

# Migration of Tumor-Specific T Cells

**Patrick Hwu**  
**MD Anderson**

**Carmen Scheibenbogen**  
**Charité, Campus Benjamin Franklin**

# **Migration of Tumor-Specific T Cells**

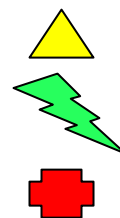
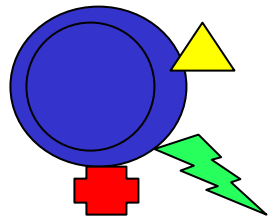
- **non-random**
- **determined by characteristics of T cells  
and the specific microenvironment**
- **tumor cells exploit similar mechanisms as  
leukocytes**

# Migration of leukocytes

## Multi-step process of adhesion:

- Selectins: Tethering of T cells on the endothelium
- Chemokine receptors: activation of integrins
- Integrins: firm adhesion.

### Lymph node homing



**L-Selectin**

**CCR7 activated by CCL19/21**

**LFA-1**

# **Chemokines and Chemokine receptors**

- **>50 chemokines identified (small cytokine-like proteins)**
- **appr. 20 chemokine-receptors identified**

# **Chemokines and Chemokine receptors**

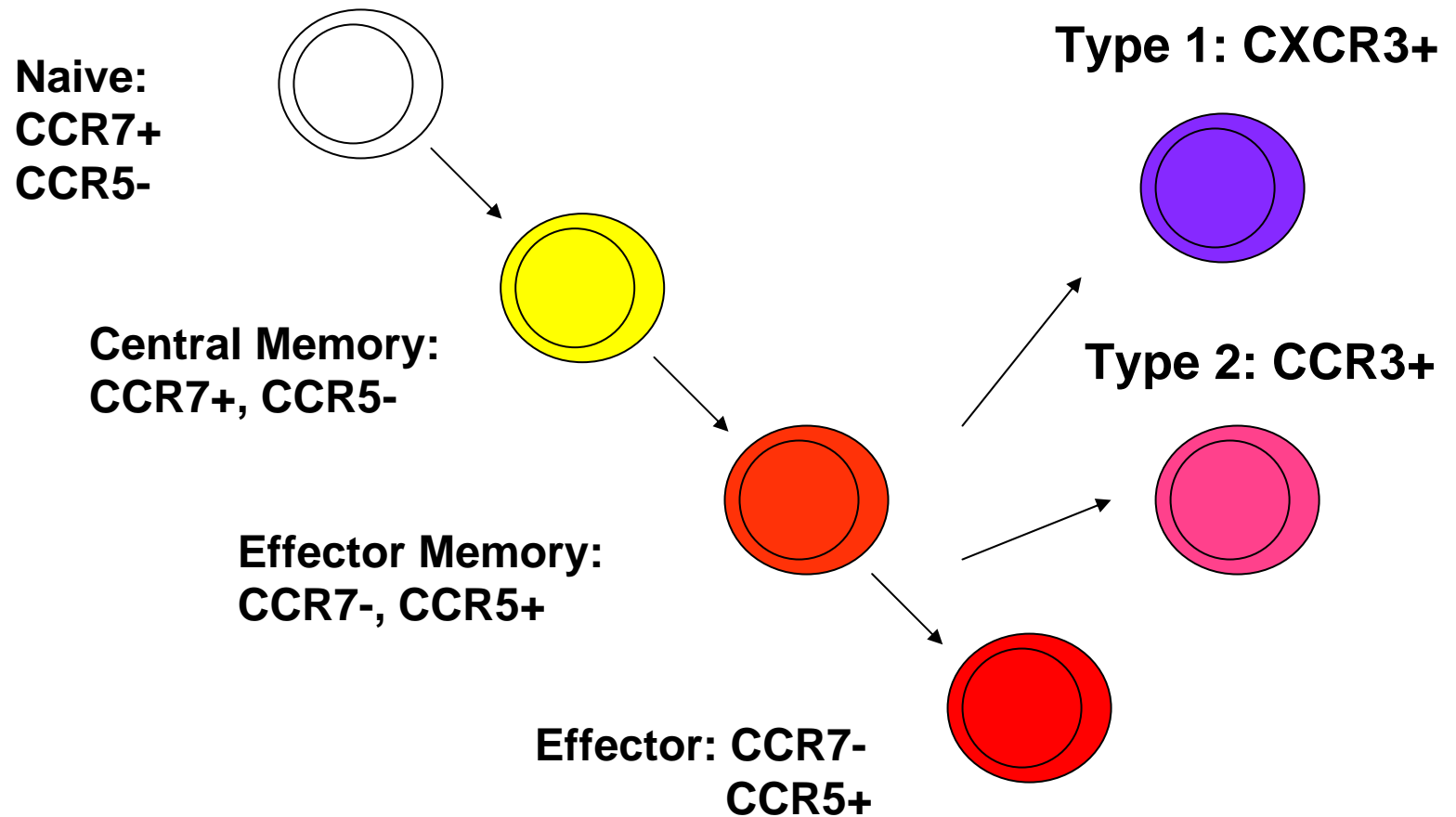
**Homeostatic chemokines/ - receptors**

- **mucosa: TECK - CCR9**

**Inflammatory chemokines/ - receptors**

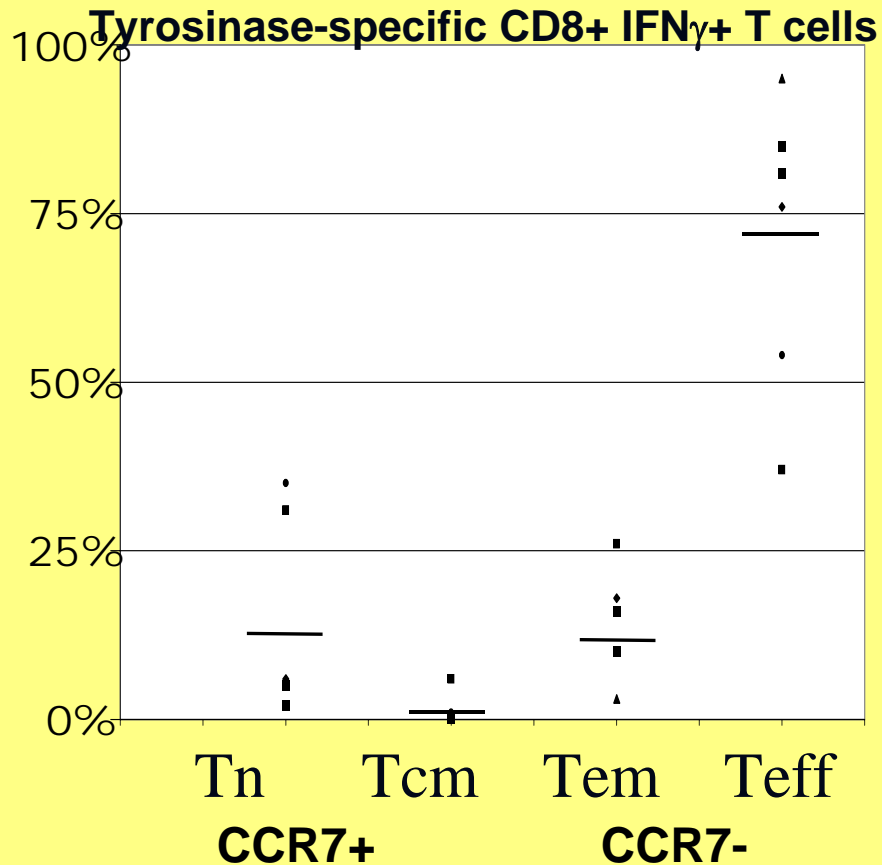
- **Mig - CXCR3**

# Chemokine receptor expression during T cell differentiation

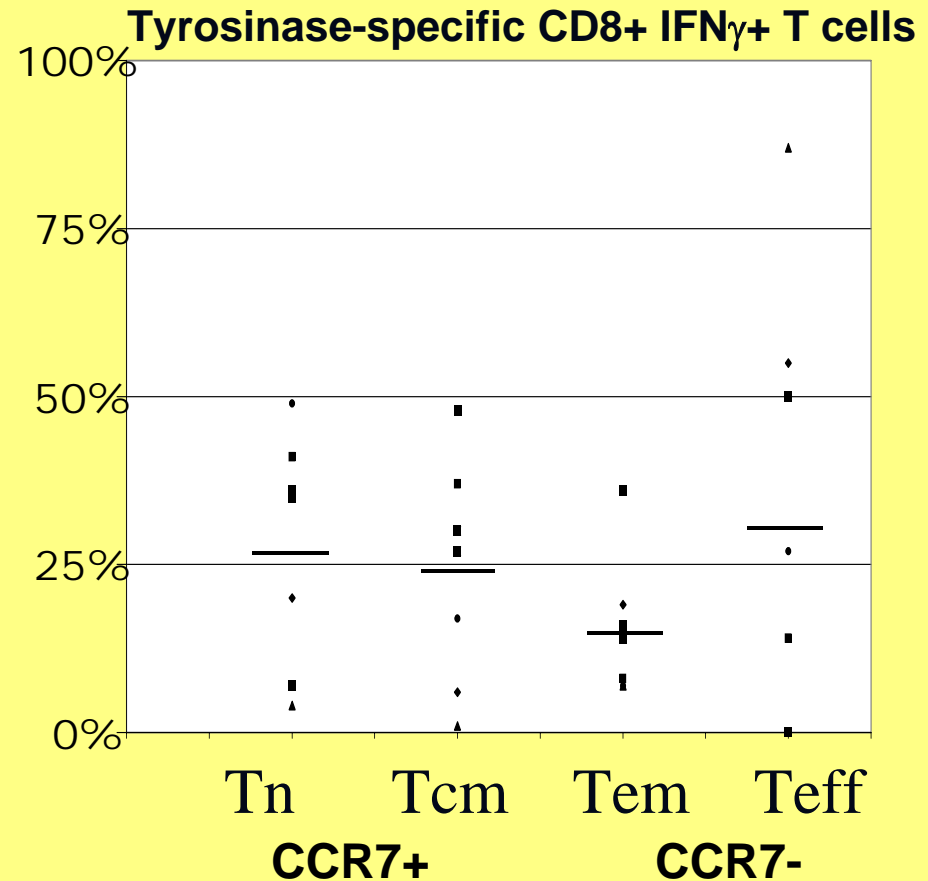


# Distribution of vaccine-induced T cells depends on T cell differentiation

## Peripheral blood



## Bone marrow



# **Accumulation of T cells in tissues**

- **Migration (entry)**
- **Increased proliferation/ reduced apoptosis**
- **Reduced exit**



# **Targets of T cells in immunotherapy**

**Therapeutic vaccination/adoptive transfer:**

- **ability to migrate into the tumor**

**Adjuvant vaccination:**

- **ability to migrate into many compartments**

# **Methodological approach to assess migration of T cells**

- **Migratory phenotype**  
