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Dynamics of Memory Stem Cells

Becca Asquith

BACKGROUND

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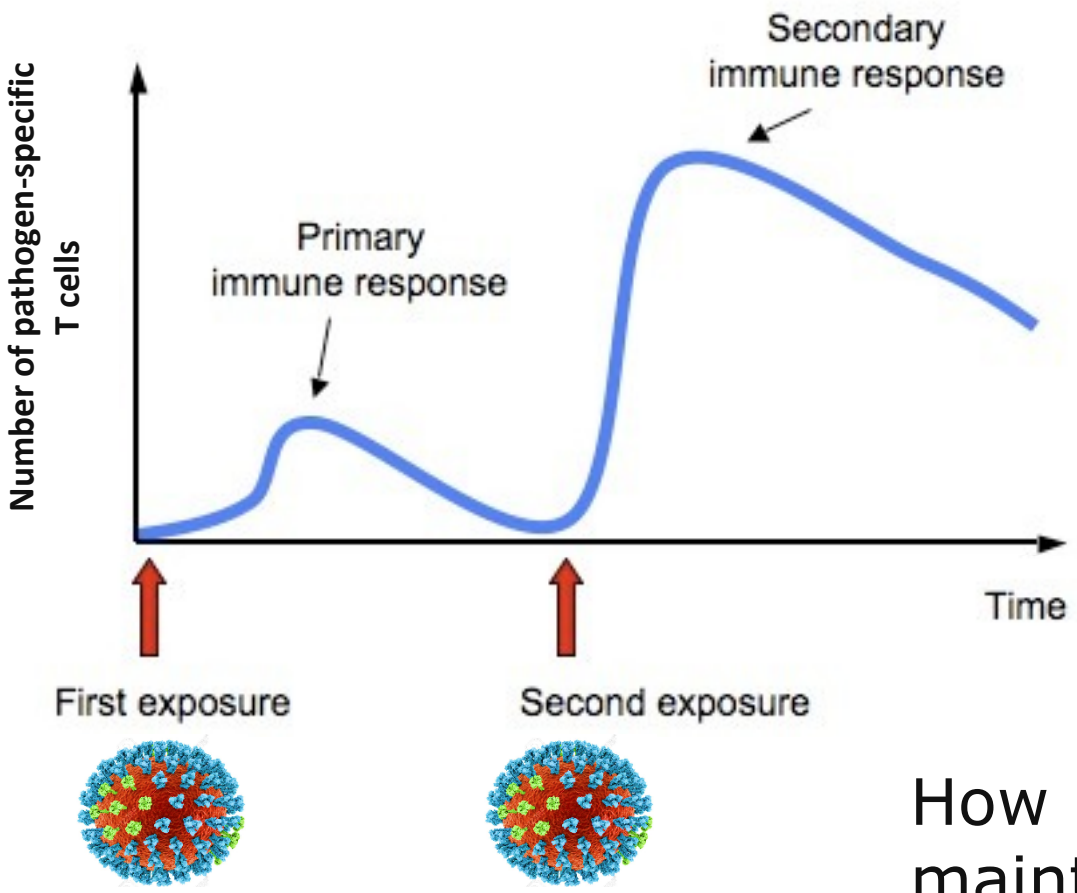
T cell Immune Memory



How is immune memory maintained for decades?

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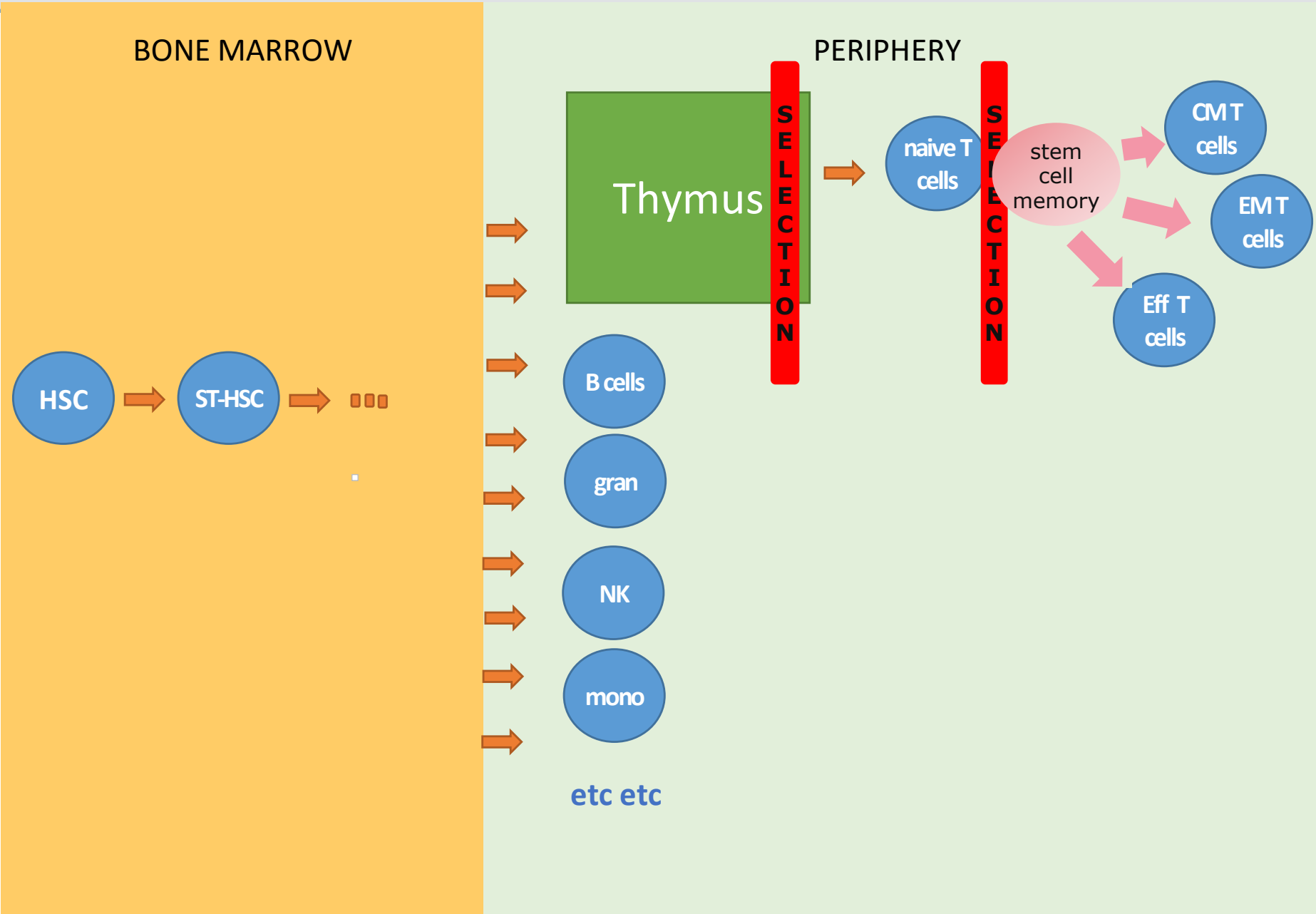
Hypothesis: T memory stem cells



