Effect of Cytomegalovirus Infection on Immune Responsiveness

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Sanquin Blood Supply Foundation

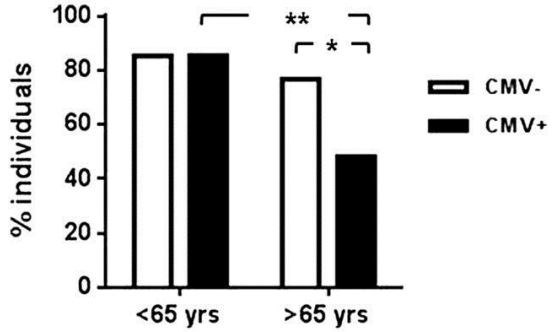
OUTLINE

- **CMV infection and vaccination responses**

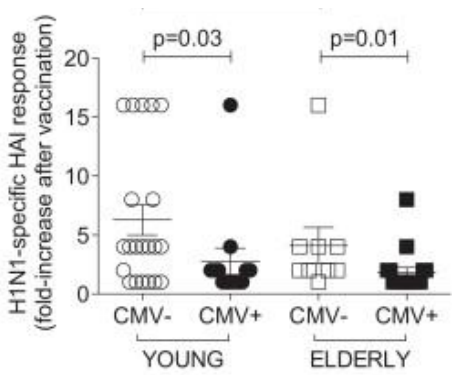
- **Effects of CMV infection on**
  - ***$CD8^+$ T cell numbers***
    - ***Blood versus Lymph Nodes***
  - ***Proteomes and Transcriptomes of differentiated $CD8^+$ T cells***
  - ***Markers of inflammation***