**Chemokine receptor/Adhesion antigen expression**
- **Migratory potential**  
**Chemokine receptor function**
- **Migration/Accumulation in vivo**  
**Detection of specific T cells in tumor and specific compartments**

# **Analysis of migratory potential of T cells**

## **Indirect**

- **CCR expression and function**
  - **Ca-flux**
  - **Receptor downregulation**
  - **Actin Polymerization**

## **Direct**

- **Transwell migration assay**

# **Chemokine receptors of importance for T cell migration in immunotherapy**

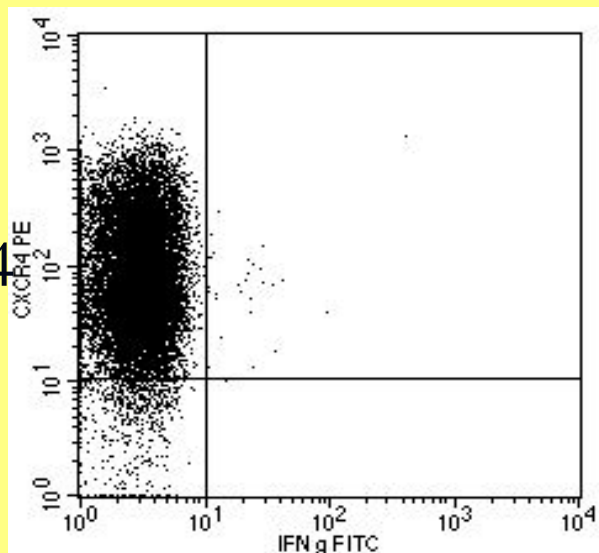
<b>Chemokine</b>	<b>ligand</b>	<b>expression</b>
<ul style="list-style-type: none"><li>• <b>CXCR4</b></li><li>• <b>CCR4</b></li><li>• <b>CCR7</b></li></ul>	<b>SDF-1</b> <b>TARC</b> <b>SLC, ELC</b>	<b>multiple</b> <b>skin</b> <b>lymph node</b>
<ul style="list-style-type: none"><li>• <b>CXCR3</b></li></ul>	<b>MIG, IP10</b>	<b>inflammation/tumor</b>