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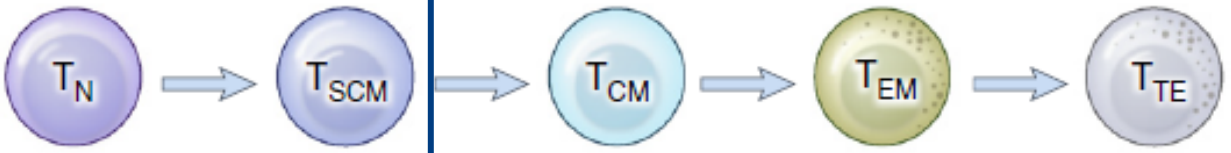
A candidate for memory stem cells: T_{SCM} cells

2-3% of PBMC



	T_N	T_{SCM}	T_{CM}	T_{EM}	T_{TE}
CD45RA	+	+	–	–	+
CD45RO	–	–	+	+	–
CCR7	+	+	+	–	–
CD62L	+	+	+	–	–
CD28	+	+	+	+/–	–
CD27	+	+	+	+/–	–
IL-7Rα	+	+	+	+/–	–
CXCR3	–	+	+	–	–
CD95	–	+	+	+	+
CD11a	–	+	+	+	+
IL-2Rβ	–	+	+	+	+
CD58	–	+	+	+	+
CD57	–	–	–	+/–	+

T_{SCM} cells: requirements for "stemness"

Multipotency
Self-renewal
Clonal longevity

Are T_{SCM} dynamics in healthy humans compatible with their putative role as memory stem cells?

METHODS

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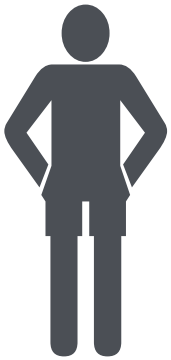
Method 1 : Stable isotope labelling (roughly)

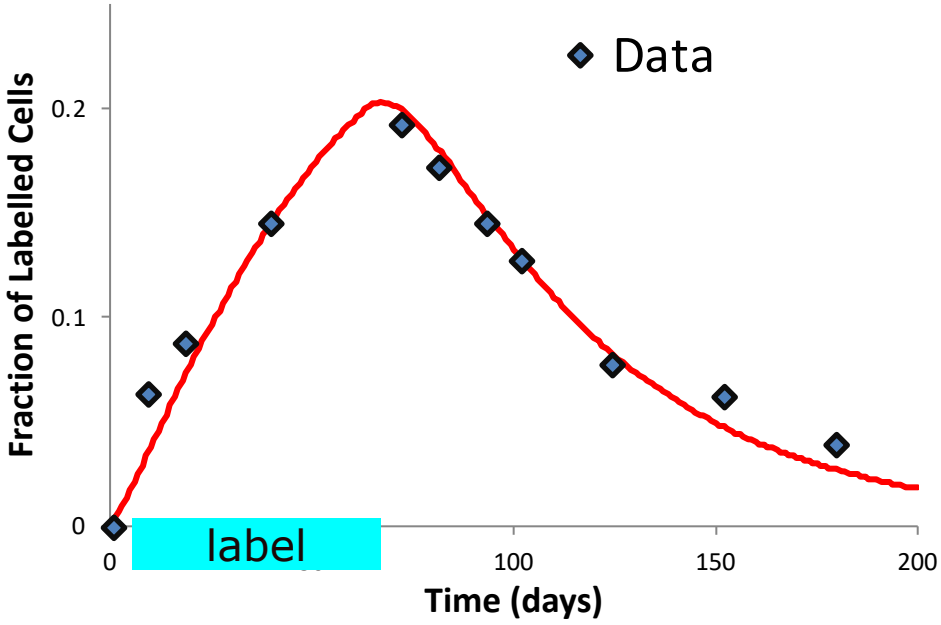
Stable isotope

label

Blood draws



$$\frac{dL}{dt} = pf(t) - d^*L$$



Vrisekoop *et al* PNAS
Asquith *et al* Trends Immunology
Macallan *et al* Nature Prot.
Busch *et al* Nature Prot.

Proliferation rate and death+differentiation rate

5 healthy subjects.
7 weeks heavy water labelling.

$CD4^+$ Naive T cells
$CD4^+$ T_{SCM} cells

$CD8^+$ Naive T cells
$CD8^+$ T_{SCM} cells

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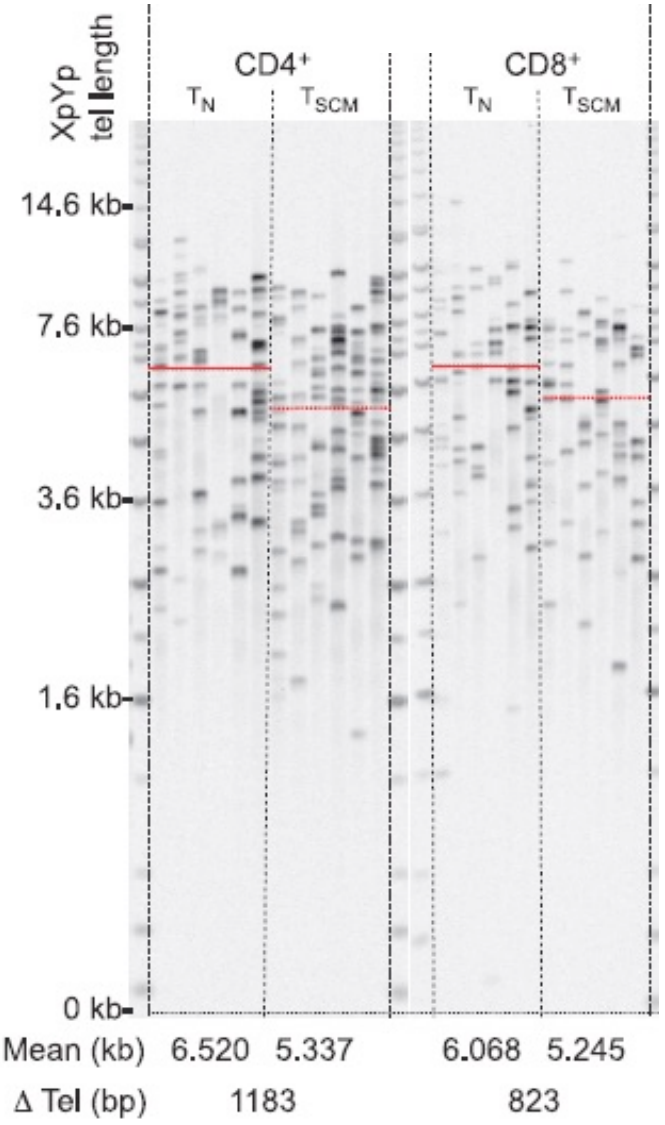
Method 2: telomere length analysis

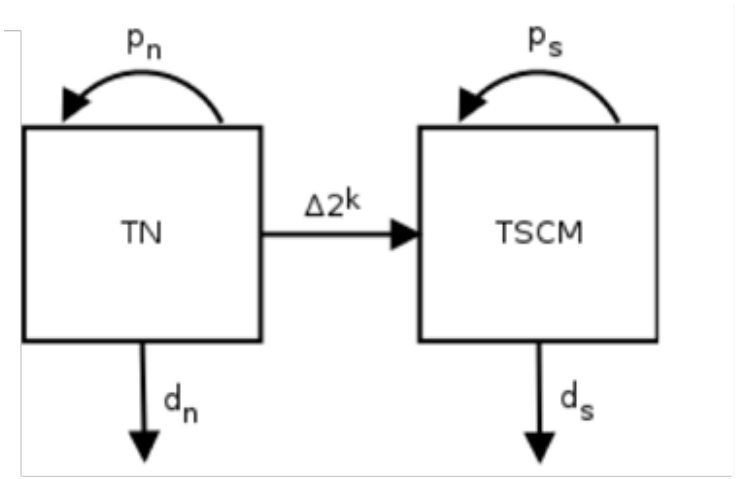
telomere length ~ divis

single cell PCR-based assay



Method 3: mechanistic models

Basic model



$$\dot{T}_N = (p_n - d_n - \Delta)T_N$$
$$\dot{T}_{SCM} = \Delta 2^k T_N + (p_s - d_s)T_{SCM}$$

$$\dot{F}_{TN} = p_n cU(t) - \left(d_n^* + \Delta\right)F_{TN}$$
$$\dot{F}_{TSCM} = \left(2^k - 1\right)cU(t)\frac{\Delta T_N}{T_{SCM}} + \frac{\Delta T_N}{T_{SCM}}F_{TN} + p_s cU(t) - d_s^* F_{TSCM}$$