CMV seropositivity decreases responses to the influenza vaccination

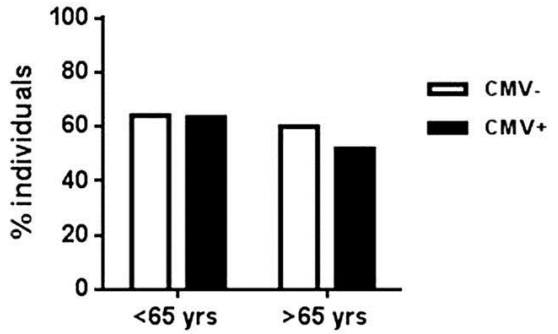
Flu-specific CD4 response

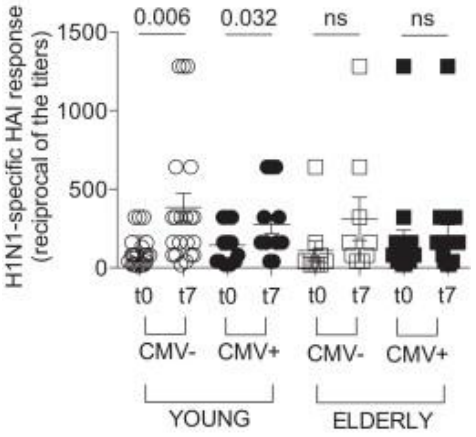


Antibody response



Flu-specific CD8 response

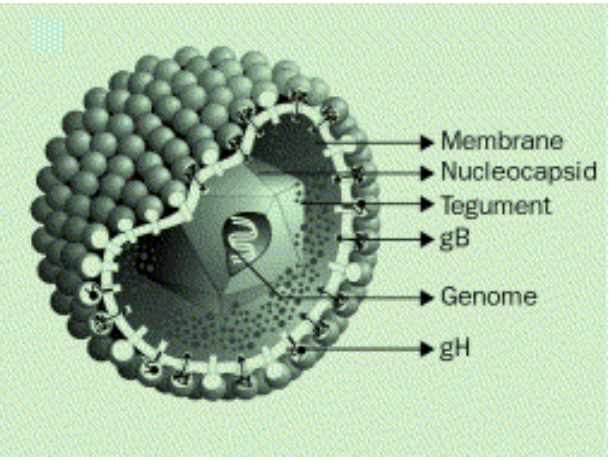




Evelyna Derhovanessian et al. J Immunol 2014;193:3624-3631

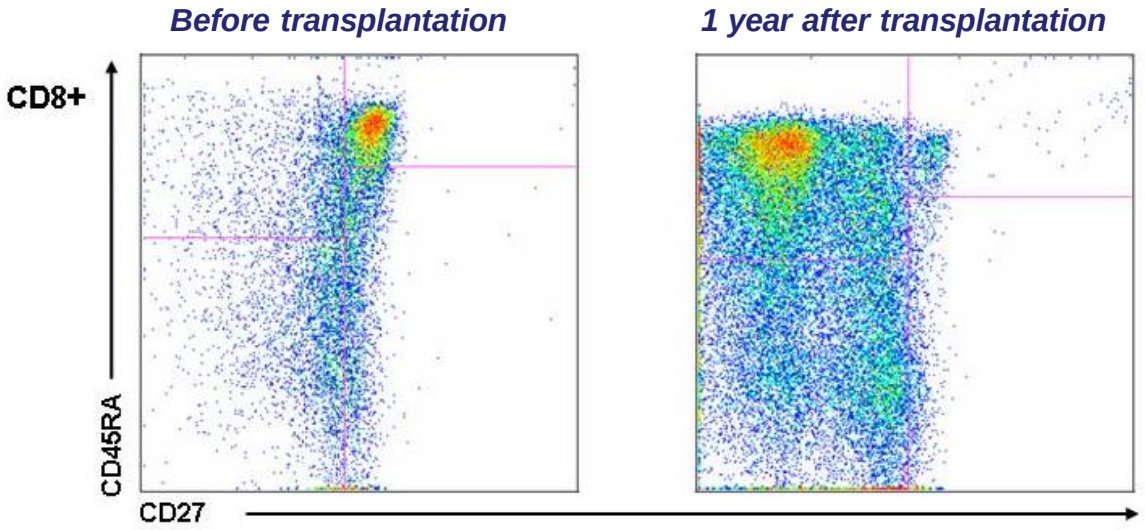
Daniela Frasca et al; Vaccine, 2015; 33: 1433–1439

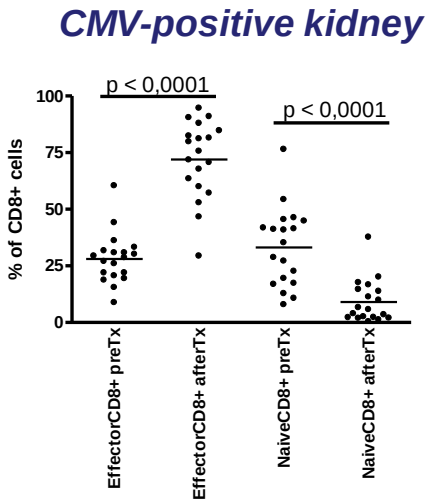
Human Cytomegalovirus (CMV)

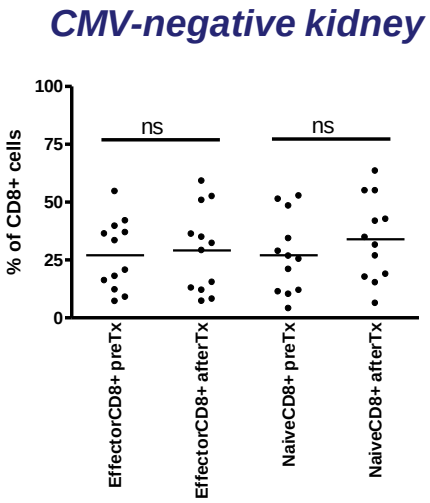


- **CMV is a persistent β-herpesvirus affecting approximately 60% of healthy individuals**
- **Main tropism: white blood cells, endothelial cells**
- **Transmission occurs by body fluids**
- **Primary infection is often asymptomatic in healthy individuals**
- **From species origination on CMV has been within the human population (mutual adaptation)**
- ***Immune responses to CMV are by far the most potent anti-viral responses in humans***

