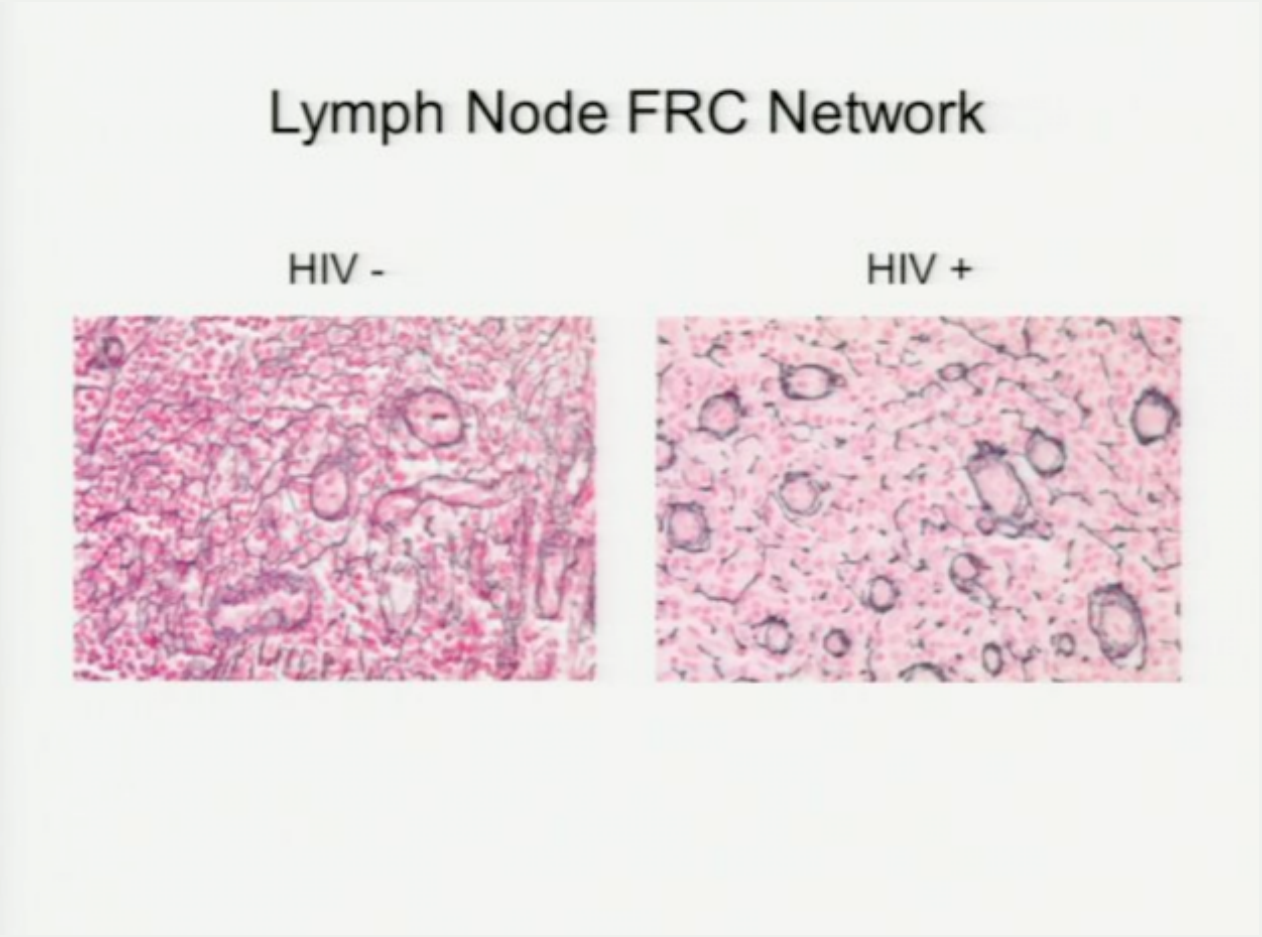
J Clin Invest (2002) 110:1133

Timothy W. Schacker,[1] Phuong L. Nguyen,[2] Gregory J. Beilman,[3] Steven Wolinsky,[4] Matthew Larson,[1] Cavan Reilly,[5] and Ashley T. Haase[6]