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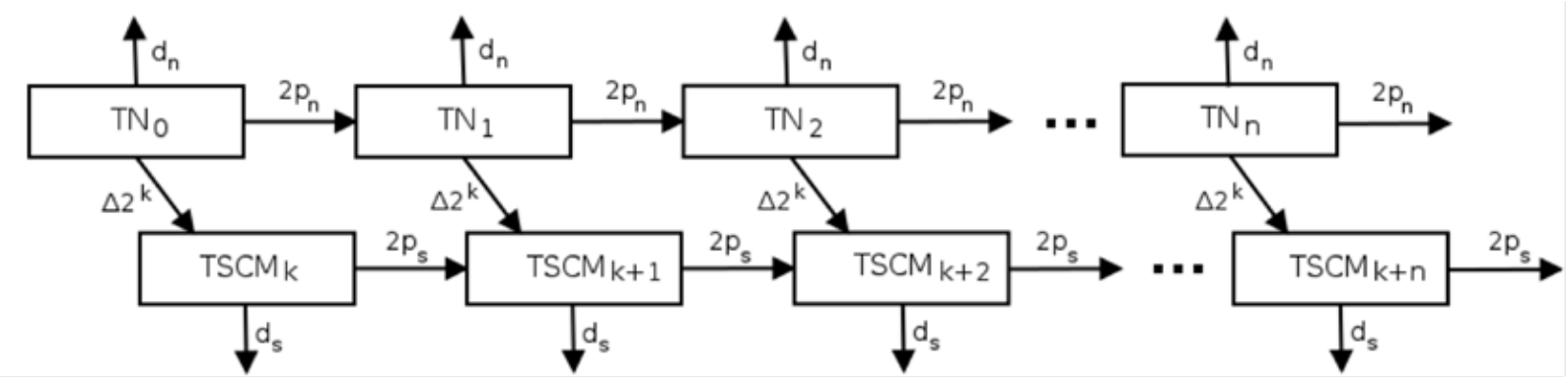
Basic model for telomeres



de Boer & Neese. JI 1998

RESULTS

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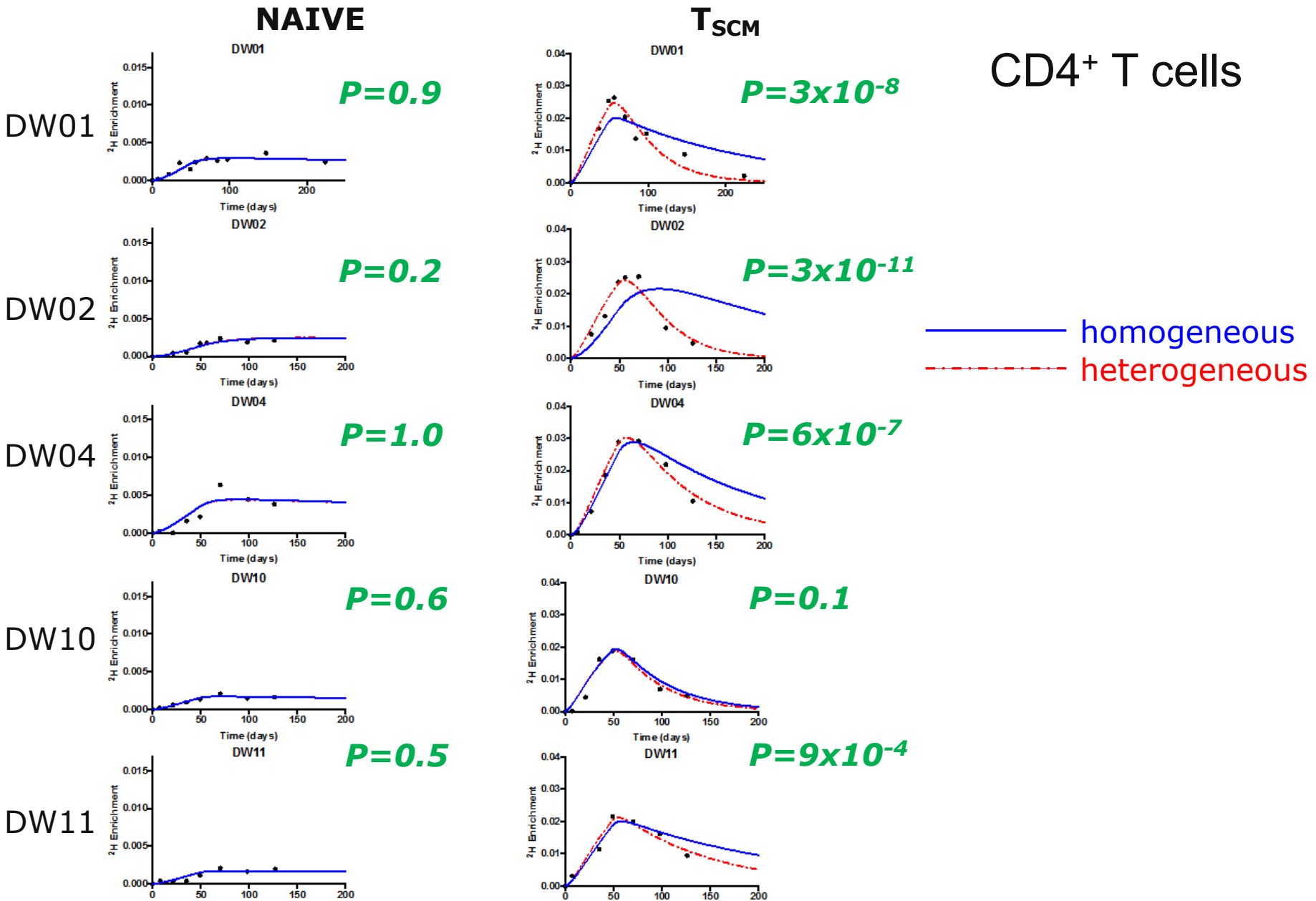
Kinetic structure of T_{SCM} pool?



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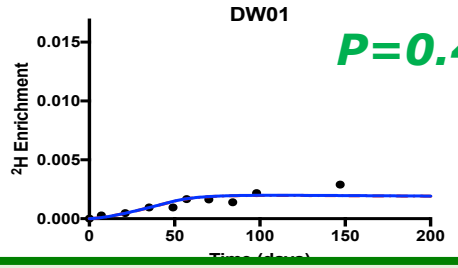
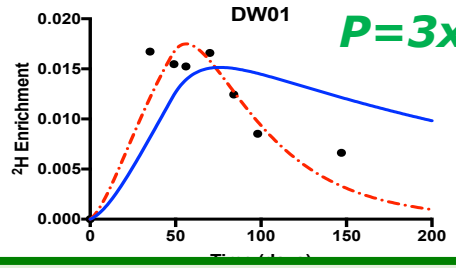
Kinetic structure of T_{SCM} pool?