**Expression of chemokine receptors on specific T cells:**

**Tyrosinase-reactive T cells are CXCR4+  
(ligand SDF-1: bone marrow, ln, liver, lung)**

**HIV peptide**

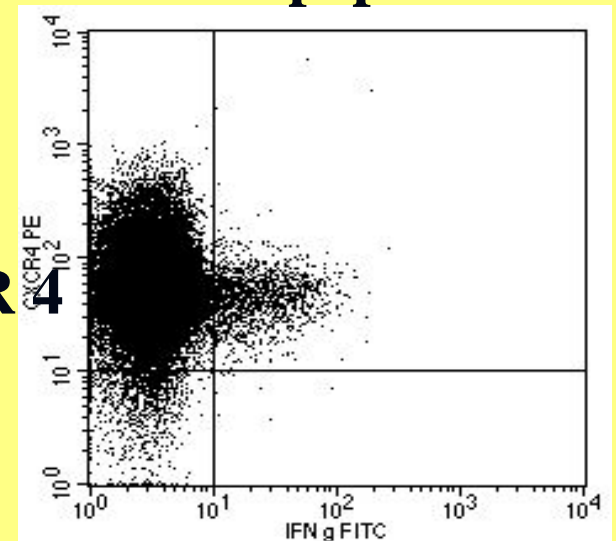
**CXCR 4**



**IFN $\gamma$**

**TYR peptide**

**CXCR4**

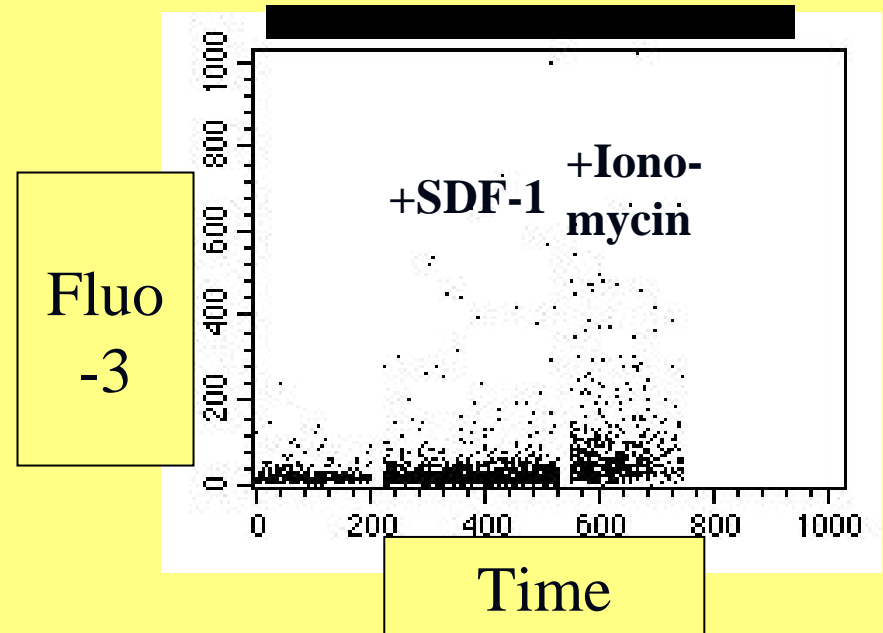
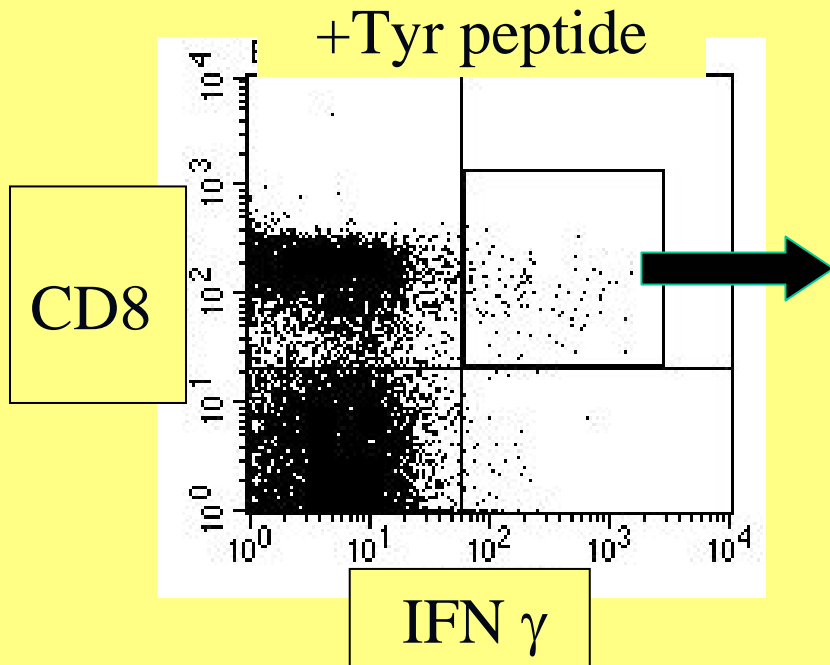