collagen deposit in LN from HIV



Schacker, CROI, 2011



Summary

- Very rapid recirculation of TDLs between blood, lung, and liver (residence time < 1 min).
- Short-residence time of lymphocytes in the spleen (average 2.5 h)
- Gamma distributed residence time of TDLs in lymph nodes and Peyer's patches (average 10 hours).
- Accumulation of TDLs in Ag-stimulated lymph nodes is due to increased entrance rate (3.5 fold).

Blood recirculation kinetics (rats)

- Total blood volume is about 20 mL
- Volume of the heart is about 1-2mL
- 30% is pumped per beat (humans)
- Heart beat is about 300 per min

Algebra

- Per 1 min, rat heart will pump (at most)

$$0.3 \times 1m\text{L} \times 300 = 90m\text{L}$$

  of blood which is about 4-5 times the blood volume.

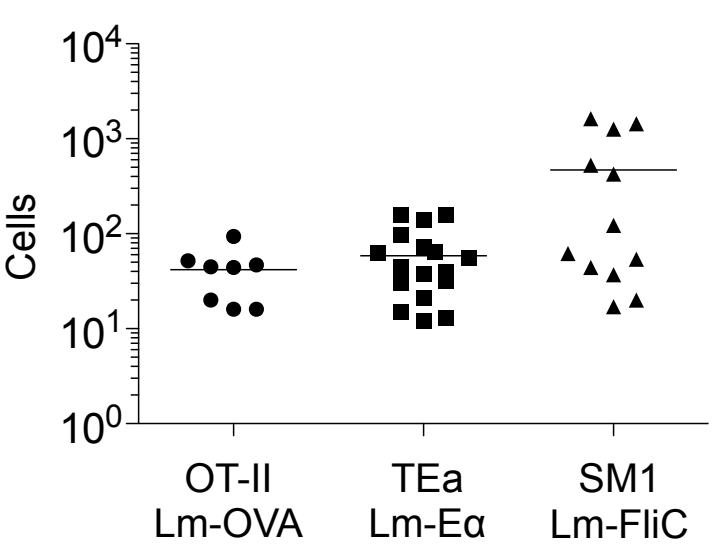
- Average blood turnover time is about 10-15 seconds. Lymphocytes are able travel via lung capillaries and liver sinusoids nearly as fast as the blood.

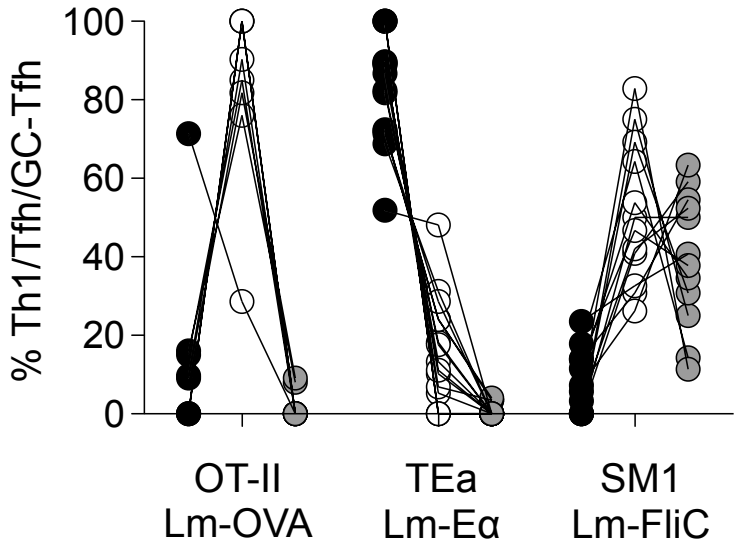
Nature or Nurture?