NAIVE **T_{SCM}**

CD8⁺ T cells

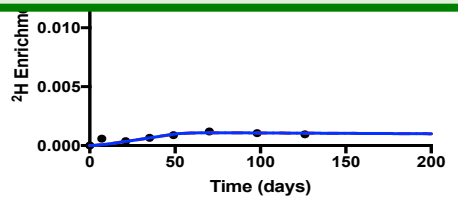
DW01

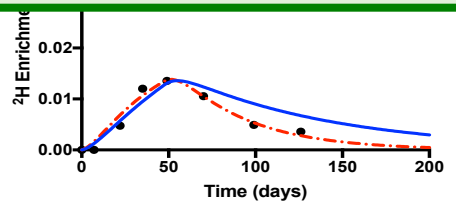




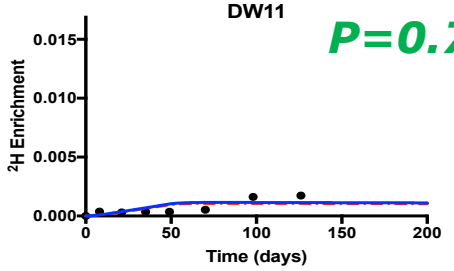
Evidence that CD4⁺ and CD8⁺ T_{SCM} populations consist of two or more subpopulations with different kinetics

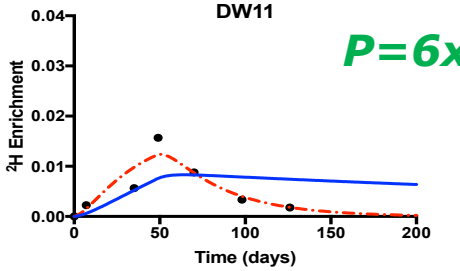
DW10



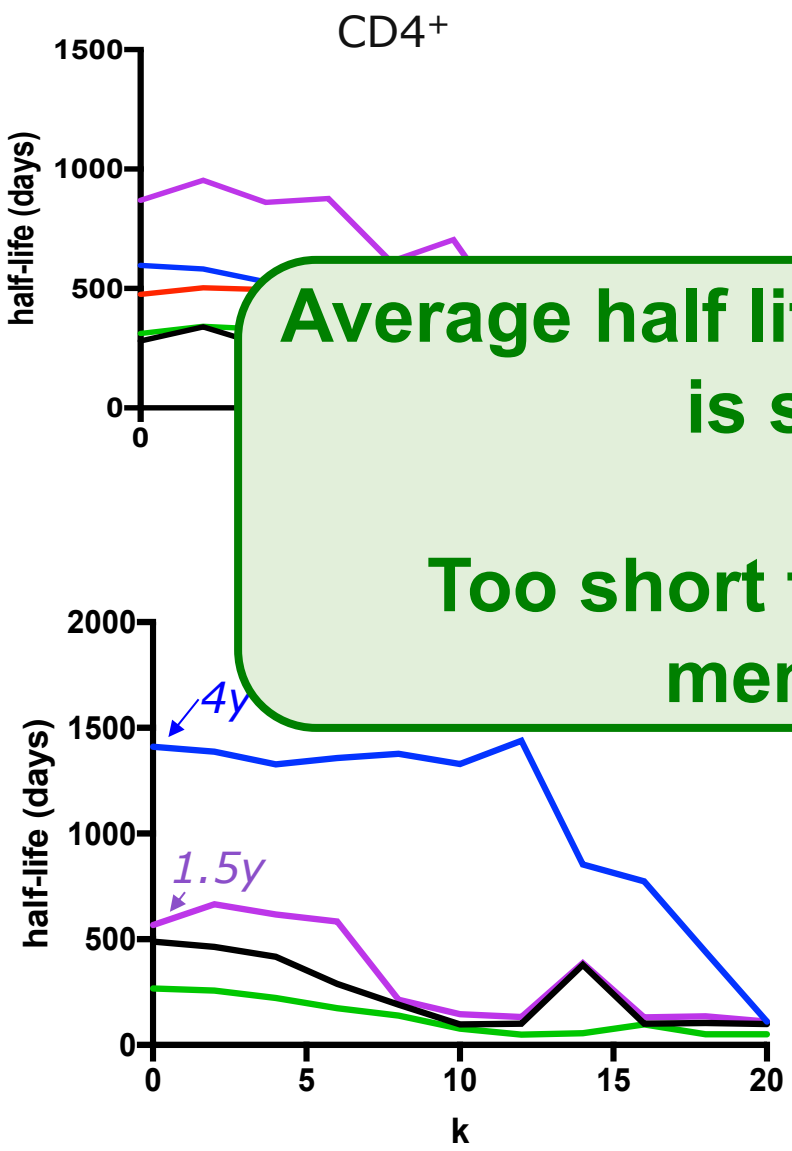


DW11





Half-life of a T_{SCM} clone



Average half life of T_{SCM} populations is short (1-2y).

Too short for maintenance of memory (8-15y)

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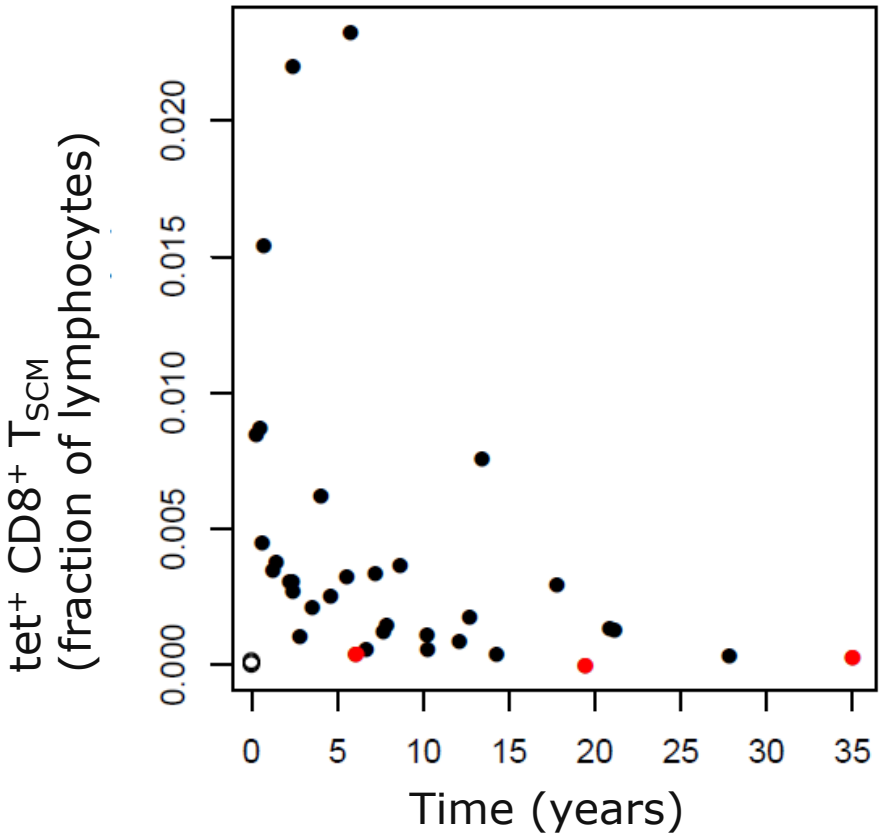
extra data set: YFV



