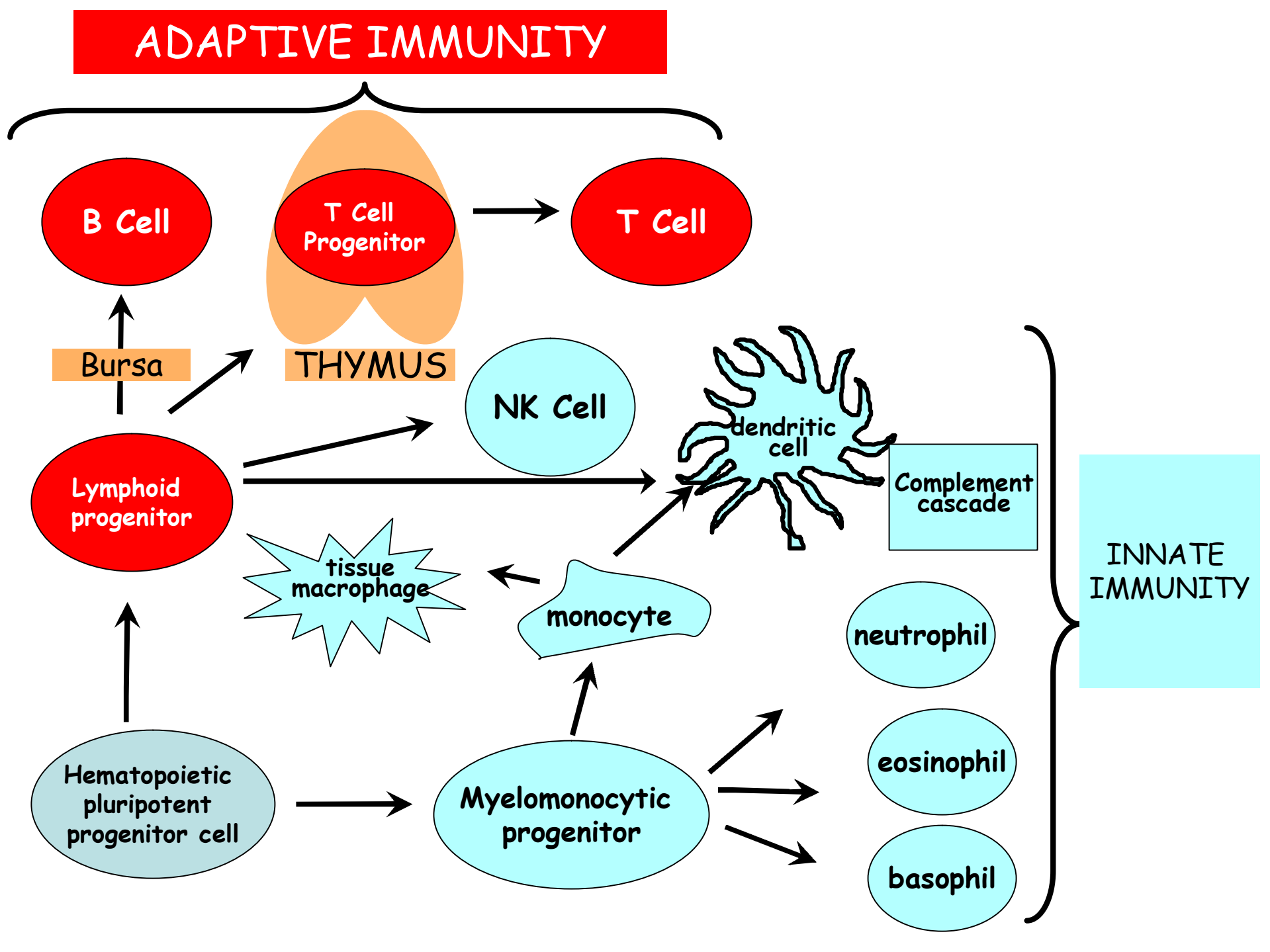
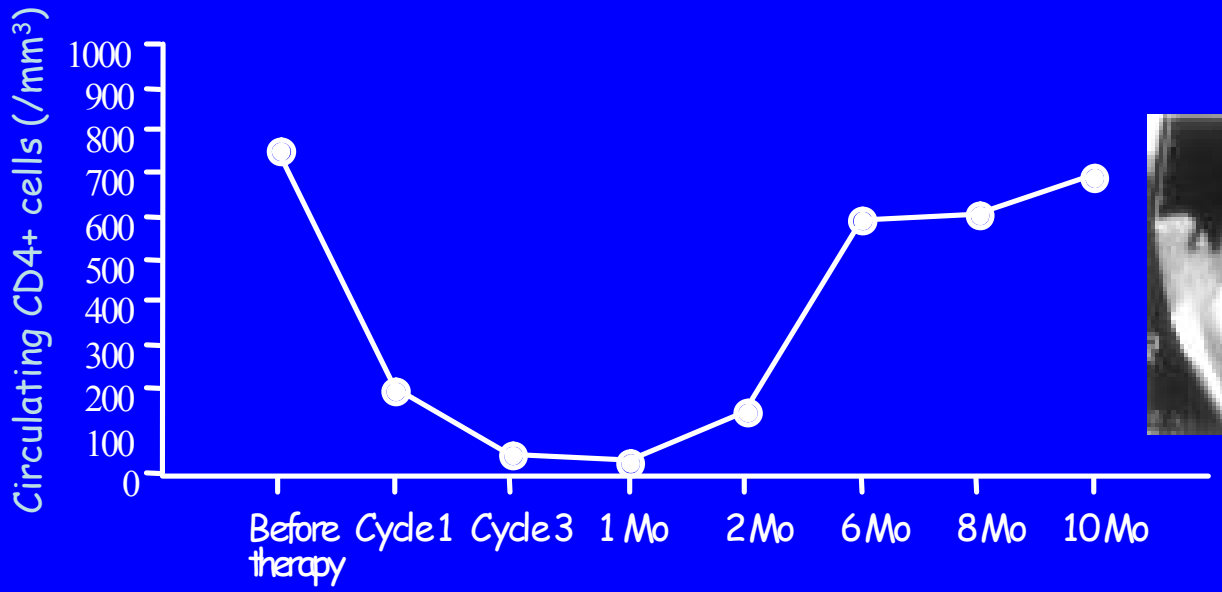
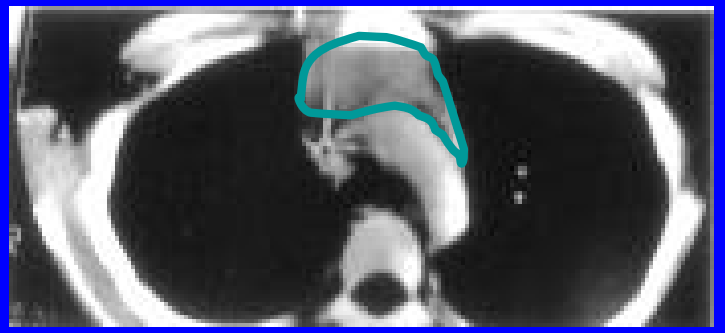
The Immune Response to Lymphopenia

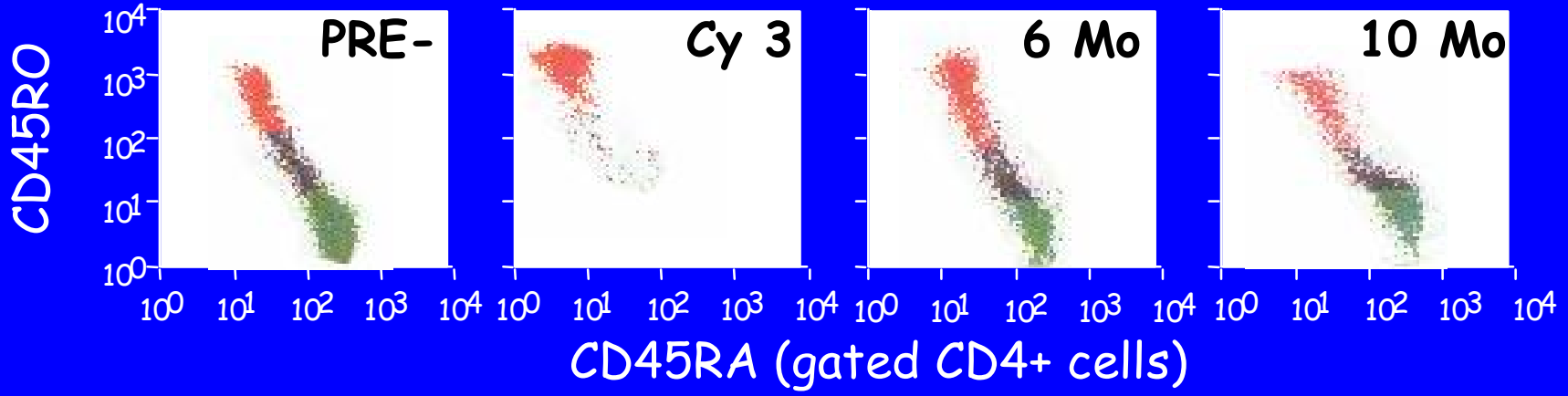
Recombinant DNA Advisory Committee
Crystal L Mackall MD
December 16, 2004