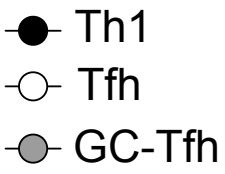
- Each naive clone has a different intrinsic capacity to produce certain effector cells types, probably determined by the (nature) of its unique TCR.

- Each naive clone has the same intrinsic capacity but can produce different effector cells types in response to extrinsic (nuture) factors, e.g., the amount of ICOS, cytokine p:MHCII.

Transfer of single TCR Tg T cells provides evidence for lots of nature and a little nurture





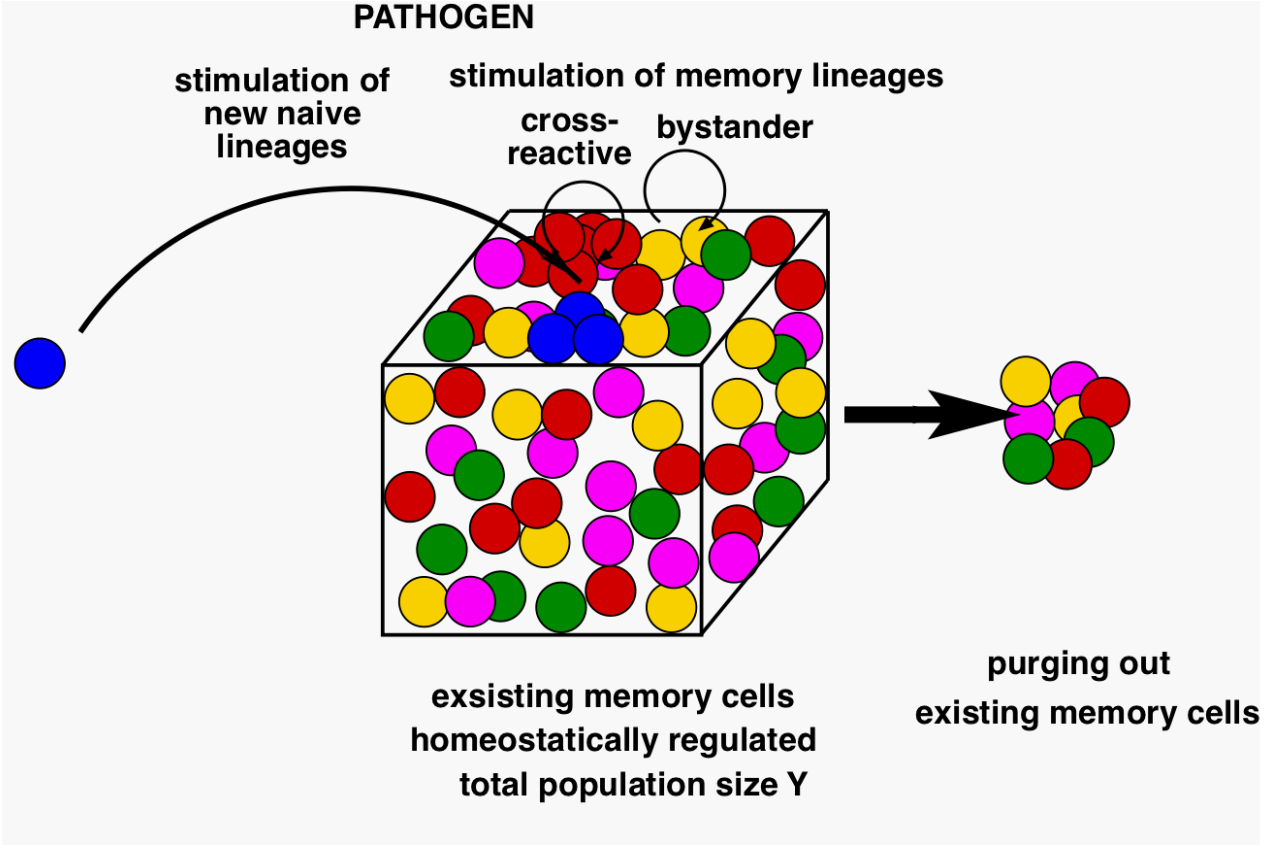