Silvia A. Fuertes Marraco,[1,2] Charlotte Soneson,[3] Laurène Cagnon,[2] Philippe O. Gannon,[2] Mathilde Allard,[2] Samia Abed Maillard,[2] Nicole Montandon,[2] Nathalie Rufer,[2] Sophie Waldvogel,[4] Mauro Delorenzi,[1,2,3] Daniel E. Speiser[1,2]*

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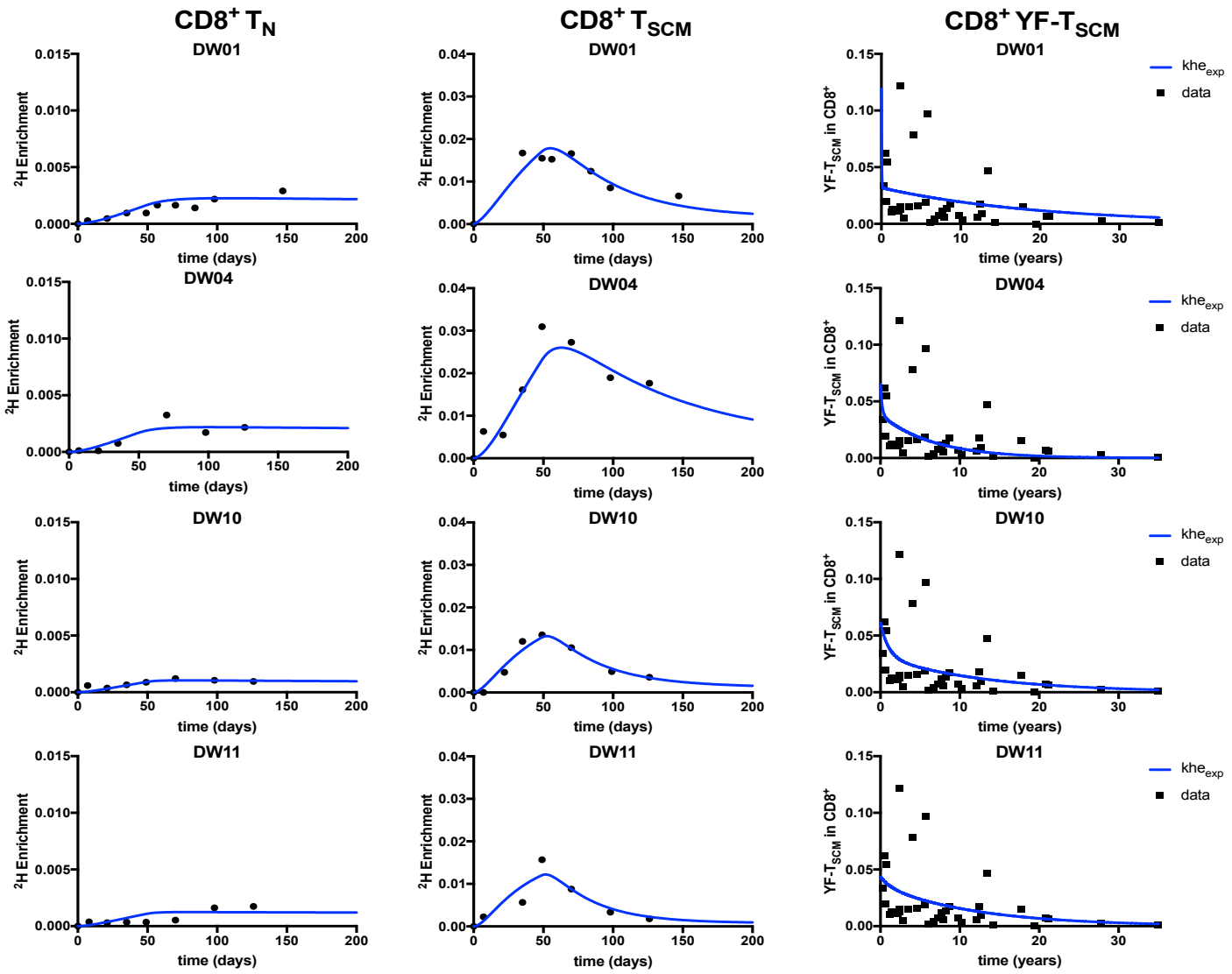
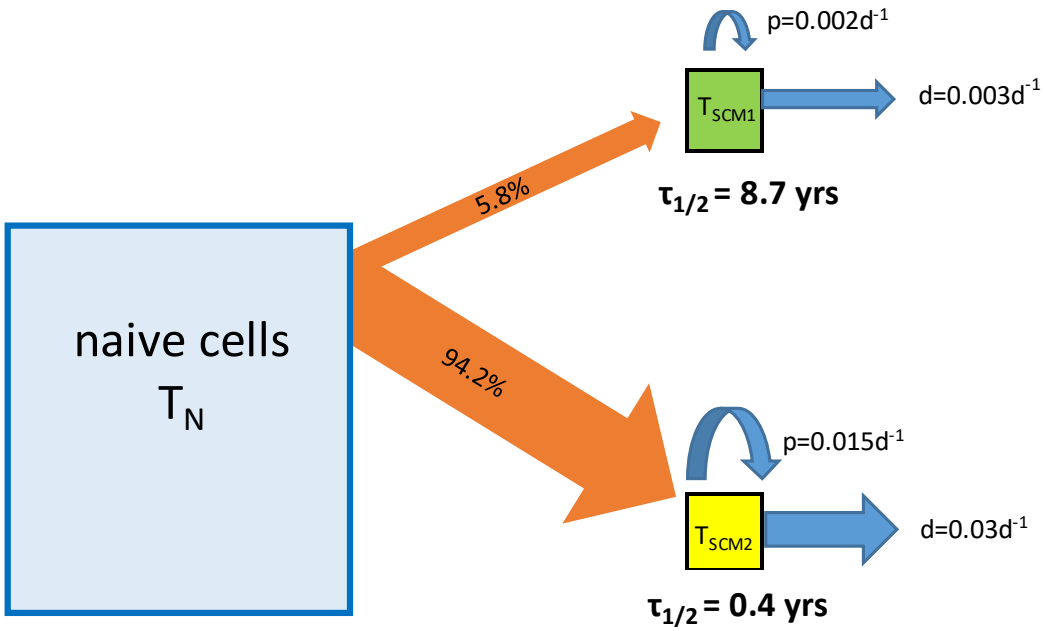

CD8+ TN
CD8+ TSCM
CD8+ YF-TSCM
DW01
DW04
DW10
DW11
2H Enrichment
YF-TSCM in CD8+
time (days)
time (years)
khe_exp
data

	half-life T_{SCM1} [years]	half-life T_{SCM2} [years]
DW01	13.92 (2.26-20.68)	0.02 (0.02-6.74)
DW04	4.59 (2.13-20.41)	0.14 (0.01-2.79)
DW10	9.09 (2.33-16.50)	0.69 (0.05-0.77)
DW11	8.39 (3.75-17.01)	0.9 (0.03-3.98)
MEDIAN	**8.74 (2.30-18.71)**	**0.41 (0.02-3.39)**