ADAPTIVE IMMUNITY
B Cell
T Cell Progenitor
T Cell
Bursa
THYMUS
NK Cell
dendritic cell
Complement cascade
Lymphoid progenitor
tissue macrophage
monocyte
neutrophil
eosinophil
basophil
Hematopoietic pluripotent progenitor cell
Myelomonocytic progenitor
INNATE IMMUNITY

Restoration of CD4+ T Cells via Thymopoiesis (Age 3)

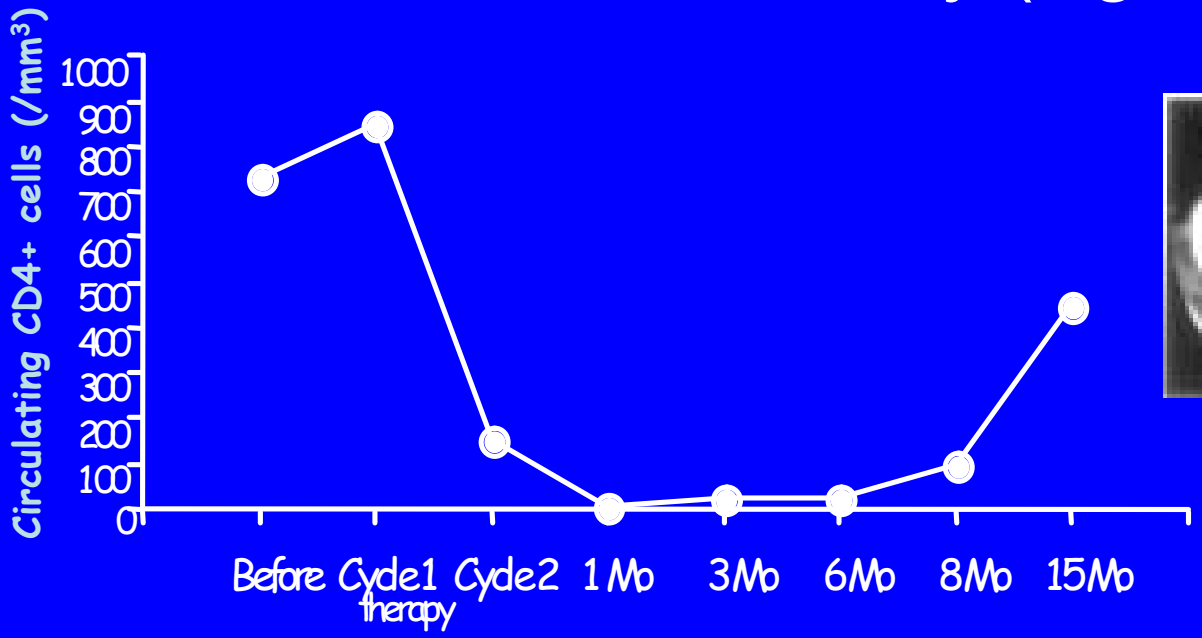


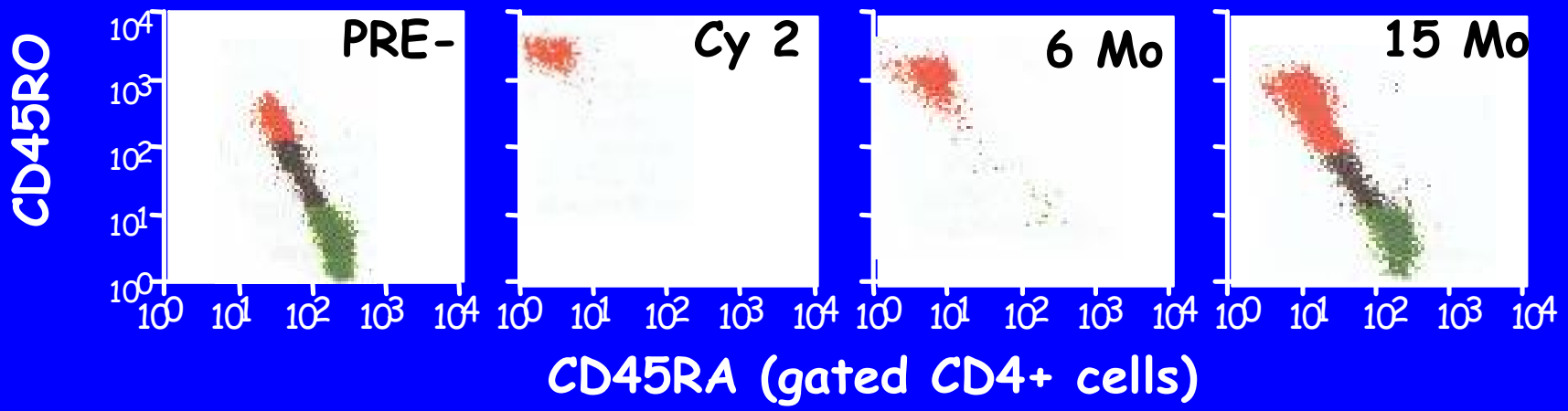




NEJM, 1995

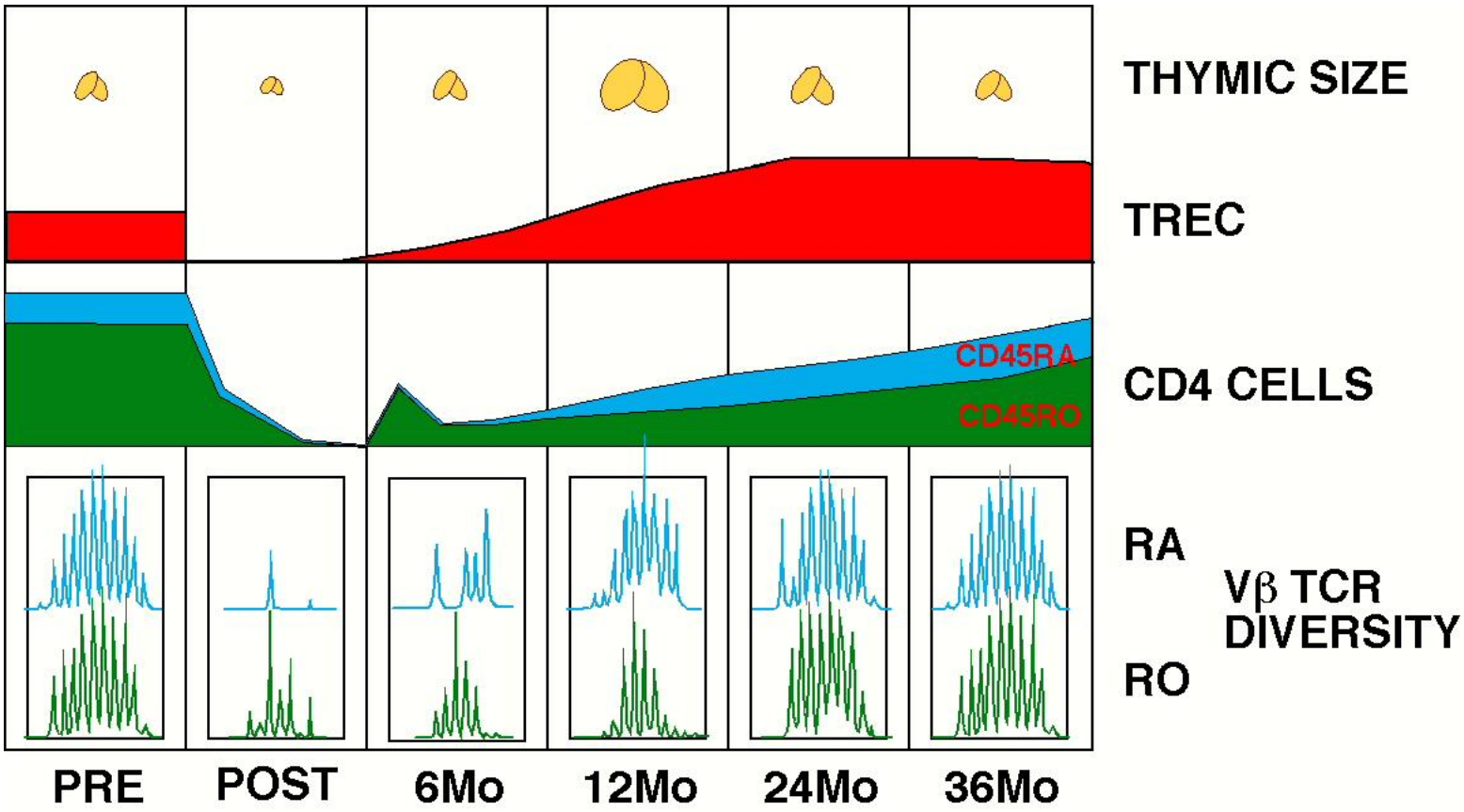
Prolonged CD4+ Depletion with Thymic Insufficiency (Age 21)