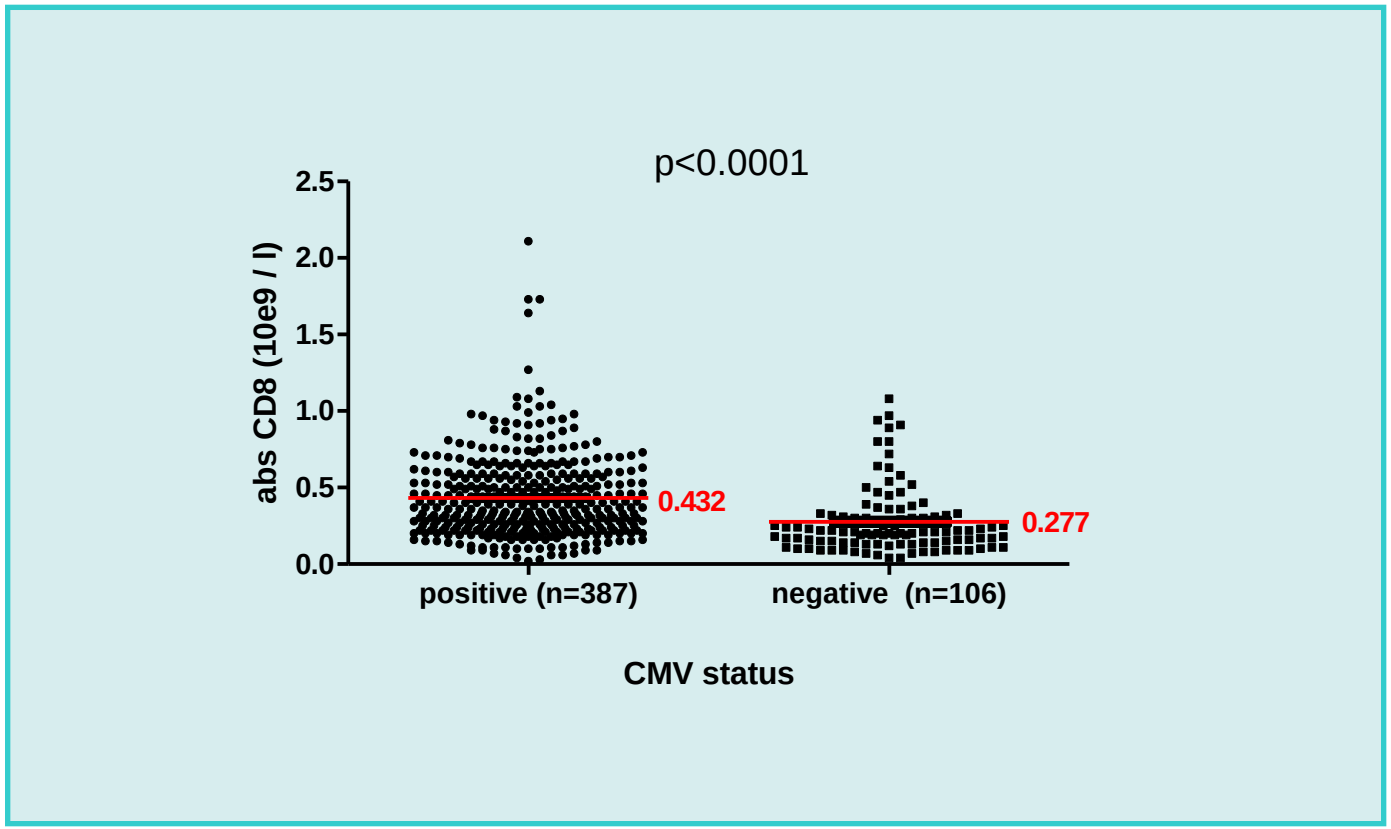
Changes in CD8+ T cell subsets as a consequence of primary CMV infection after kidney transplantation







CMV latency induces an increase in the number of circulating $CD8^+$ T cells



Changes induced in the lymphocyte pool by HCMV

- Appearance of high numbers of $CD8^+CD27^-$ T cells with constitutive effector functions
- Increase in CD8+ T cell percentages and numbers
- **Emergence of $CD4^+CD28^-$, cytolytic cells**
- **Expansion of $V\gamma2^-$ $\gamma\delta$ T cells**
- **Increase in $NKG2C^+$ NK cells**