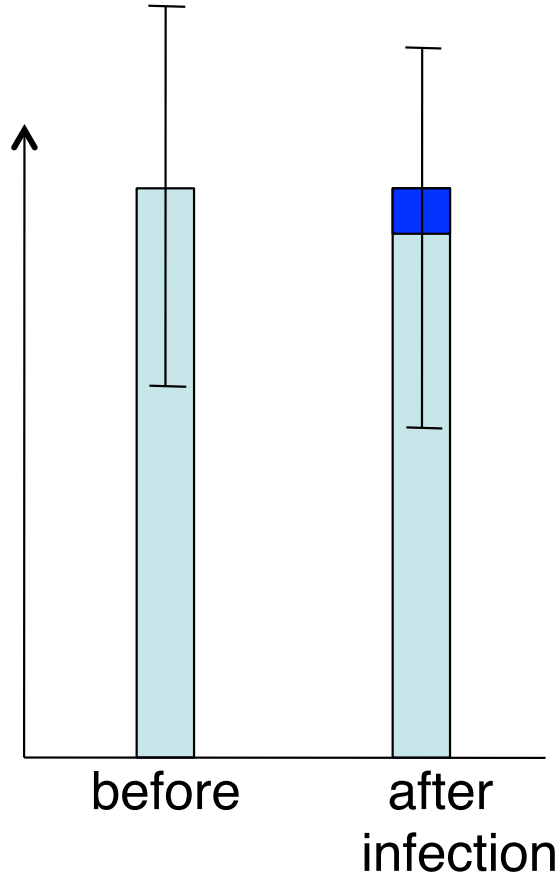
day 6-7 after infection

Prediction – loss of memory following exp. to new pathogens

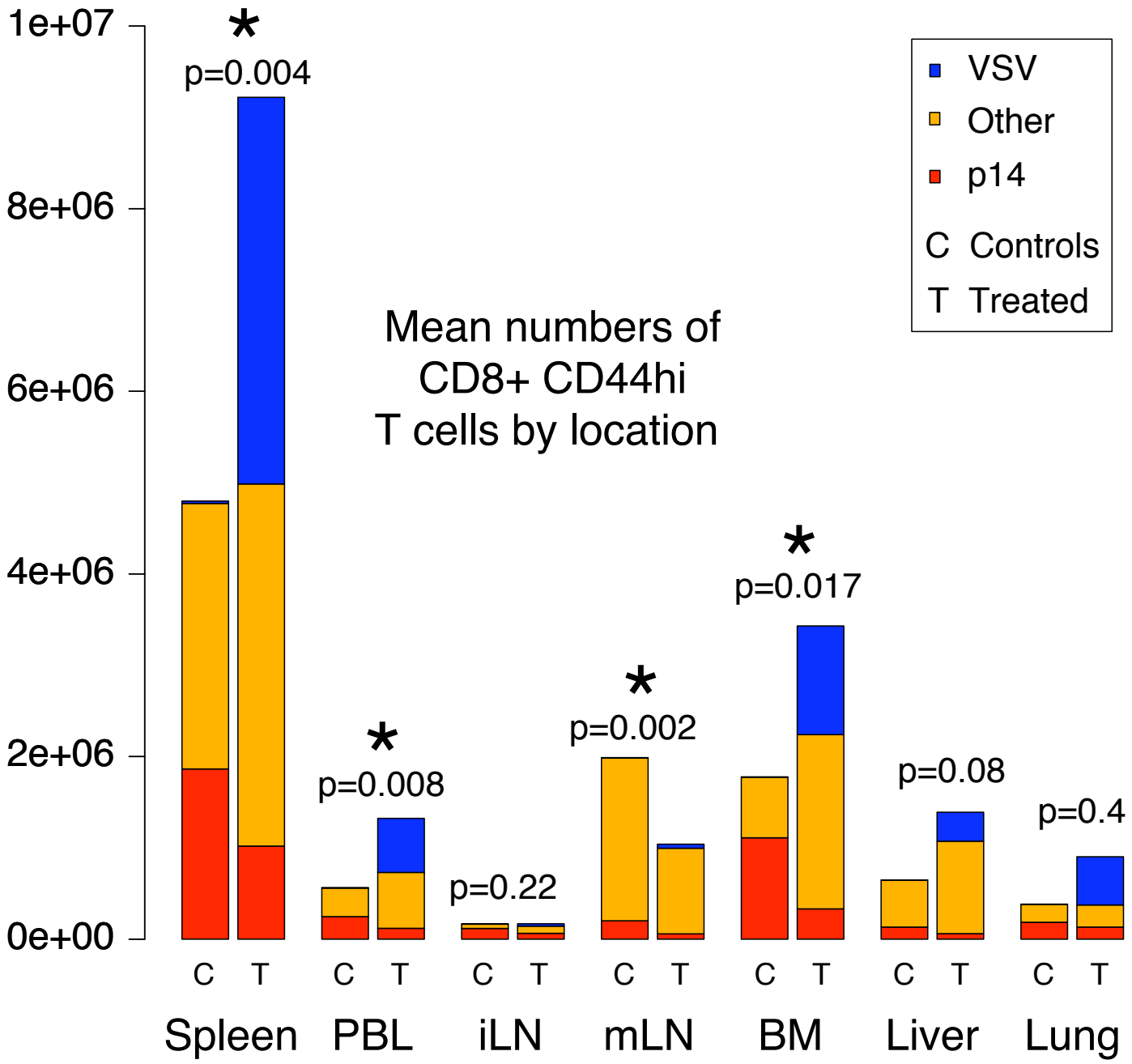
First suggested by Selin and Welsh. Some potential problems