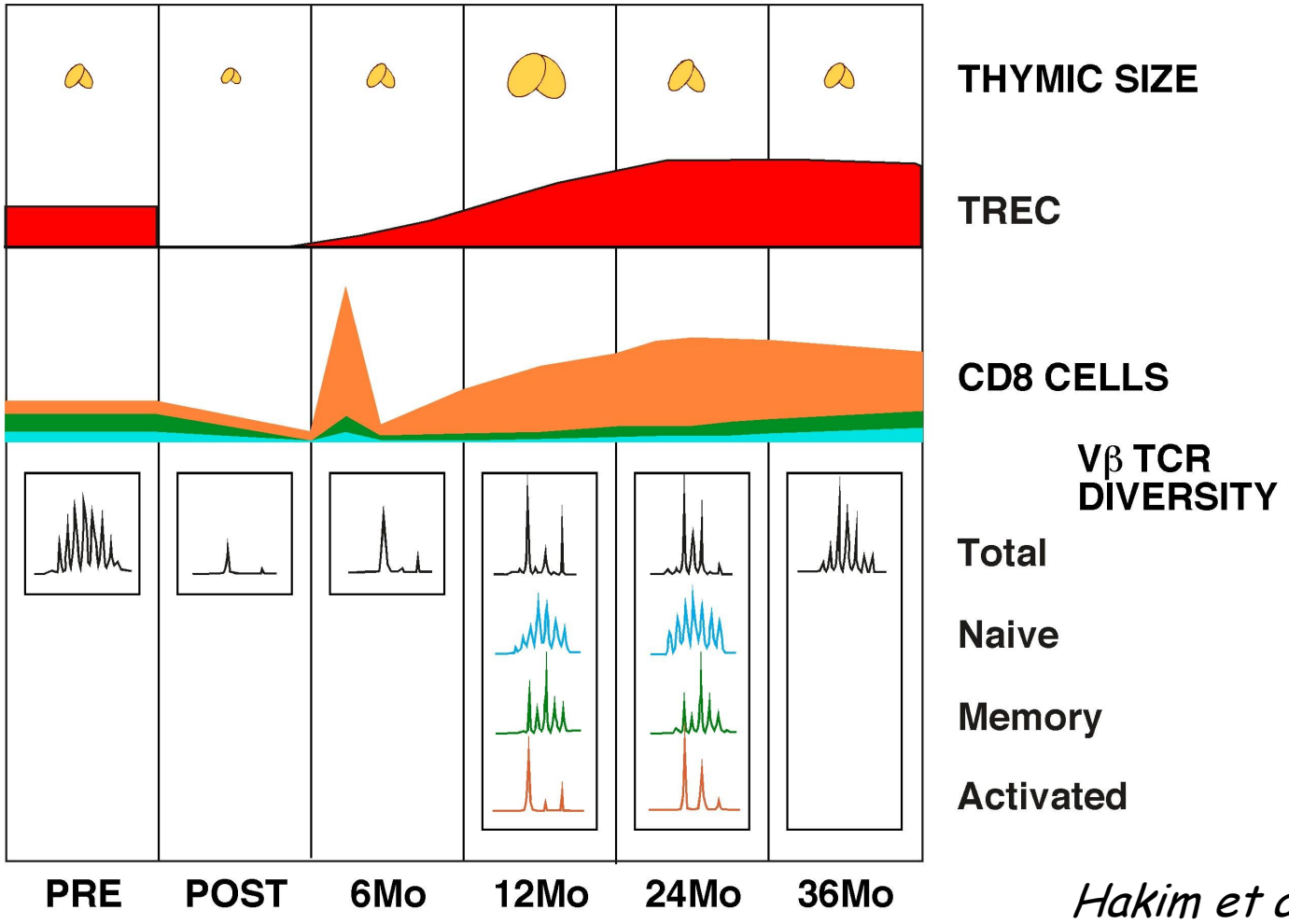
NEJM, 1995

CD4+ Immune Reconstitution in Hosts with "Thymic Insufficiency"

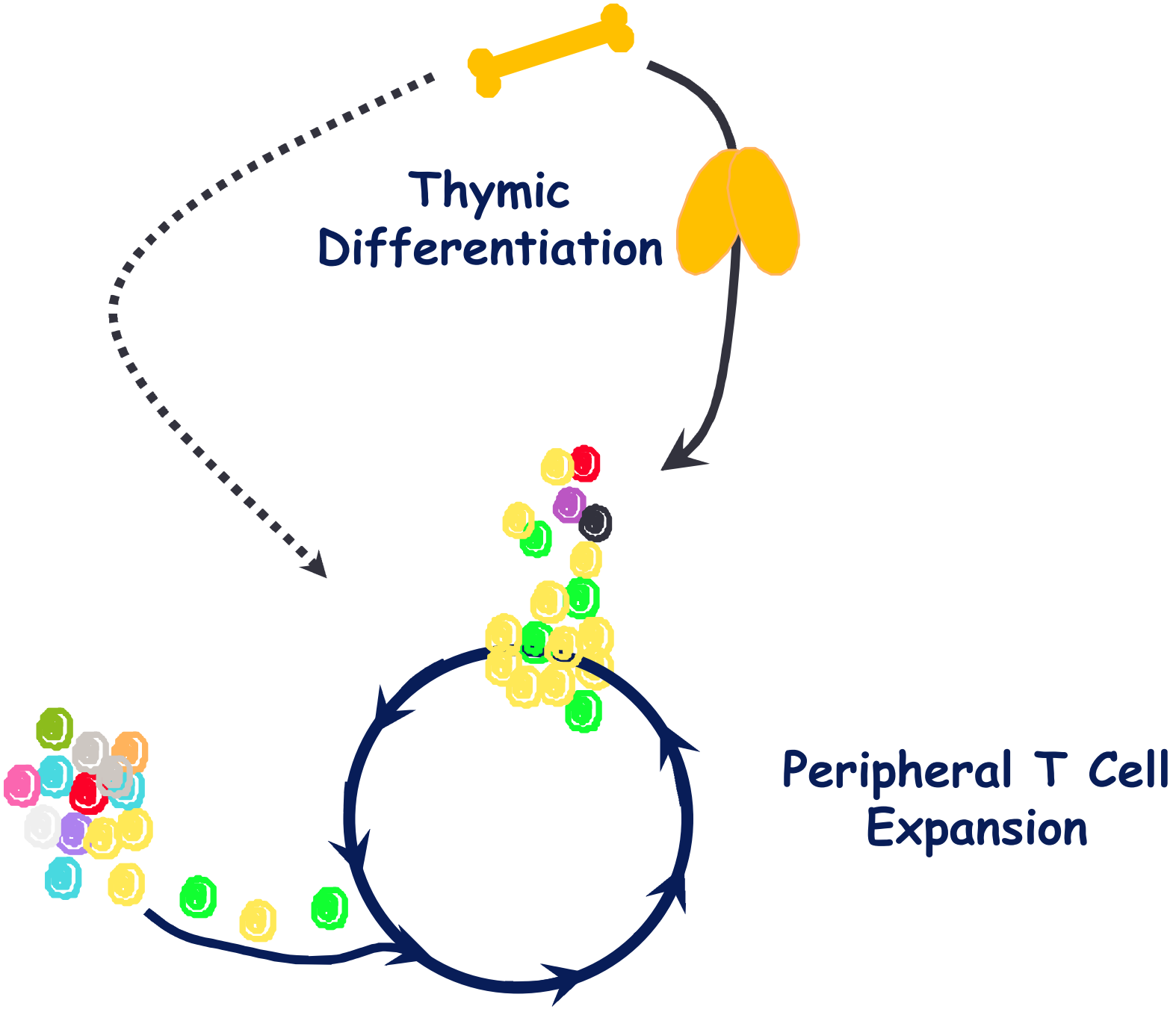


Hakim et al., submitted

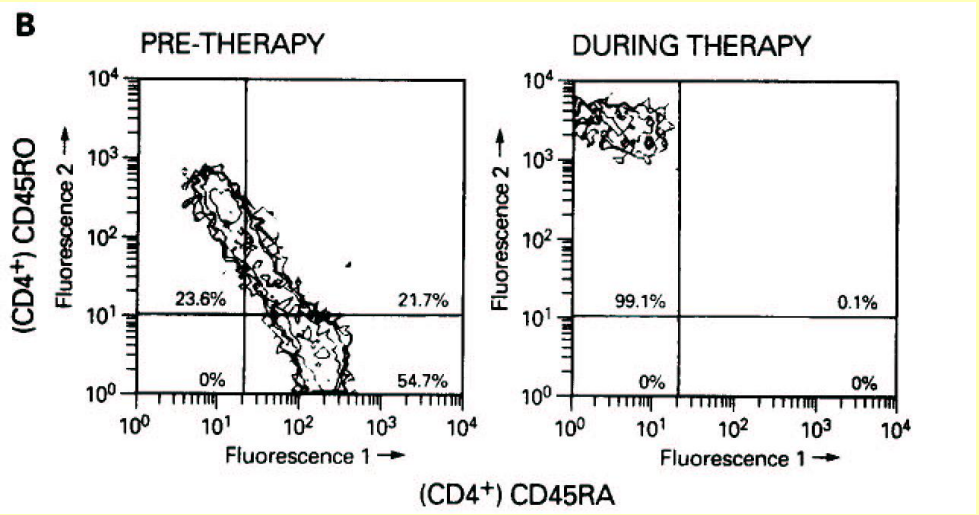
CD8+ Immune Reconstitution in Adults after Autologous BMT