Attrition of memory T cells

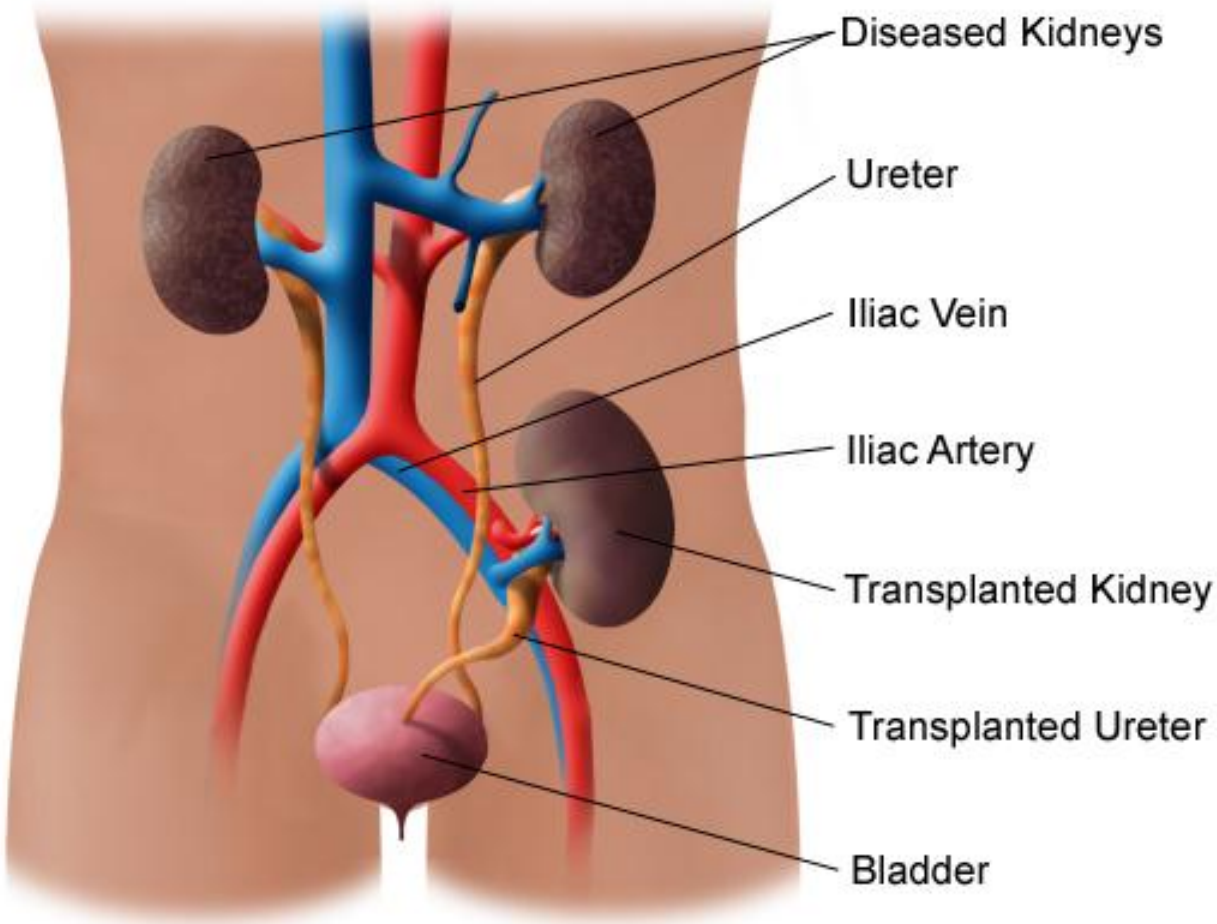
- **It has been proposed that the number of memory ($CD8^+$) T cells in a host is inflexible, and that individual cells are constantly competing for limited space.**

- **Infections or vaccines that introduce over-abundant quantities of memory CD8 T cells could have detrimental consequences for the host by displacing naive cells and memory T cells specific for previous infections.**