**IFN $\gamma$**

**However, CCRs are often not functional (Rabin et al., JI, 1999)**

# Functional analysis of CXCR4 expression on CD3+ CD8+ tyrosinase reactive T cells by Ca-flux

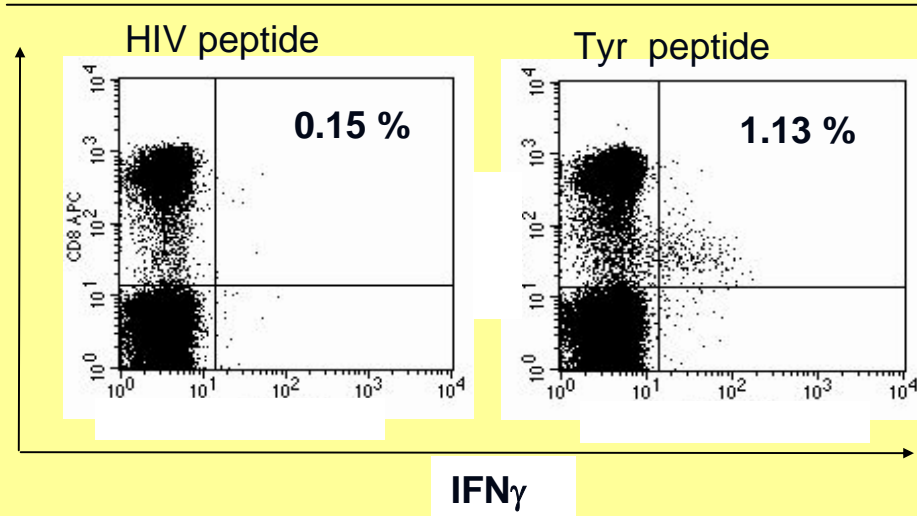
CXCR4 expressed on tyrosinase-specific T cells is functional in response to the specific ligand SDF-1



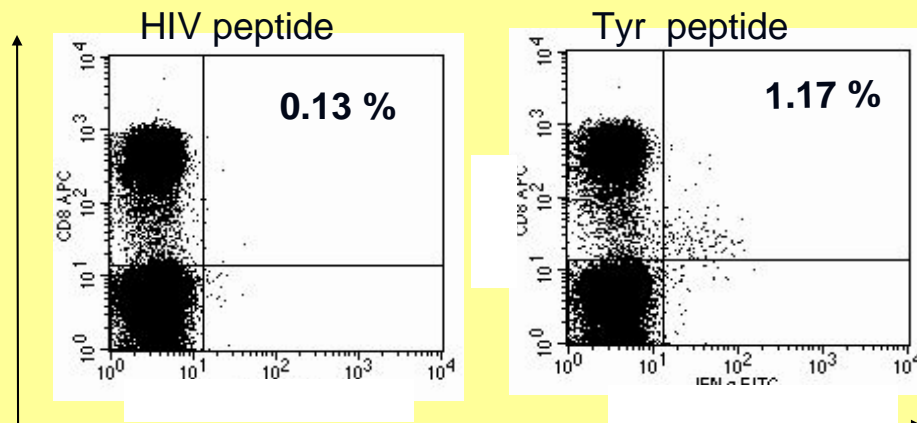
# Migration of tyrosinase-specific vaccine-induced T cells into the bone marrow

peri-  
pheral  
blood

CD8



bone  
marrow



# **Migration of T cells in immunotherapy**

## **Breakout session topics**

To discuss:

- current knowledge
  - methodological approach and
  - modulation by adjuvants/vaccination route
- of migration/migratory potential of tumor-specific T cells in immunotherapy.



# **Migration of Tumor-Specific T Cells - SBT 3.11.04**

**Patrick Hwu, MD Anderson**

**Carmen Scheibenbogen, Charité**

## **Participants**

- **Sam Hwang, NCI**
- **Stefan Martin, Univ. of Freiburg**
- **David Mullins, Univ. of Virginia**
- **John Bender, Favritte**
- **William Carson, Univ. of Ohio**
- **Alan Epstein, Univ. of South. Calif.**
- **Heidi Hoerig, Columbia Univ.**
- **Julian Kim, Cleveland**
- **Gregory Plautz, Cleveland**
- **Christian Poehlein, Earle A. Chiles Research Institute**
- **Per Thor Straten, Danish Cancer Center**
- **Natalie Dubois-Stringfellow, XOMA**

# Migration of leukocytes and tumor cells