1. Need to measure total cell numbers (not percentages).
2. Inter mouse variation in numbers of cells about 50%.





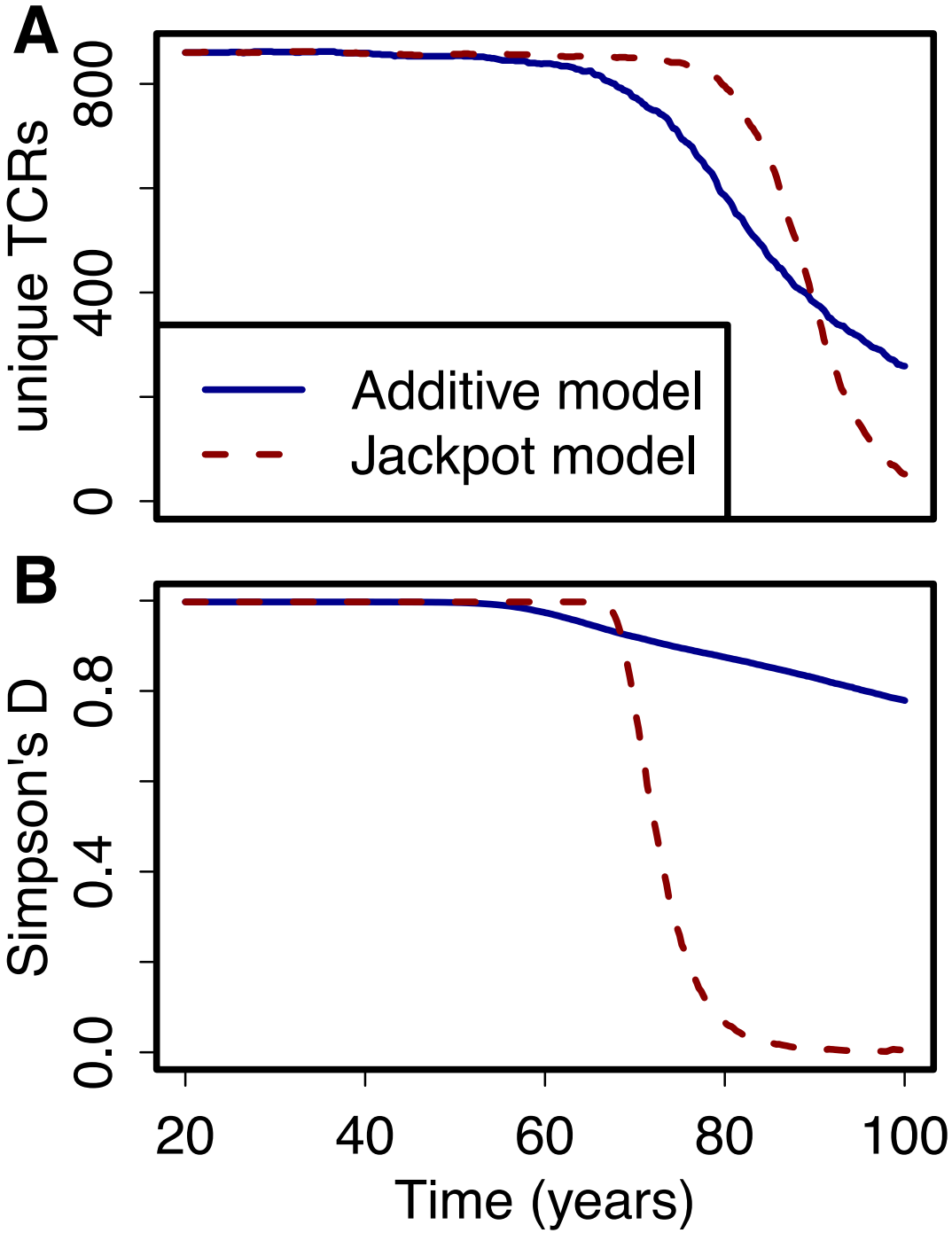
Specificity of memory CD8 cells



Implications and conclusions

While the form of selection has yet to be determined, these alternative “selection” models fit the observed data much better than the conventional model.

Our finding has implications for immunosenescence therapy: **thymic rejuvenation will have little effect under a selection model,** since new TCR lineages from the thymus will be less fit than the mutated lineage(s) in the population.

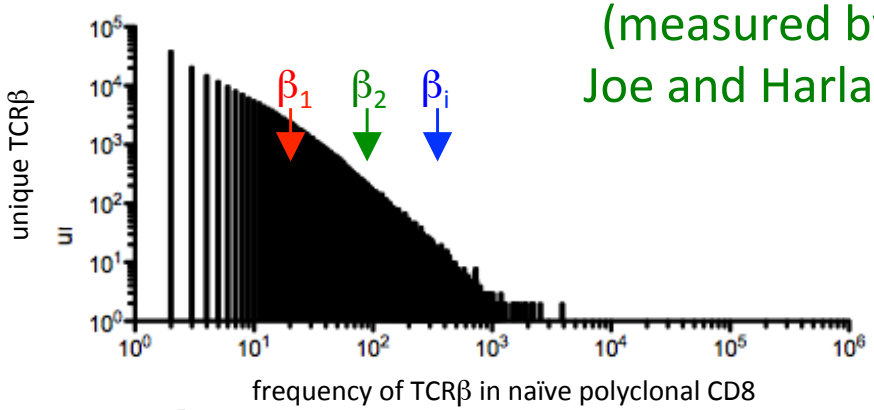


A potential solution

wild-type (H-2^b)

sequence TCRβ

marginal frequency distribution of TCRβ in naïve H-2^b polyclonal



(measured by Joe and Harlan)