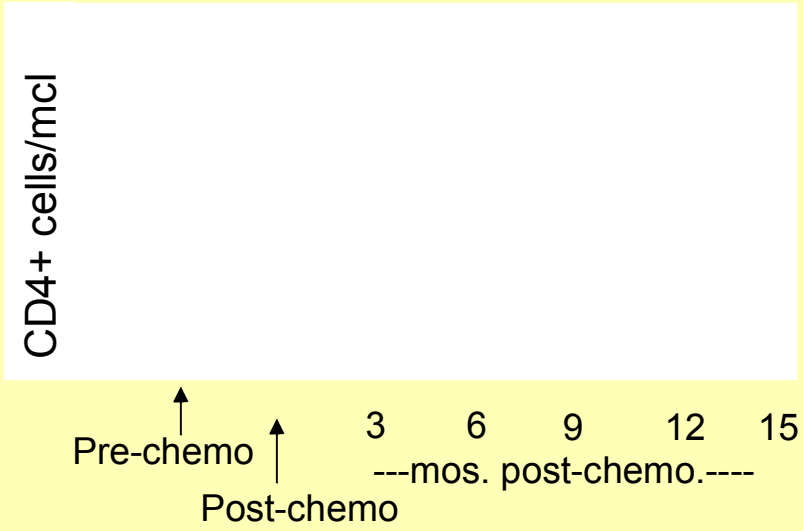


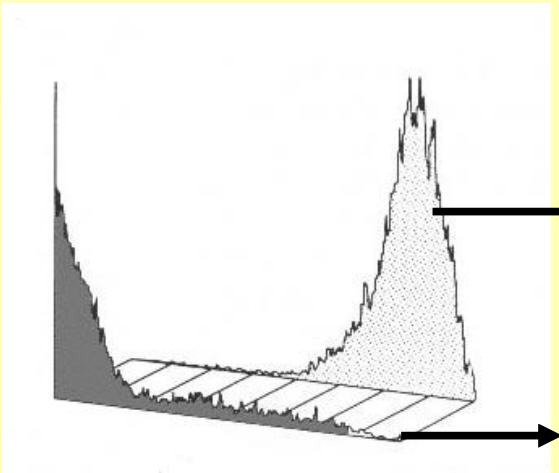
Hakim et al., submitted


Thymic
Differentiation
Peripheral T Cell
Expansion

Homeostatic Peripheral Expansion Lead to Accumulation of Activated T Cells, Which Are Prone to Apoptosis





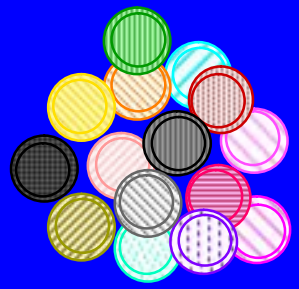


Blood, 2004 HLA-Dr on T cells

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

Hakim, Blood, 1997

CD45RA+/62L+
TREC+



T CELL
CYCLING

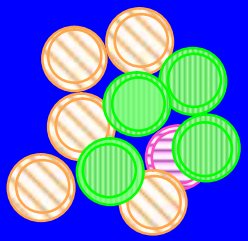
APOPTOSIS

THYMOPOIESIS

THYMIC SUFFICIENCY

THYMIC INSUFFICIENCY

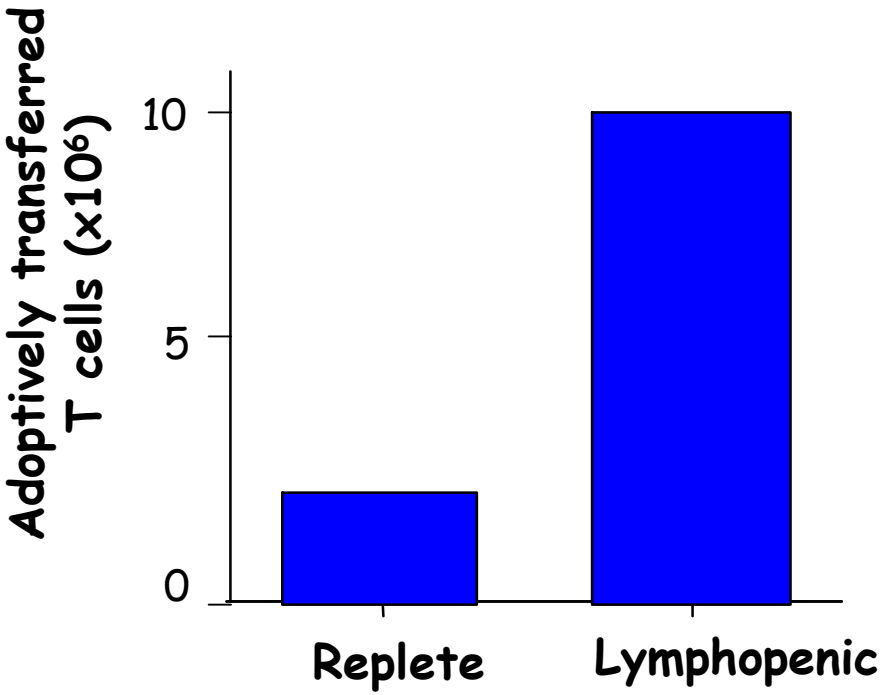
CD45RA+/62L+
TREC+



THYMOPOIESIS

APOPTOSIS

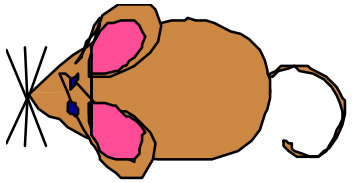
Peripheral Expansion of T Cells Is Increased in T Cell Depleted Hosts



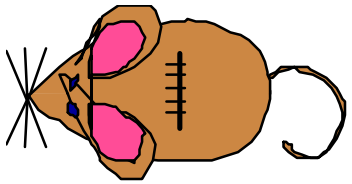
Blood, 1994

- Miller, Stutman - 10,000 fold expansion, ***J Immunol, 1984***
- Bell, Sparshott - nude rats, ***J Immunol, 1987***
- Osias Stutman - ***Immunol. Rev. 1986***