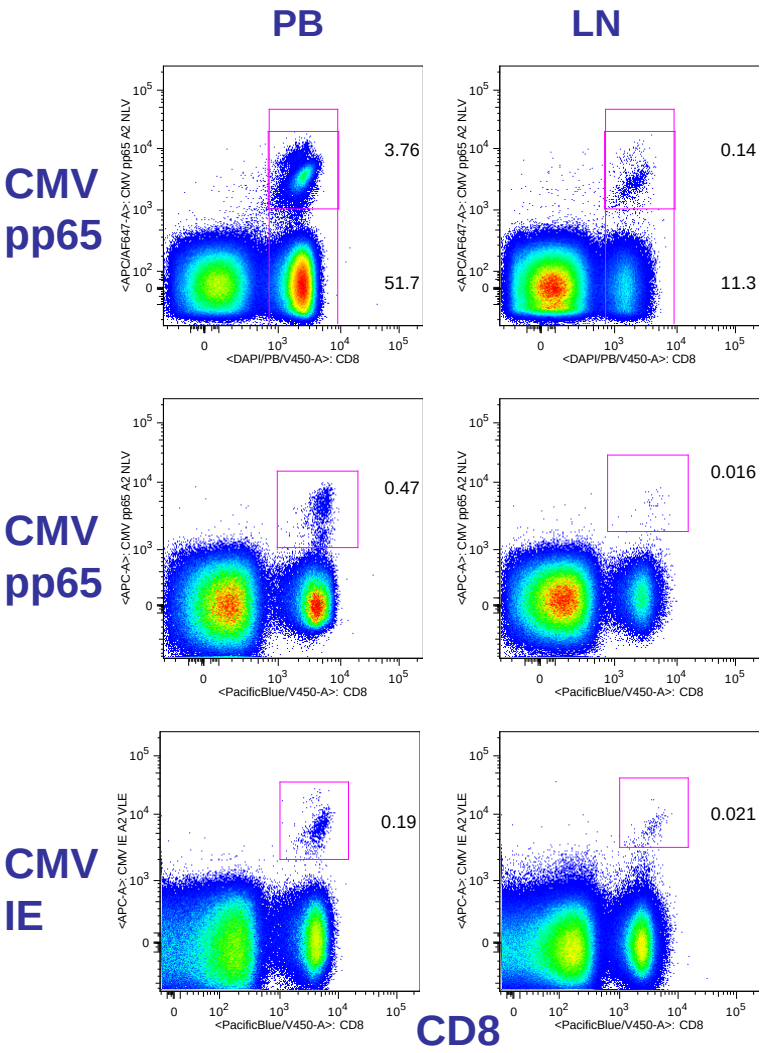
- **(Especially) elderly frequently have strong expansions of (oligoclonal) $CD8^+$ T cells that are often associated with latent cytomegalovirus infection.**

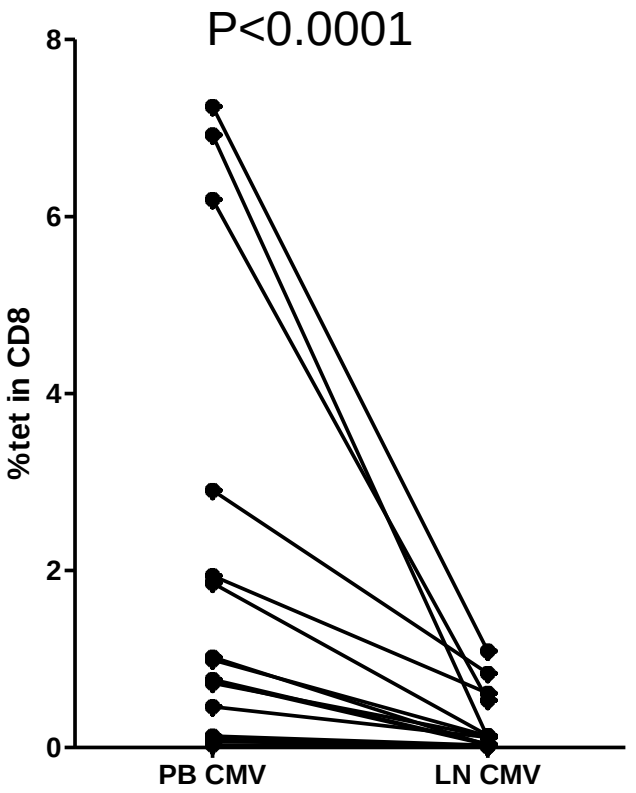
➢ **Could occupation of immunological space by these cells in Lymph Nodes be contribute to low responses in CMV-infected people?**