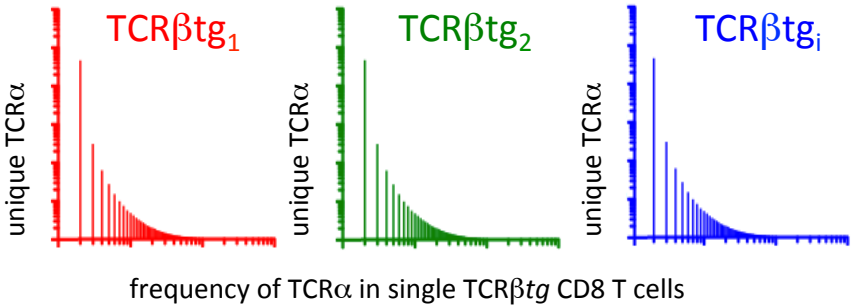
TCRβ*tg* (H-2^b)

(TCRβtg$_1$, TCRβtg$_2$…TCRβtg$_i$)

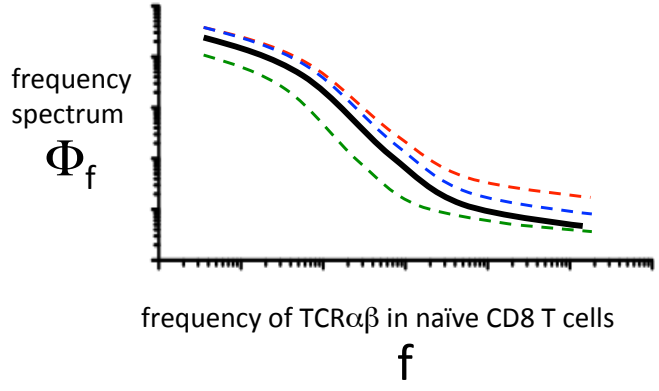
sequence TCRα

conditional frequency distribution of TCRα in each TCRβtg

(proposed)



joint frequency distribution of TCRαβ



also compute:

species richness

Simpson's diversity ($D = 1 - \Sigma\Phi_f^2$)

& other composite measures

Conclusions I:

The naive TCRβ repertoire:

a. **Is highly biased**

b. **Has very similar properties among individual mice**

   genetically identical, including MHC, young, clean environment,…

c. **While randomly made, it has a well defined structure**

Similarity suggests common underlying principles

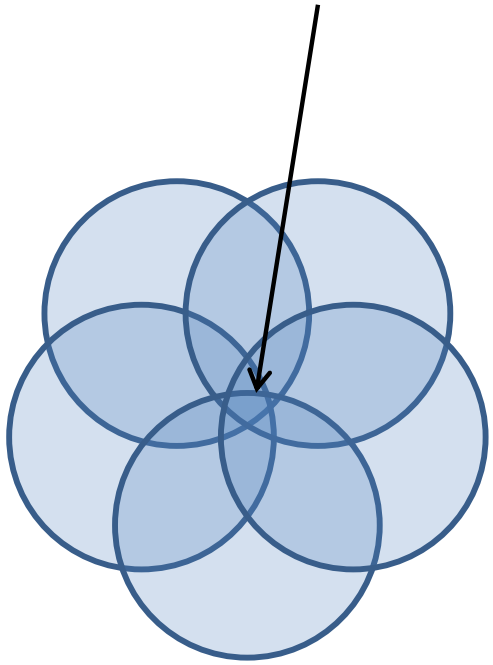
Mechanistic explanations for biases ?

Conclusions II:

- **Bias in primary repertoire allows for seemingly contradicting properties:**

Huge diversity (against unknown pathogens) together with

a **predictable public "core" set of TCRs** (against frequent pathogens? Self?)



Immunological homunculus? (I. Cohen)

Some lessons and questions

In vivo quantification of early kinetics of T cell response is feasible

Comparisons of actual numbers obtained using different models are likely meaningless

How many features can be reliably estimated without over-fitting?

What is model accuracy??