Lymphopenic Hosts Have Increased T Cell Expansion in Response to Cognate Antigen

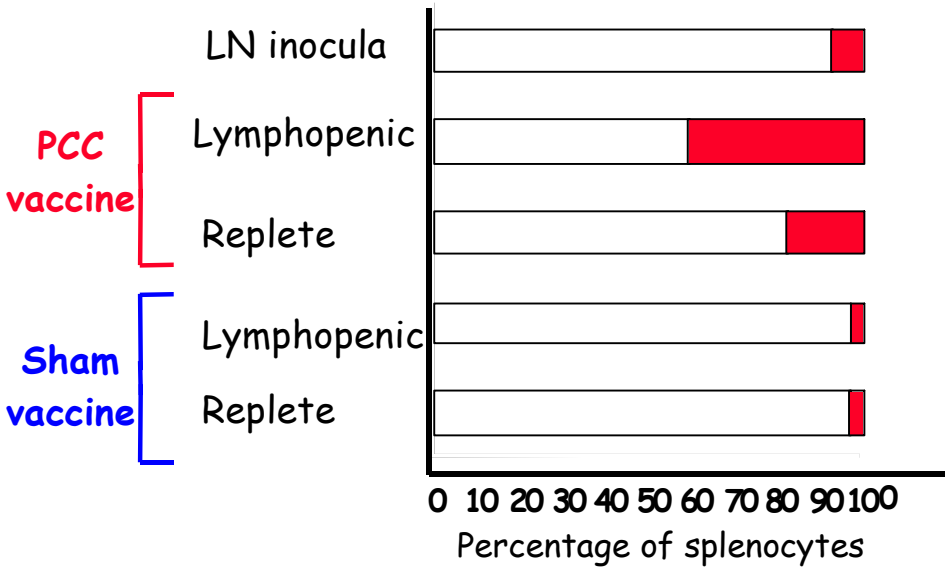


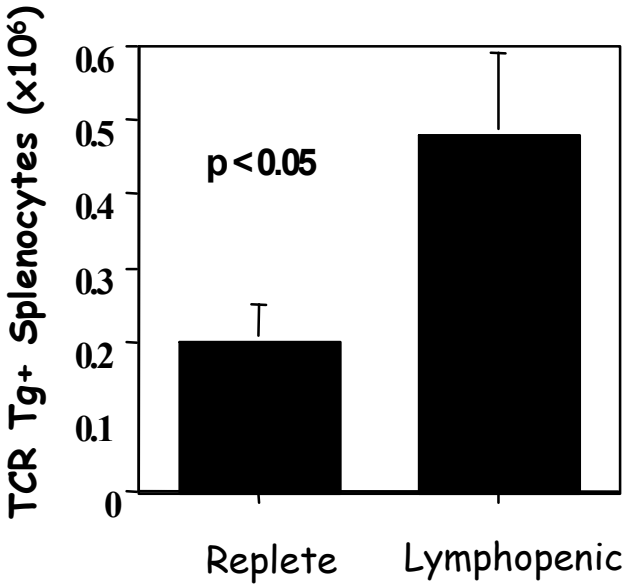
Thymus Bearing
= T cell replete



Thymectomized
= lymphopenic

Bone Marrow Tx
TCR Tg+ LN + Ag

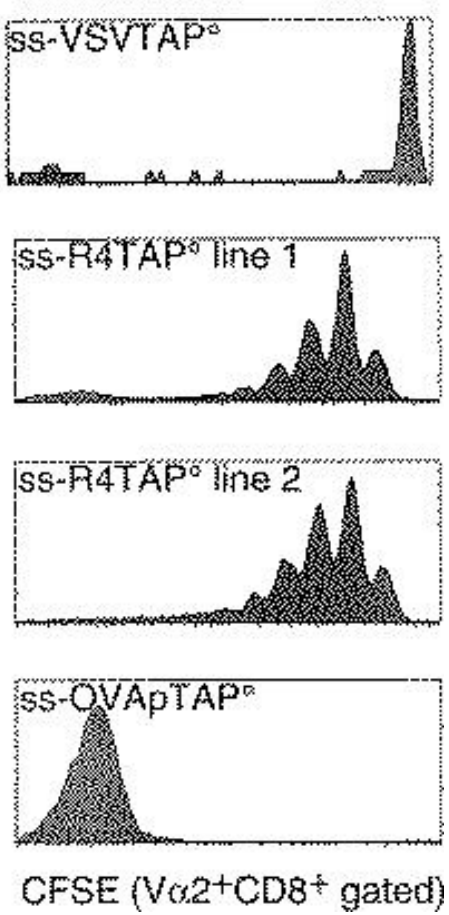




J Immunol, 1996

Low Affinity Antigens Induce Proliferation During Homeostatic Peripheral Expansion

Model:
- Adoptive transfer of OT-1 TCR Tg+ (RAG-/-) cells into a T cell deficient host
- TAP deficient host
- Controlled antigen expression
- Monitor proliferation via CFSE



Ag expression

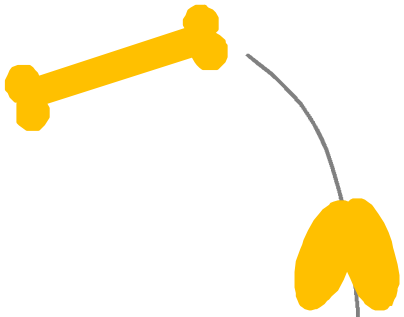
VSV: no affinity

R4: antagonist (low affinity)

Ova: agonist (high affinity)