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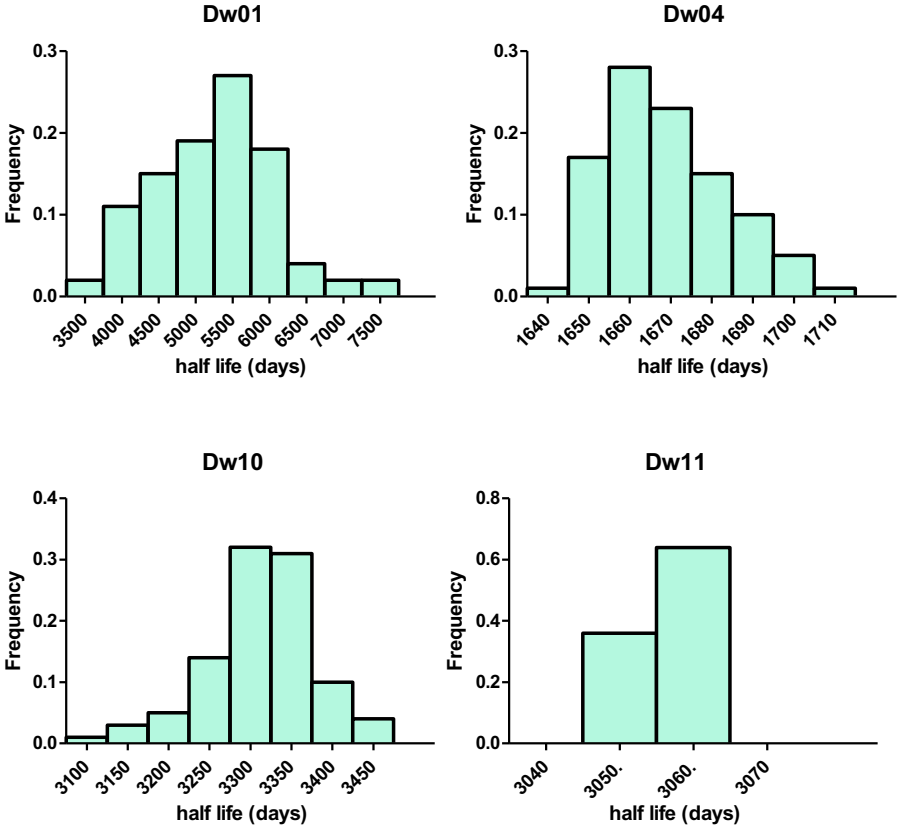
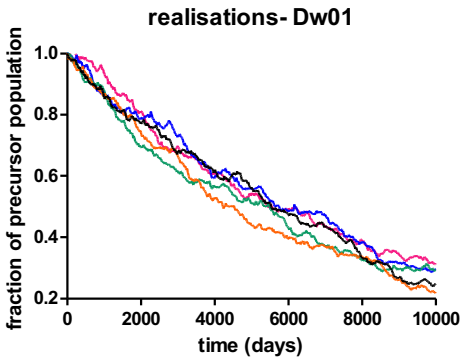
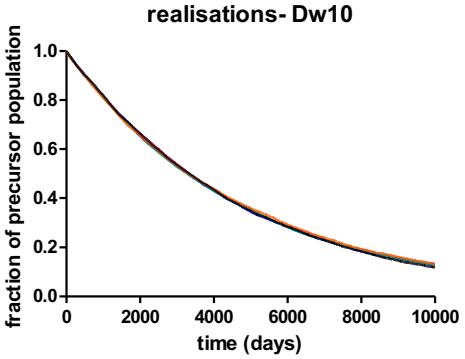
too stochastic?







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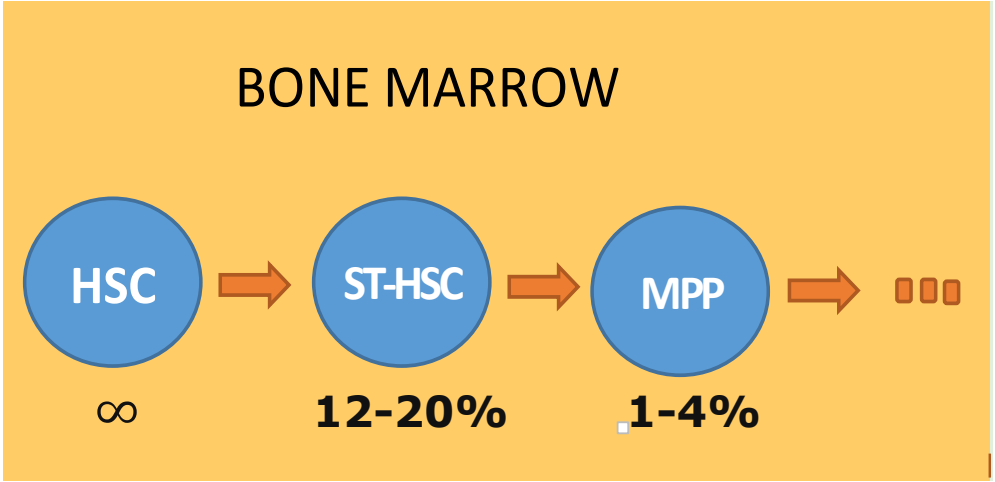
degree of self-renewal

how long a cell lives without dying or differentiating

$$\text{degree of self renewal} = \frac{1}{input\ rate} = \frac{1}{d - p}$$

id	Self-renewal [d]
DW01	7300 (1800,12500)
DW04	2400 (1200,5300)
DW10	4800 (1400,8400)
DW11	4400 (1700,9500)
MEDIAN	**4600 (1500,8900)**

15% of our lifespan



Busch et al Nature 2015 (mice)

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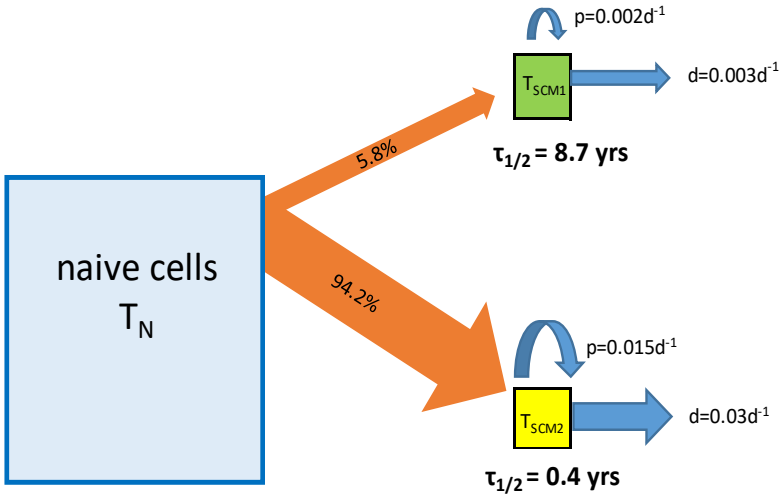
SUMMARY SO FAR



- heterogeneous
- Slow subpop:
  - $\tau_{1/2} \approx 9$ years
  - nearly self-renewing (>1000d)