Isolation of lymphnodes from the para-iliacal area



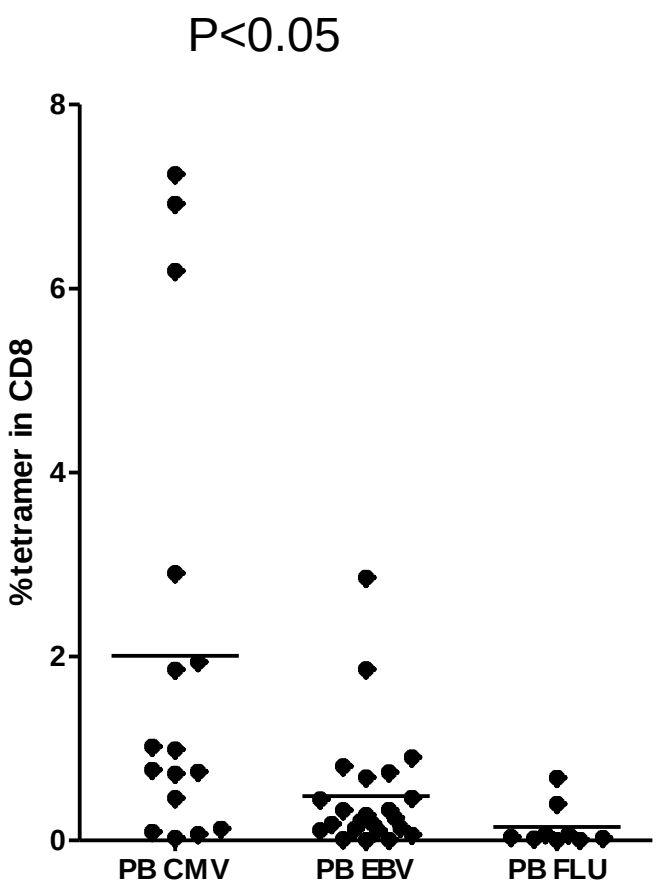
CMV-specific CD8+ T cells have a low frequency in Lymph Nodes

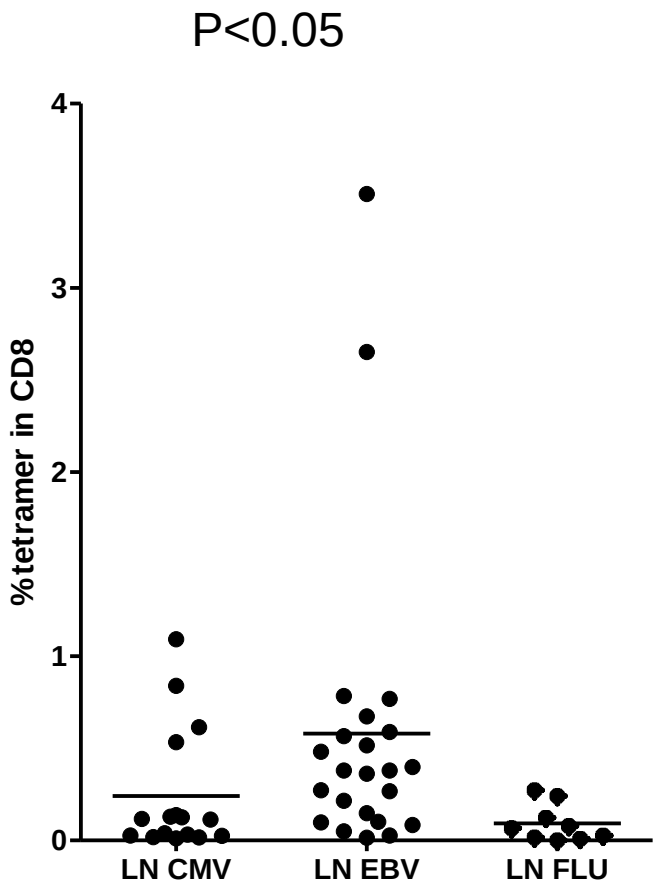




Remmerswaal et al, BLOOD, 2012

In lymph nodes EBV-specific cells exceed CMV-reactive





Could CMV-expanded ($CD8^+$) T cells interfere with priming of naive and memory T cells in human Lymph Nodes?