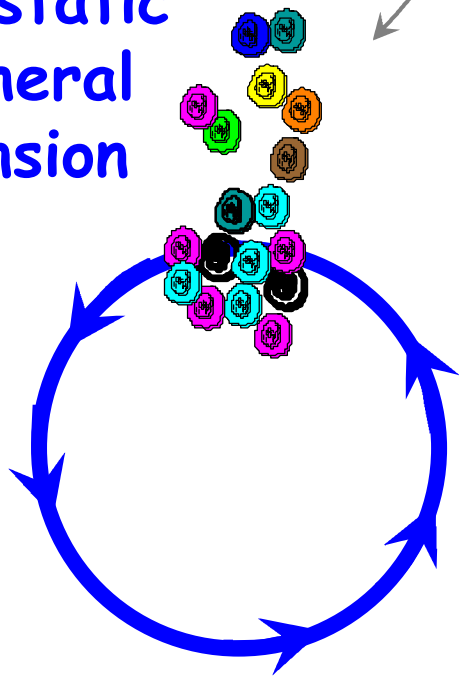
Goldrath et al. Immunity 1999

Progenitor Pool

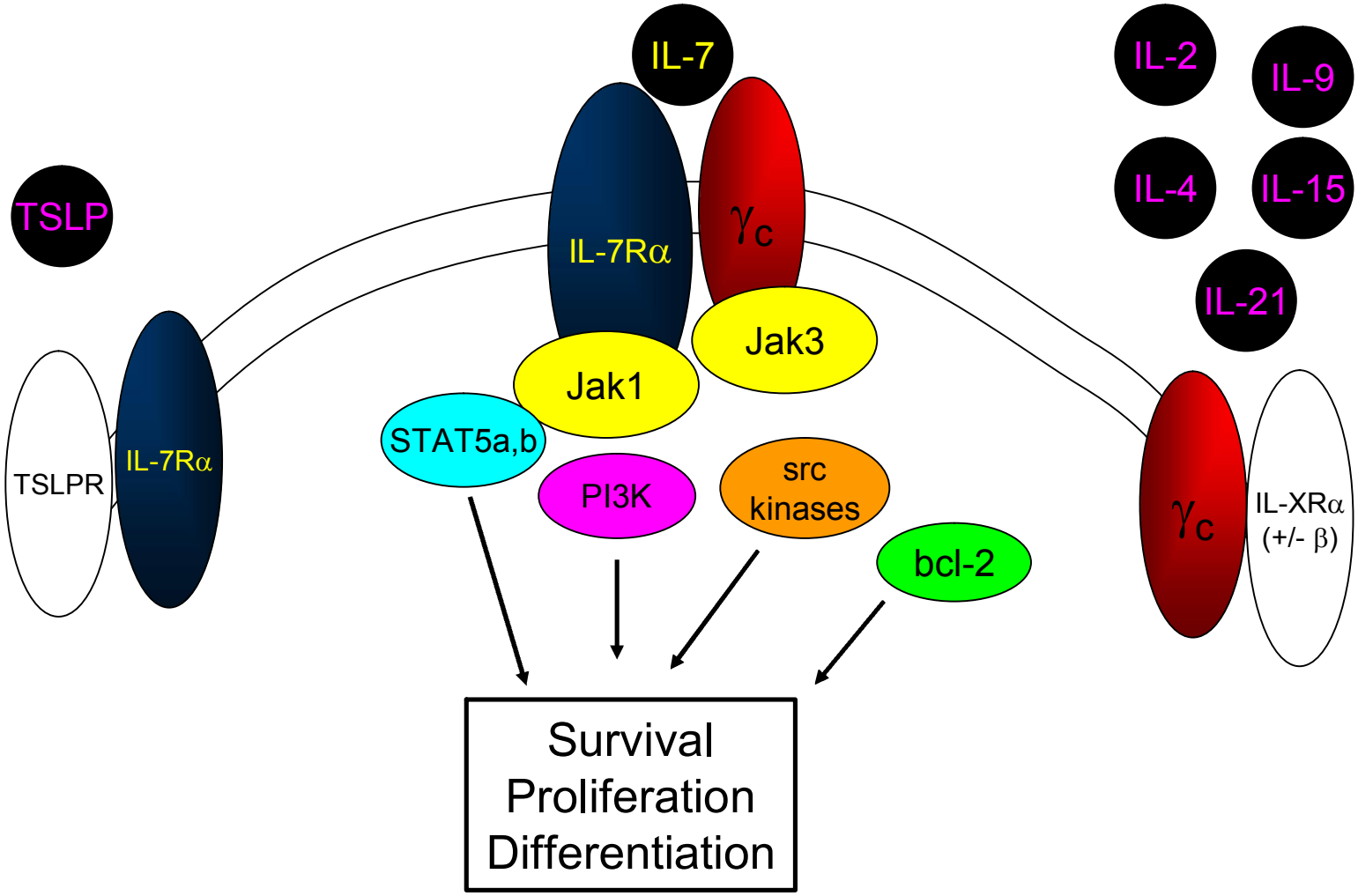


Thymic Differentiation

Homeostatic Peripheral Expansion

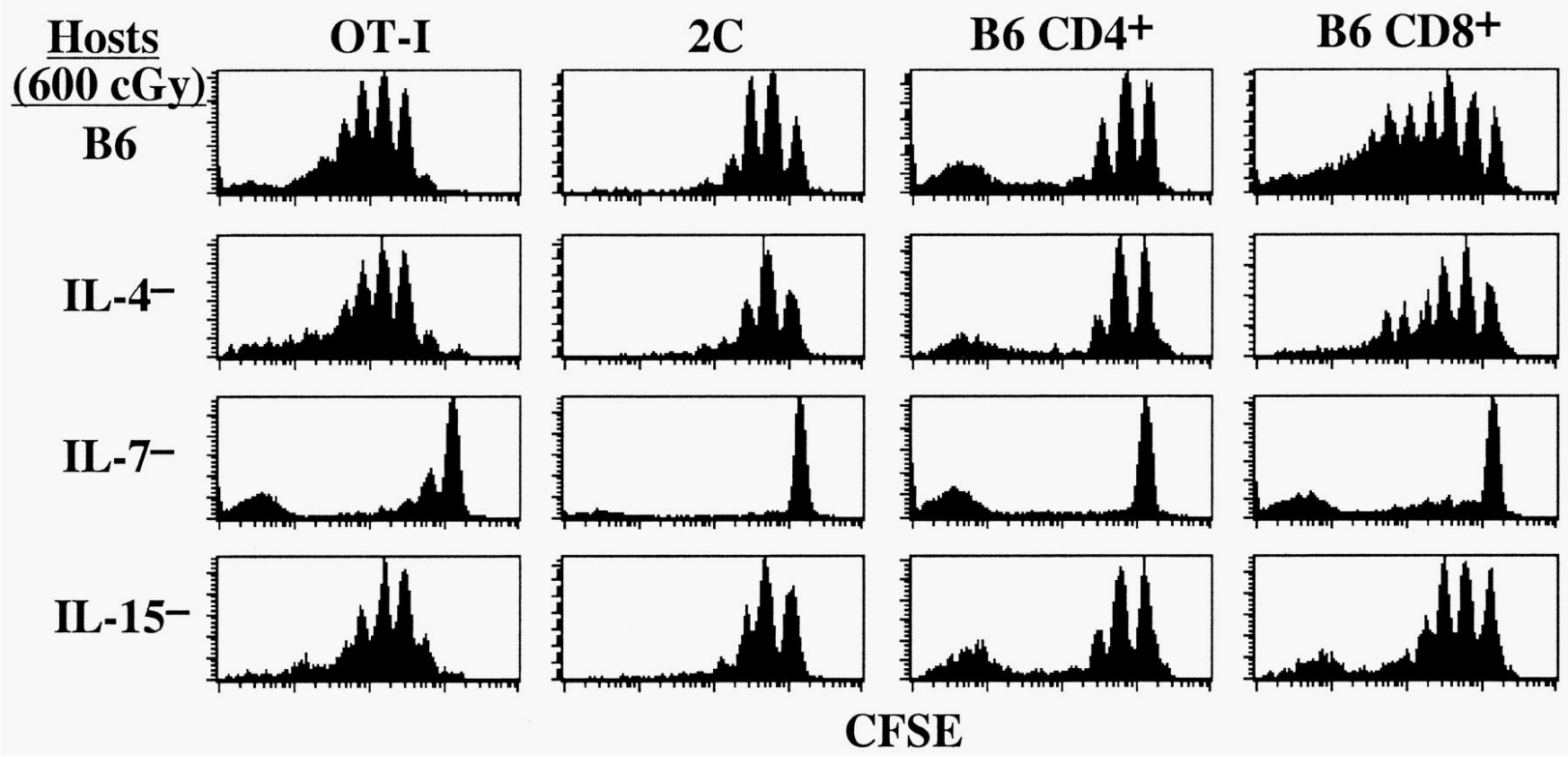


- involves both naïve and memory cells
- exaggerated proliferation to high affinity antigen
- proliferation to low affinity/self antigens



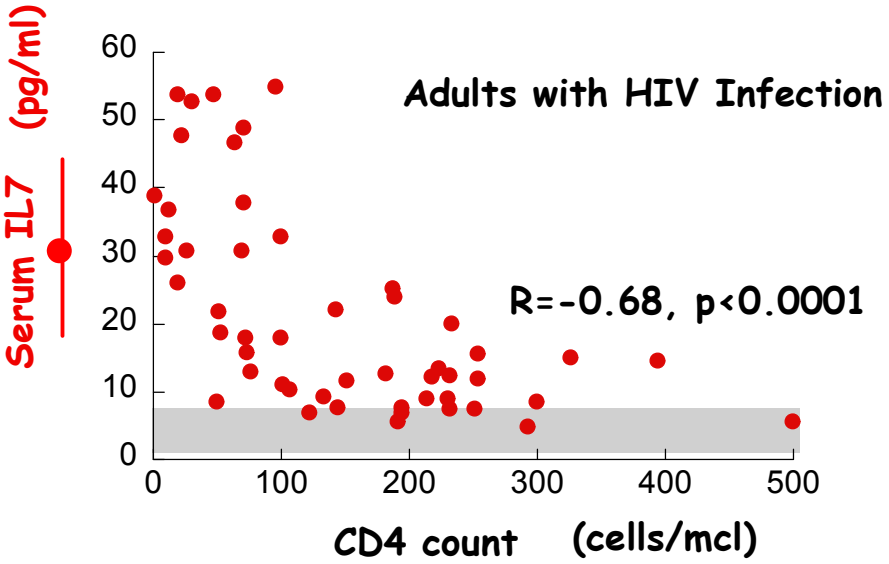
IL-7: Required for T and B Cell Development in Mice and for T Cell Development in Humans

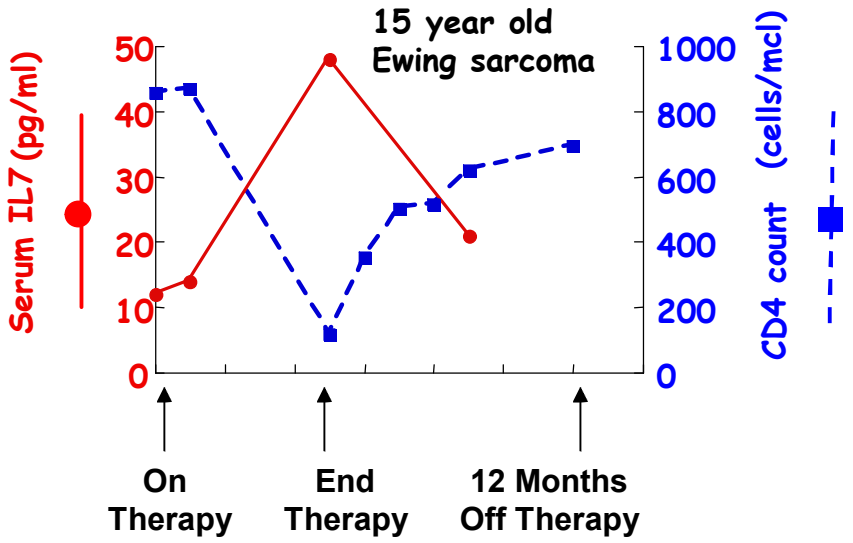
Homeostatic Peripheral Expansion in T Cell Depleted Hosts Requires IL-7



Tan, PNAS, 2001

IL-7 Levels Rise in Response to CD4+ T Cell Depletion





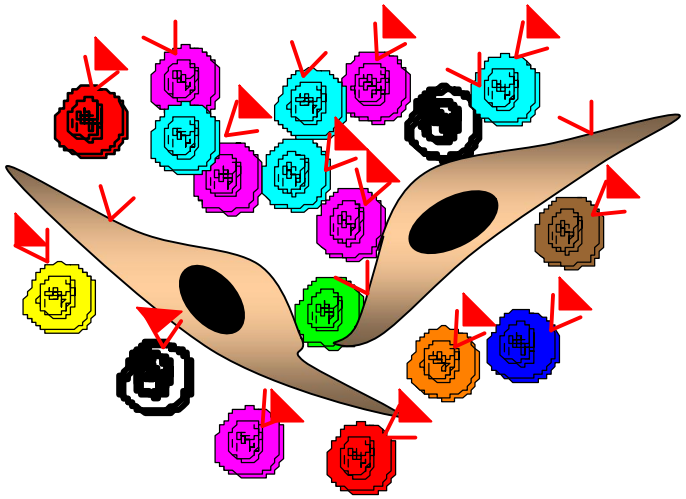
Working Model: "Homeostatic Cytokines" Such as IL7 Accumulate During T Cell Depletion