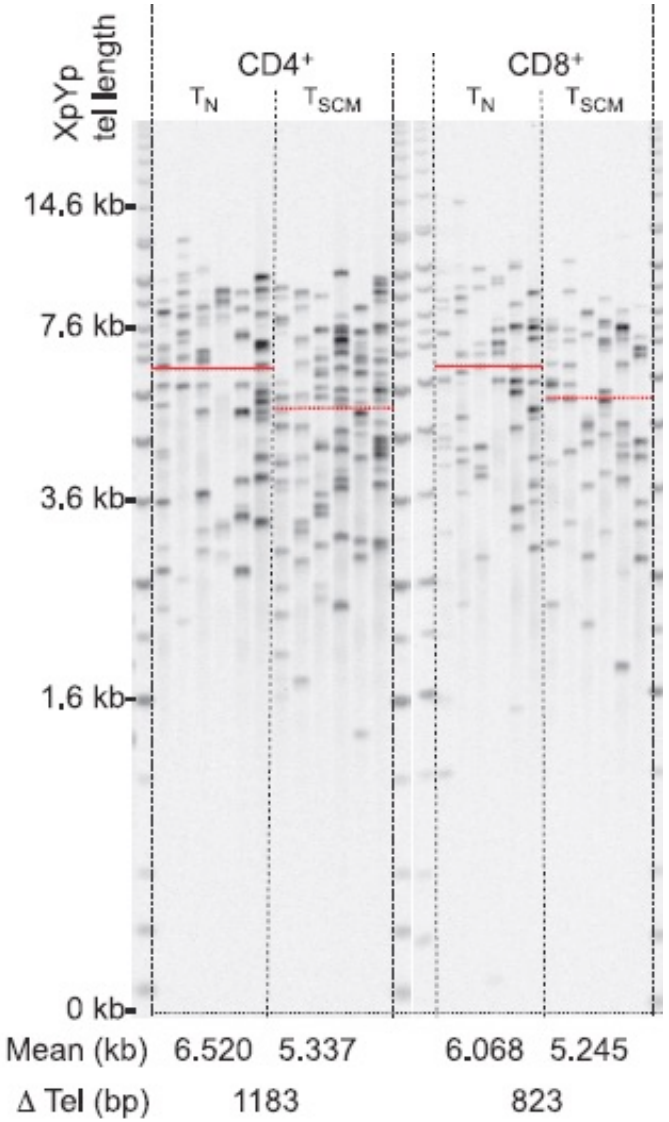
T_{SCM} dynamics in healthy humans are compatible with their putative role as stem cell memory cells

next steps

better use of the telomere data

phenotype of the “true” stem cell popula

where do T_{SCM} cells come from?



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Acknowledgements

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Laureline Rodger

Duncan Baird

University of Lausanne

Silvia A. Fuertes Marraco

BEATING BLOOD CANCER

Bloodwise

SEVENTH FRAMEWORK PROGRAMME

RESEARCH COUNCILS UK

wellcome trust

Investigator

MRC Medical Research Council

CNPq

Conselho Nacional de Desenvolvimento Científico e Tecnológico

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Recruiting postgrad / postdoc

We are looking for a theoretician (background maths/ physics/ bioinformatics or similar) to join our group

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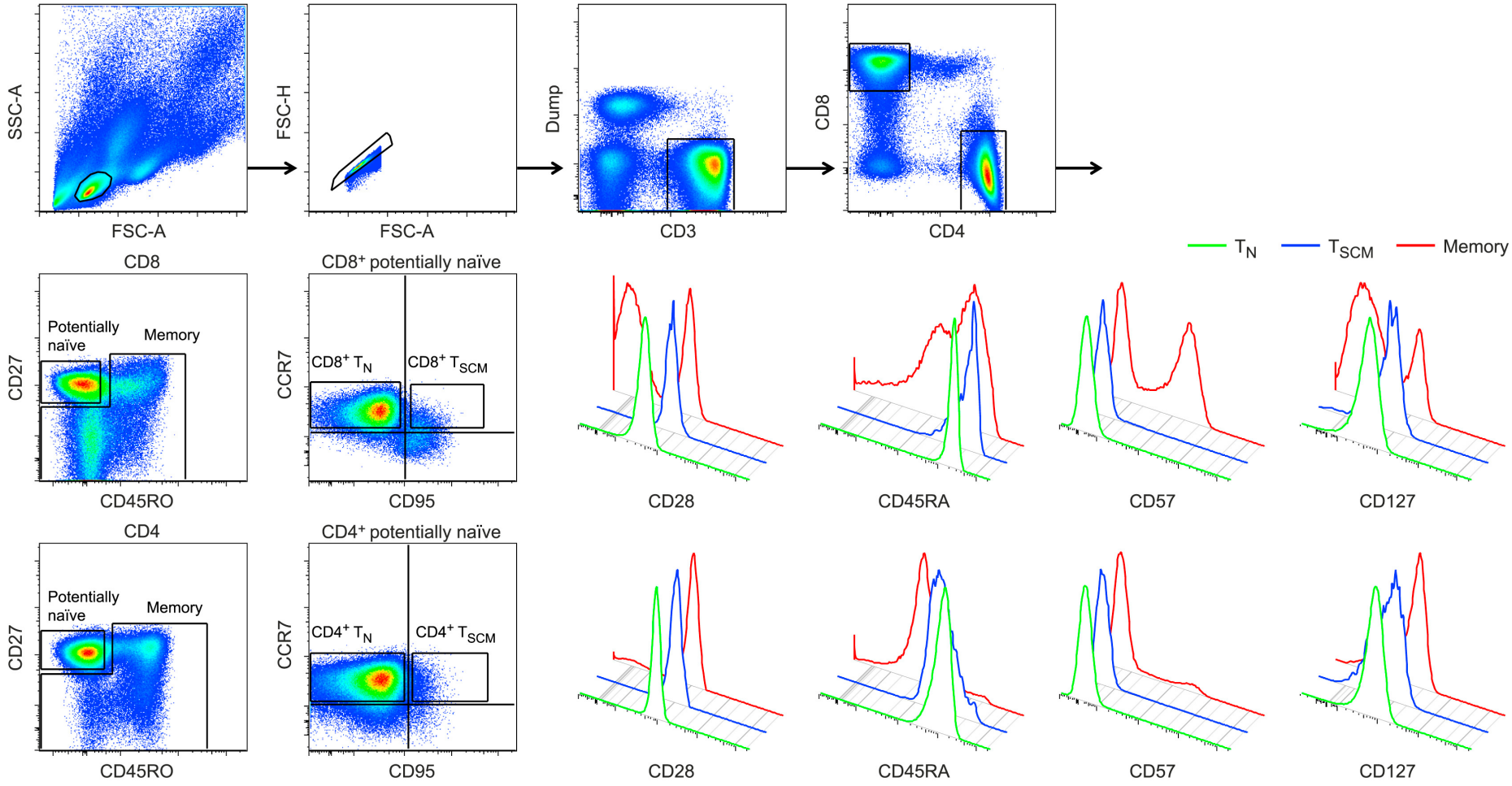
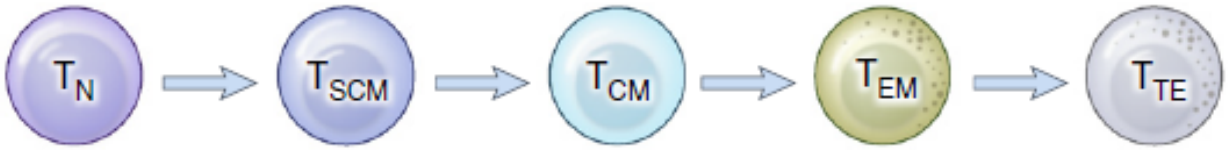
MED01450

b.asquith@ic.ac.uk

Gated on CD45RO- CD27bright CCR7+ CD95+



Pheno: CD28+ CD45RA+ CD57- CD127+



CD45RA	+	+	–	–	+
CD45RO	–	–	+	+	–
CCR7	+	+	+	–	–
CD62L	+	+	+	–	–
CD28	+	+	+	+/–	–
CD27	+	+	+	+/–	–
IL-7Rα	+	+	+	+/–	–
CXCR3	–	+	+	–	–
CD95	–	+	+	+	+
CD11a	–	+	+	+	+
IL-2Rβ	–	+	+	+	+
CD58	–	+	+	+	+
CD57	–	–	–	+/–	+