Unlikely,

CMV-specific $CD8^+$ T cells do not accumulate in lymph nodes and also $CD4^+CD28^-$ cells are largely excluded

(Havenith et al., Int Immunol, 2014)

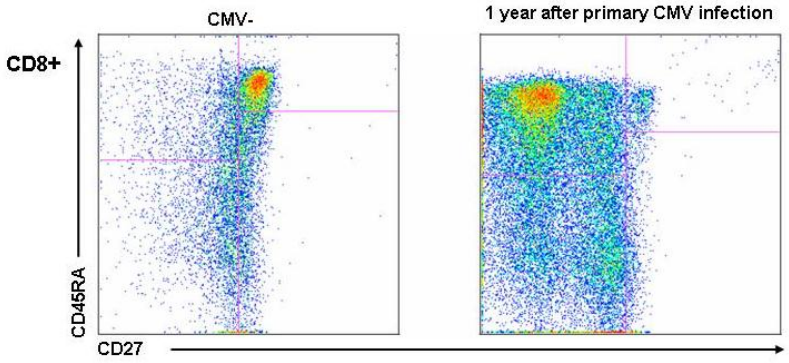
If not space, what about function?

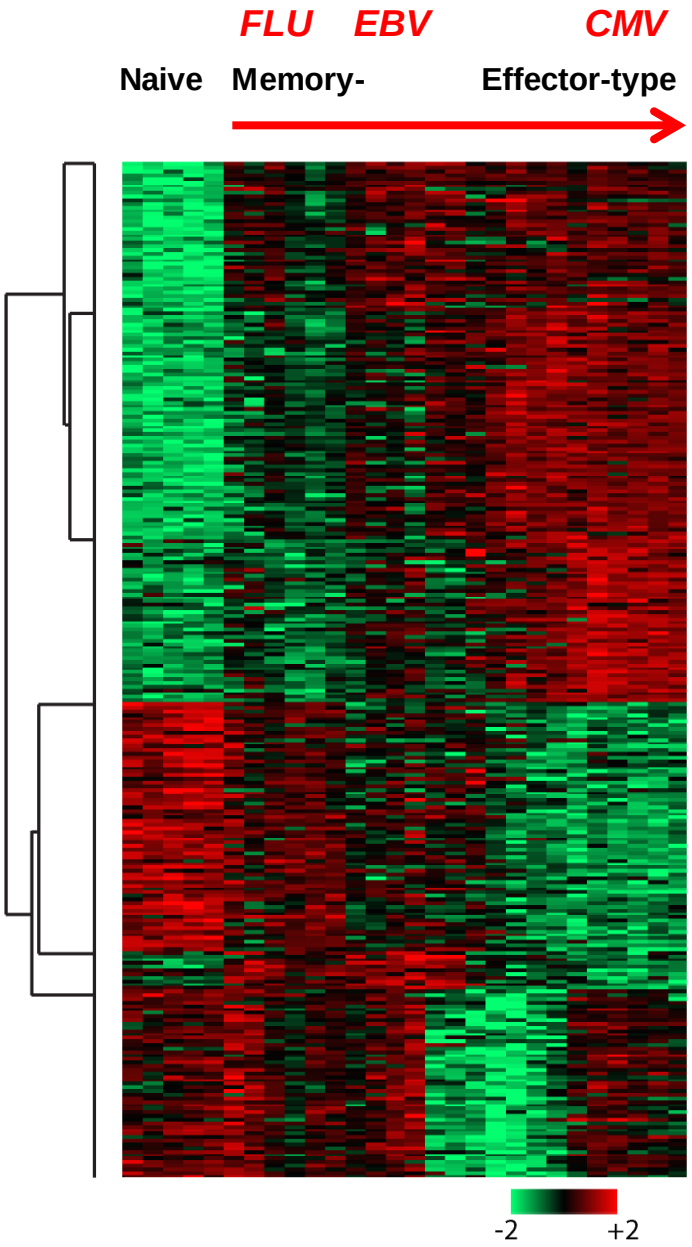
Properties of $CD8^+CD45RA^+$ $CD27^-$ T cells