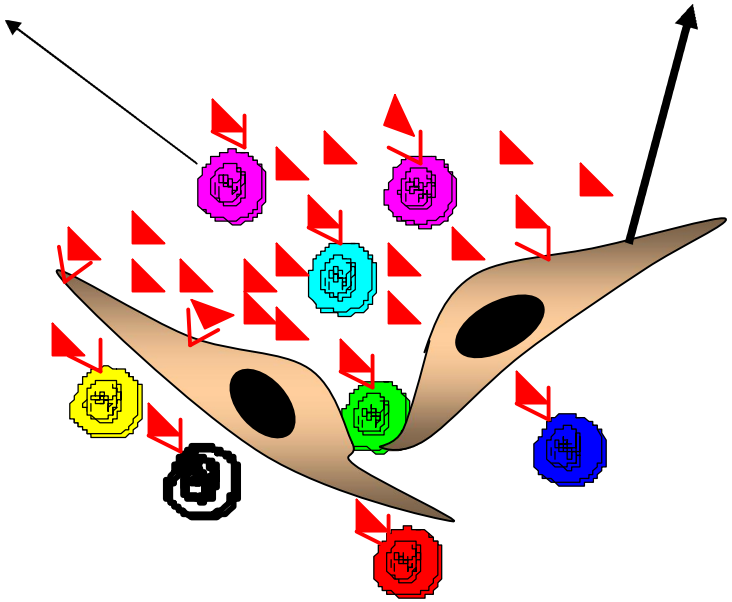
IL7

IL7 receptor

T Cells

IL7 Producing Stromal Cell

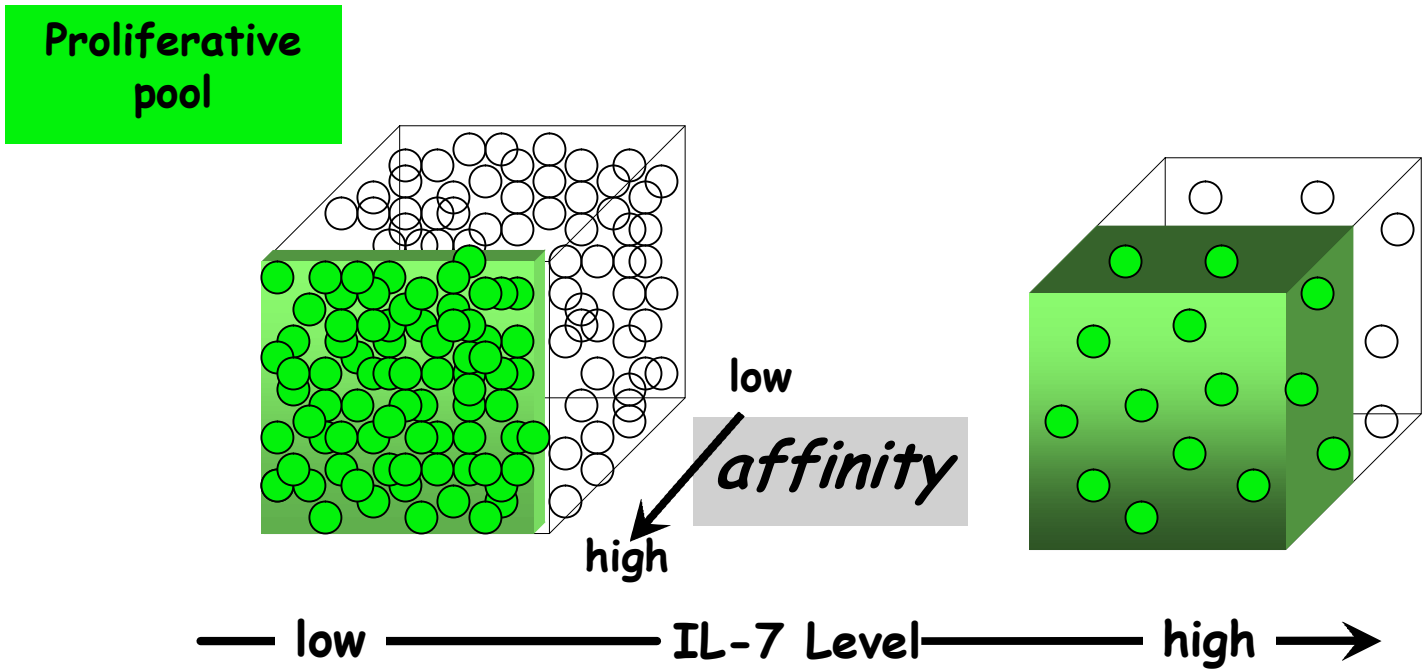




T Cell Replete

T Cell Depleted

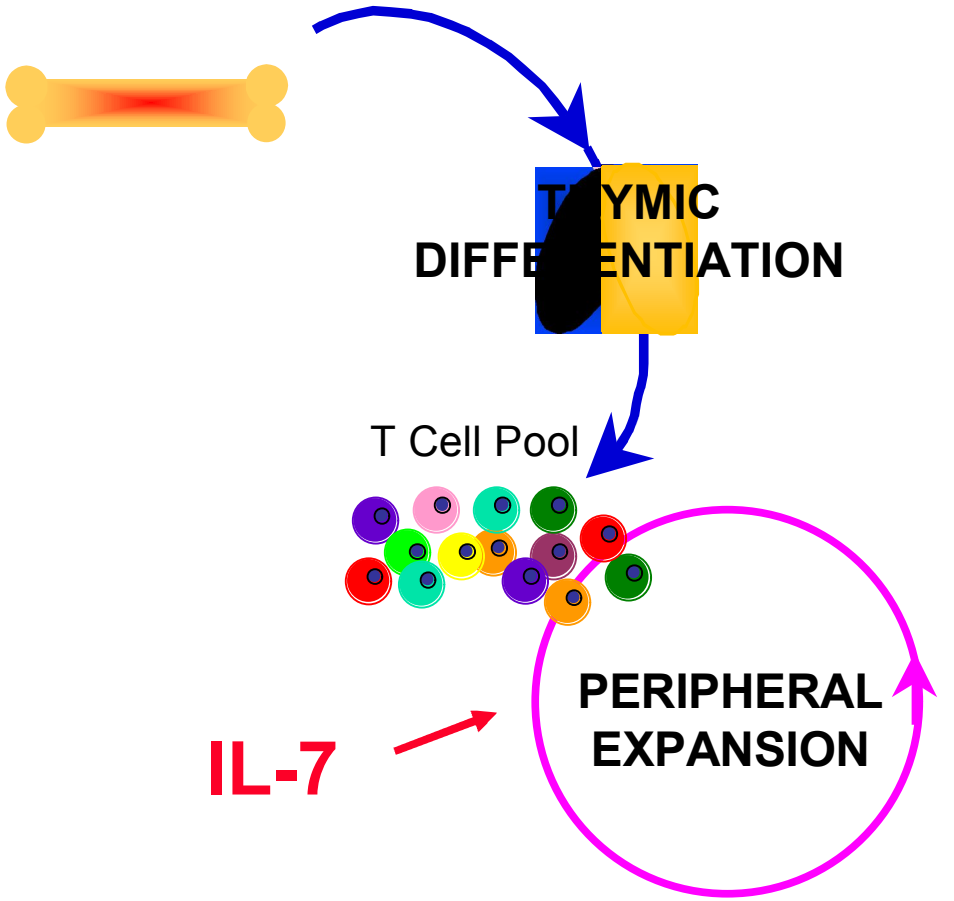
Modeling the IL7 Effect: A greater proportion of the T cell repertoire contributes to the immune response



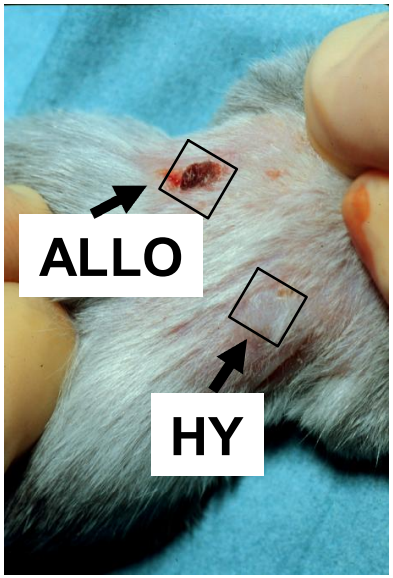
Lymphopenia Predisposes to Autoimmunity/Augments Immune Response to Tumor Antigens

- Murine models:
  - autoimmune gastritis (Gleeson, PA)
    - neonatally thymectomized mice
    - Adult thymectomy + cyclophosphamide
  - Colitis in mice depleted of CD4+CD25+ Treg cells (Sakaguchi)
  - Homeostatic proliferation elicits antitumor immunity (Dummer, JCI)
- Human setting
  - Immune Repopulation Syndromes in HIV
    - Examples
      - Immune Recovery Vitritis (Karavellas et al.)
      - Exascerbation of progressive multifocal leukoencephalopathy
      - Graves disease
    - Tend to be limited to one organ
    - Associated with previous infection/inflammation in that organ
  - Dudley et al., Science, 2003.
    - Potent antitumor responses in melanoma associated with adoptive transfer
    - Autoimmune iritis following adoptive transfer of CTL in TCD humans with melanoma

