


**Immune Reconstitution Following Hematopoietic Cell Transplant**

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**Conflicts of Interest**

- Speaker Bureau
  - Millennium Takeda
  - Celgene
- Advisory Board
  - Eisai



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**Learning Objectives**

- Outline the biology of normal lymphoid ontogeny
- Explain the detrimental effects of immunosuppressant, antibodies, corticosteroids and graft-versus-host disease on the immune system



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## Recalling the Basics

- Innate Immunity
  - Physical barriers
  - Neutrophils, macrophages, NK cells
- Adaptive Immunity
  - Cellular response to pathogens via antigen presenting cells
  - Humoral response via antibodies

CIRM/TTU  
LMB/BSU

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## Lymphoid Ontogeny

- Immunocompetence mediated via:
  - Natural Killer (NK) cells (CD56+CD16+)
  - B-lymphocytes (CD19+/CD20+)
  - T-lymphocytes (CD3+, CD4+, CD8+)
    - Antigen-specific T-lymphocytes
      - Virus infected cells
      - Assist B cells production of antibodies towards respiratory bacteria
      - With granulocytes respond to fungal infections

CIRM/TTU  
LMB/BSU

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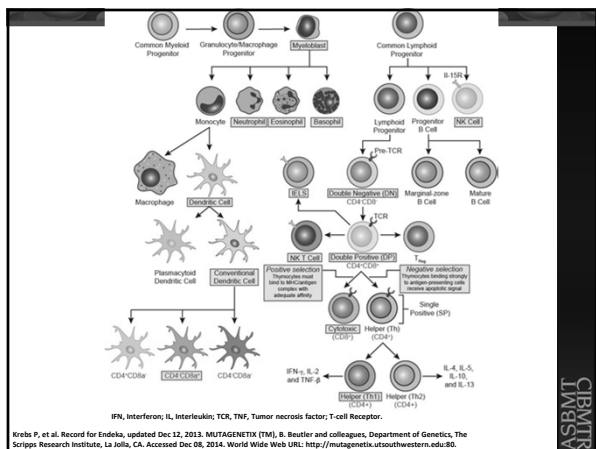
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LMB/BSU

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### Thymic Proliferation

**Thymic function deficiency**

- Age
- Radiation
- Chemotherapy
- Infection
- Graft-versus-host disease (GVHD)

Krebs P, et al. Record for Evidence, updated Dec 12, 2013. MUTAGENIX (TM), B. Beutler and colleagues, Department of Genetics, The Scripps Research Institute, La Jolla, CA. Accessed Dec 08, 2014. World Wide Web URL: <http://mutagenix.usouthwestern.edu/85>

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### Thymic Emigrants

- T cells and common lymphoid progenitor do NOT possess “stemness”
- Thymopoiesis is required to expand the TCR repertoire
  - T lymphocytes containing TCR excision circles (TRECS)
- TRECS found in the periphery represent thymopoiesis
- CD4+/CD25+ regulatory T lymphocytes

Storek J, et al. Transplantation. 2002;73:1154-8. Hanynes BF, et al. Annu Rev Immunol. 2006;18:529-60.

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### Older Age, Less Thymus

**TREC<sup>+</sup> CD4 T cells (x10<sup>9</sup>/l) at 1 year posttransplant**

**Patient Age at Transplant**

$r = -0.41$   
 $p = 0.01$

Storek J, et al. Transplantation. 2002;73:1154-8.

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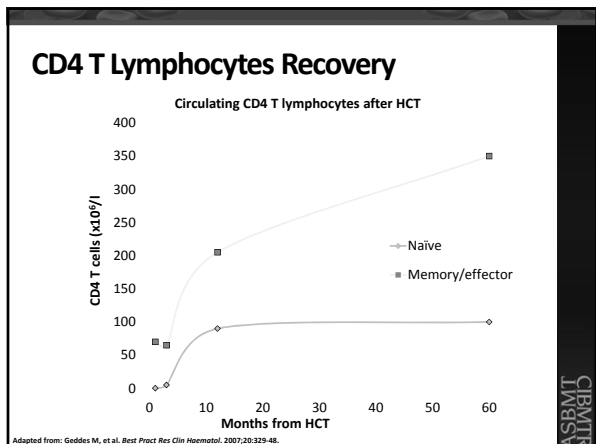
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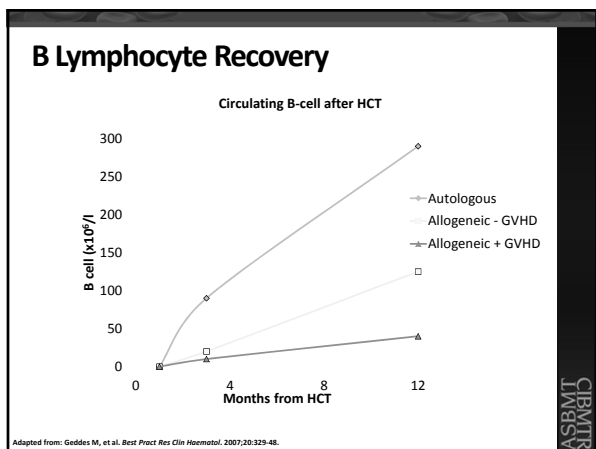
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### Phenotypical Analysis HCT Recipients

Recovery	Auto	Allo
ALC > 500/mcL	15d	27-30d
Normal CD3+/mcL	6-8 wk	12 wk
CD8+/mcL	4 mo	5 mo
CD4+/mcL	6 mo	7 mo
CD4:CD8	6-9 mo	
CD16+ CD 8 (dim)	1 mo	

ALC, absolute lymphocyte count

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**Assessment of Immune Reconstitution**

- Immunophenotyping
  - Absolute CD4
  - CD4/CD8 ratio
  - T cell subsets by flow cytometry
- Immunoglobulins
- Functional Assessment
  - T cell proliferative studies
  - Antibody response following vaccination
    - Diphtheria, tetanus, pneumococcal
  - TREC quantification, PCR
  - T cell receptor spectratyping

Seggewiss R, et al. Blood. 2010;115:3861-68.