	Proliferation rate (d-1)
Slow TSCM	0.002
Fast TSCM	0.015
Naïve (this study)	0.0005
Naïve (9w water)	0.0004
Memory (24h glu)	0.02
Memory (9w water)	0.006

Naïve < slow TSCM < fast TSCM < memory

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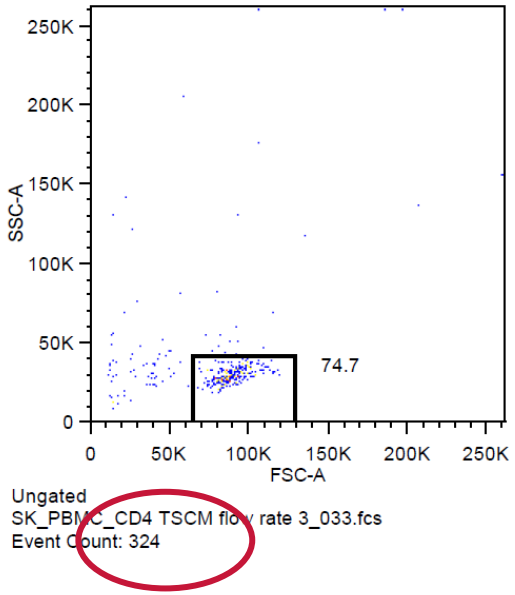
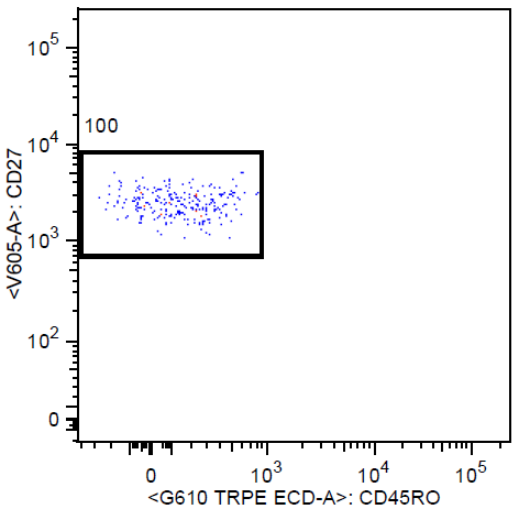
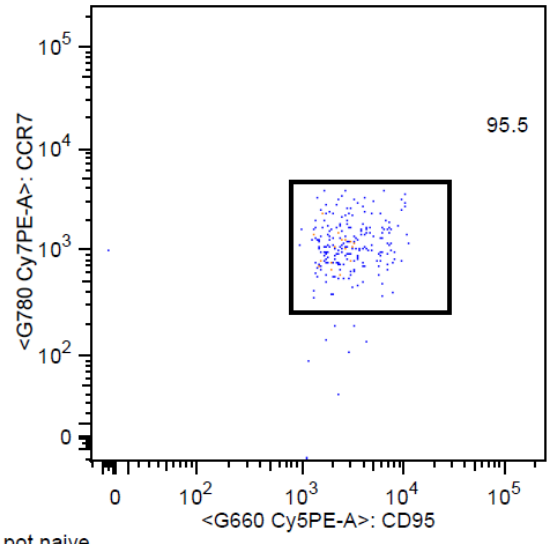
Purity checks CD4+ TSCMs

TSCM purity_130617KL.jo







NB v low event #

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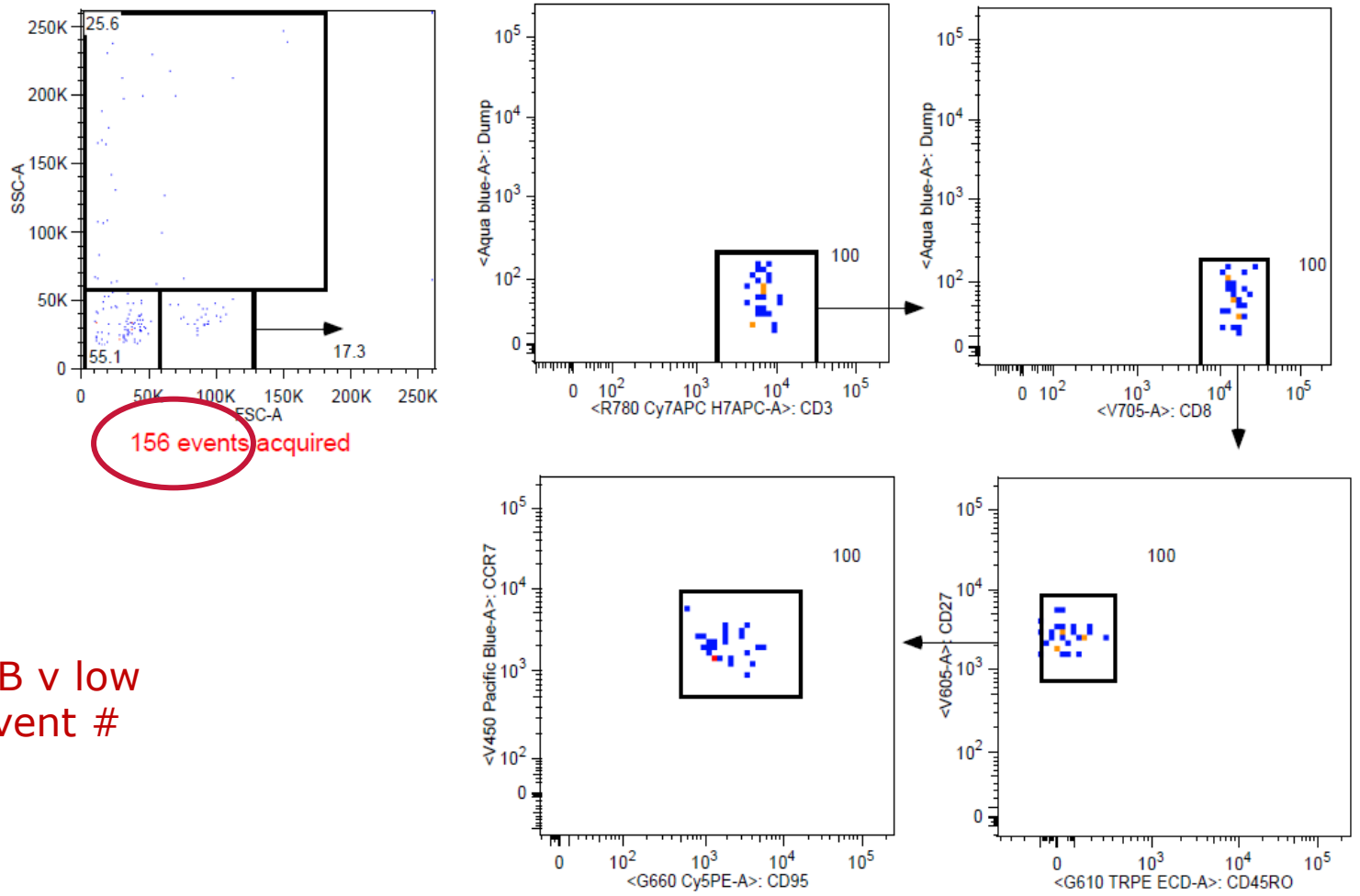
Purity check CD8+ TSCM



NB v low event #