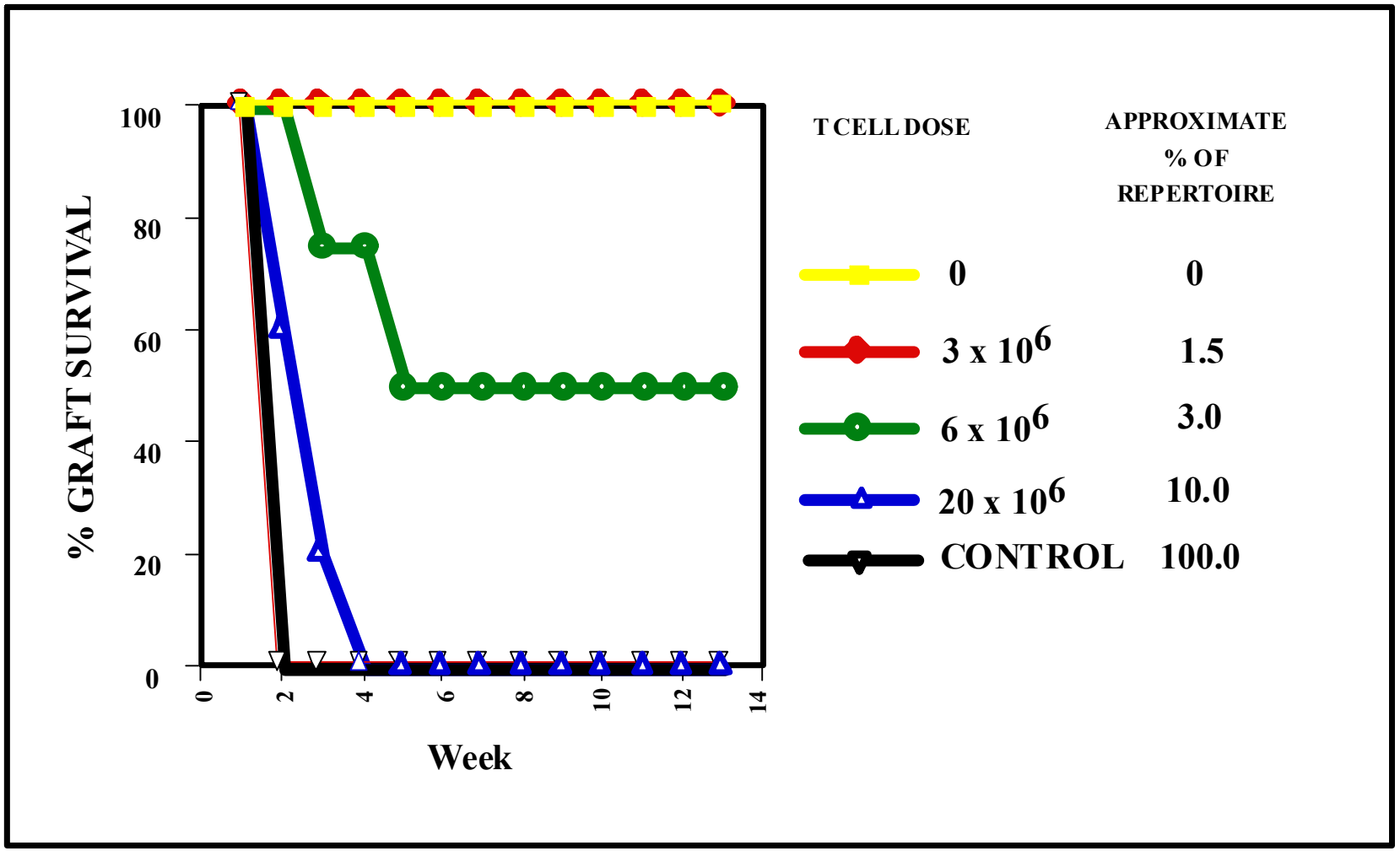
Exploiting Homeostatic Peripheral Expansion for Immune Based Therapy for Cancer



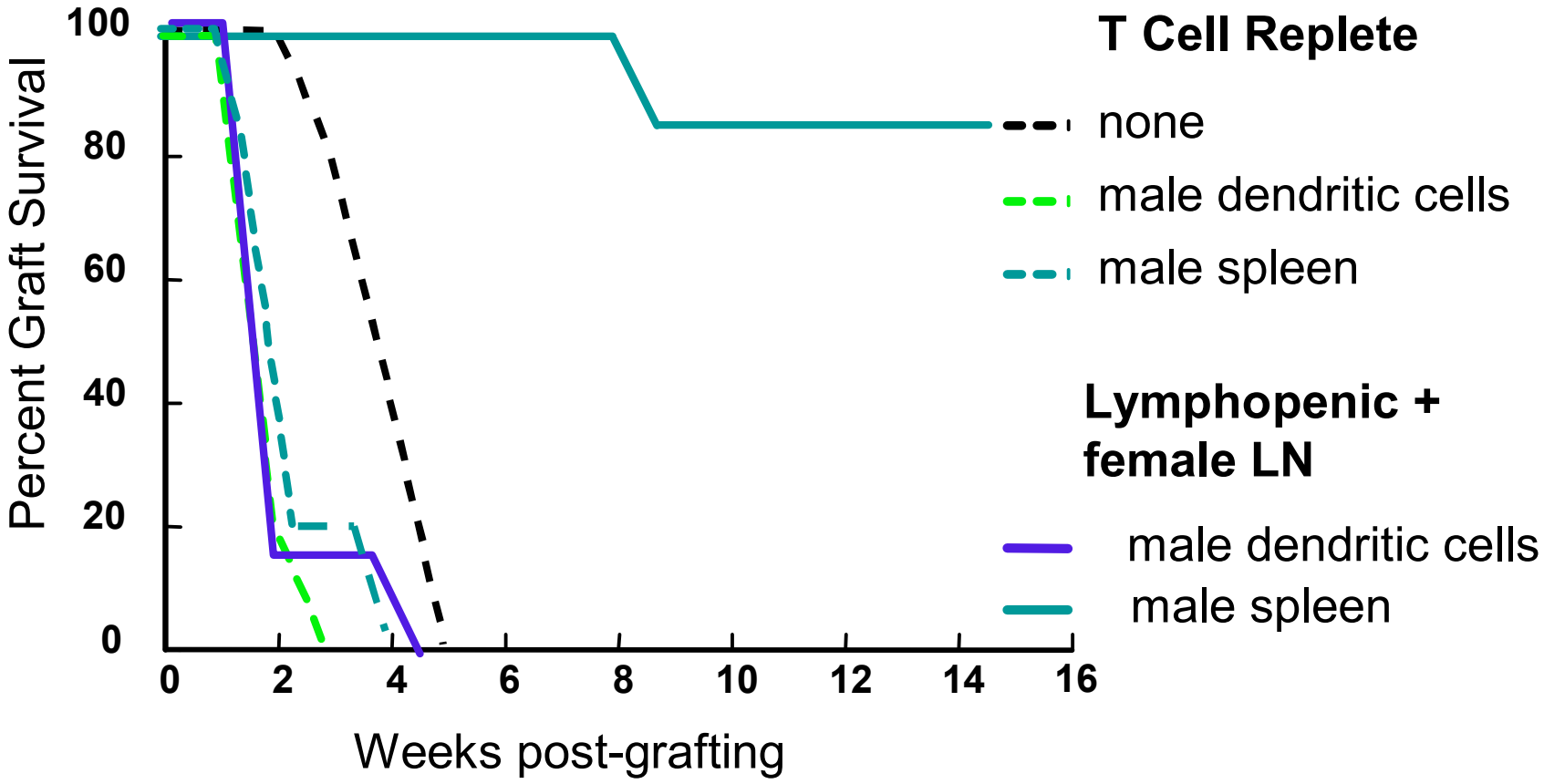
- Exploitation for tumor immunotherapy
- Began by determining requirements for HY graft rejection



Approximately 10% of the Murine T Cell Repertoire Is Necessary to Restore HY Responses in Athymic Hosts



Lymphopenic Hosts are Susceptible to Tolerance since Mixed Populations of “Professional” and “Non-professional” APCs Sensitize T Cell Replete but Tolerize Lymphopenic Hosts



Lymphopenic Hosts develop Toleragenic CD8+ Cells in this Model

Recognition of the Peripheral Self by Naturally Arising CD25 +CD4 +T Cell Receptors

Hsieh & Rudensky, Immunity, August, 2004

- CD4+CD25+ and CD4+CD25- repertoires are equally diverse, but show little overlap
- Retroviral transduction of Va repertoire from CD4+CD25+ cells (but not CD4+CD25- cells) into TCRbeta transgenic (x RAG1-/-) causes dramatic expansion and wasting disease in lymphopenic mice
- Retroviral transduction of Va repertoire from CD4+CD25+ cells (but not CD4+CD25- cells) into bone marrow results in CD4+CD25+ repertoire

Conclusion: CD4+CD25+ repertoire is largely self-reactive, therefore on a cell-to-cell basis, homeostatic peripheral expansion would be more efficient than that observed for the CD4+CD25- repertoire.

Induced Lymphopenia to Augment Immune Responses

Yin:

•CD4 lymphopenia will be prolonged with clinical complications related to the degree

•diminished repertoire diversity may limit responses to weak antigens

•high rate of apoptosis will likely limit efficacy

• regulatory cells may be induced in this setting (Treg, CD8s)

Yang:

•increased magnitude of proliferation to high affinity antigen

•induction of proliferation to low affinity/self antigens

•induced largely by the accumulation of the immunostimulatory cytokine IL7 in response to CD4 depletion

•depending upon method of depletion, regulatory cells may also be depleted

Future Goals for Modulating T Cell Homeostasis in Tumor Immunotherapy

- Avoid broad immunosuppression
- Retains T cell receptor repertoire diversity which is needed for diverse immune response
- Pharmacologic rhIL7 to Replicate Homeostatic Expansion in T Cell Replete Hosts
  - ? rhIL15, ?others
- Selective Depletion of Regulatory Cells

Contributors

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