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LMBGSS

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**ARS Question 1**

Following allogeneic transplantation a broad TCR repertoire may be a result of which of the following:

1. Functional thymus
2. CD34+ cell dose
3. Age
4. Common lymphoid progenitor cells

Antin JW, et al. Biol Blood Marrow Transplant. 2005;11:213-22.

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**Autologous HCT**

- Following peripheral blood cell administration
  - At 3 months
    - CD8 > CD4
  - At 1 year
    - CD4 counts are normalized
  - Serologic response to vaccines may be delayed up to 12 months
  - Rarely have opportunistic infections

Antin JW, et al. Biol Blood Marrow Transplant. 2005;11:213-22.

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### Allogeneic HCT

- No prospective studies documenting time until lymphocytes respond to antigenic stimuli
- Herpes virus
  - Antigen-specific T lymphocytes present at 2 months
- TREC related to age and thymic function
- CD20+ B Lymphocytes present at 1-2 months
- Reduced IgG, IgA, and IgM for 6 months

Gratama JW, et al. Transplantation. 1986;41:719-24.  
Storck L, et al. Bone Marrow Transplant. 1994;14:783-90.

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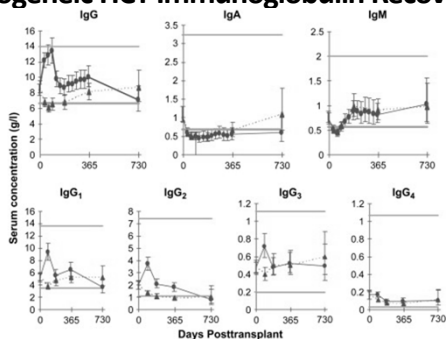
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### Allogeneic HCT Immunoglobulin Recovery



Sullivan KM, et al. Biol Blood Marrow Transplant. 1996;2:44-53.

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### T-cell Depleted HCT

- No immunophenotypic T lymphocytes are seen for 3 months
- Defects in cytokine production exist
  - IL-2
- Minimal T lymphocyte in cell product
  - Stem cell must proliferate and thymic function must be adequate
- Haploidentical HCT may have decreased CD4 counts for years

Wolfe K, et al. Blood. 1984;64:380-5. Wu, CJ et al. Blood. 2000;95:352-9. Volpi I, et al. Blood. 2001;97:2514-21.

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### Chronic Graft-versus-Host Disease

- Paradoxical hallmark is manifestation of
  - Immunodeficiency
  - Autoimmunity
  - Alloimmunity
- CD4+ CD25+ Tregs suppress autoreactive lymphocytes
- FOXP3, master regulator in T lymphocytes

FOXP3, forkhead box P3

Zorn E, et al. *Blood*. 2005;106:2909-11.

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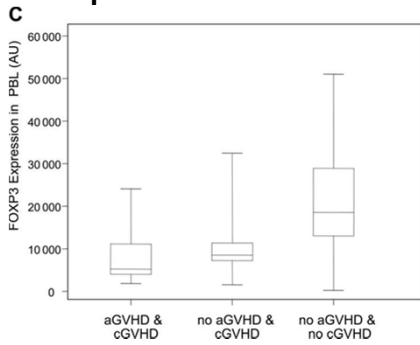
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### FOXP3+ Expression



Zorn E, et al. *Blood*. 2005;106:2909-11.

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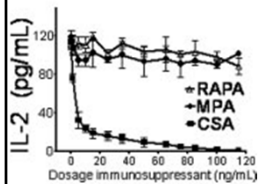
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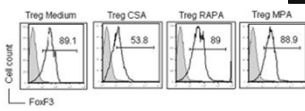
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### Immunosuppression on Cytokine and Treg



In vivo IL-2 levels via ELISA

CSA, cyclosporine A; MPA, mycophenolic acid; RAPA, sirolimus.



FOXP3 Treg expression is decreased with calcineurin inhibition

Zisler R, et al. *Blood*. 2006;108:390-99.

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### ARS Question 2

The presence of chronic graft-versus-host disease may have a direct detrimental effect on which type of cells:

1. Common lymphoid progenitor
2. FOXP3 Tregs
3. CD5 T lymphocytes
4. Common myeloid progenitor

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### Improving Immune Reconstitution?

- Reduced intensity or non-myeloablative transplants
- Umbilical cord
  - More Tregs than adult product, but less product
- Thymus, thymus, thymus
  - Keratinocyte growth factor
  - Sunitinib to enhance thymic function
- IL-2 and IL-7

Seggewiss R, et al. Blood. 2010;115:3881-88.

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