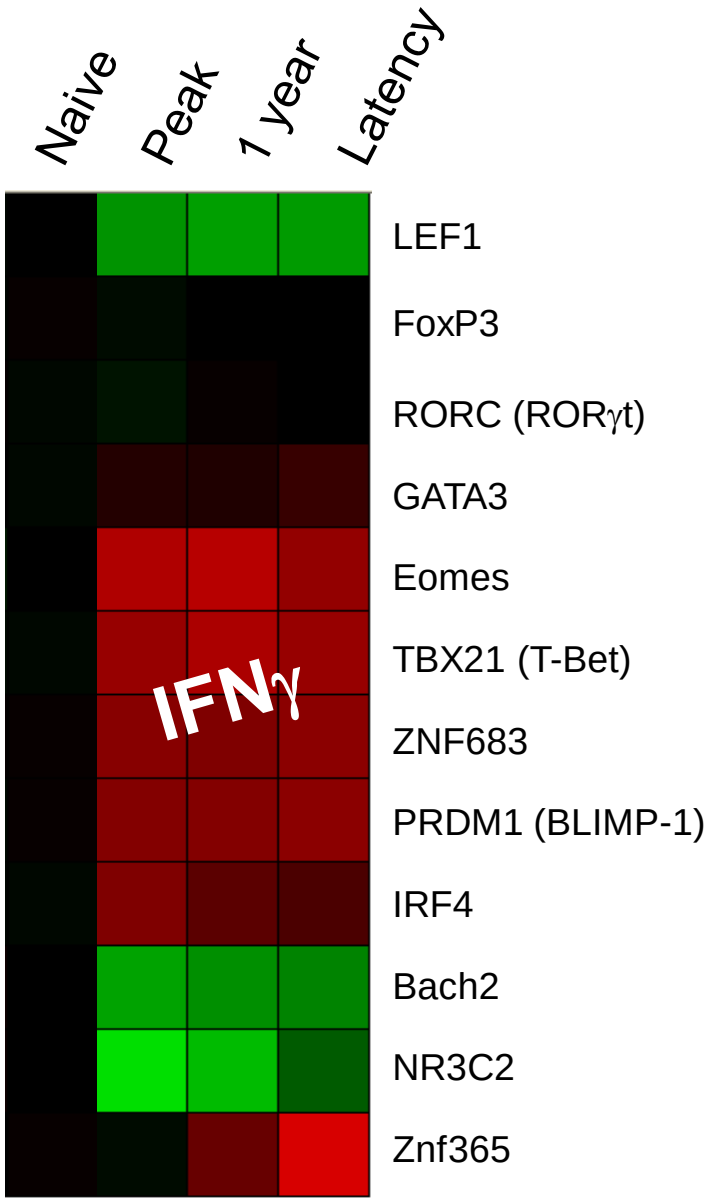
- **Population of resting T cells with low proliferation and low death rate *(Wallace et al., J Immunol, 2004)***
- **Characteristic marker profile: $CCR7^-$, $CD28^-$, $CD57^+$, $2B4^+$, $CD11a^{bright}$, GPR56, CX3CR1**
- **Inducible expression of IFNγ and TNFα, but not IL2**
- **Constitutive expression of perforin, granzymes A and B; direct cytolytic activity: *resting* effector-type cells**
- **Population increases with age and in situations of mild immunosuppression**

Gradual proteome changes with increased T cell differentiation

Michiel van Aalderen &
Maartje van den Biggelaar







Transcription factors regulated during human CMV-induced $CD8^+$ T cell differentiation

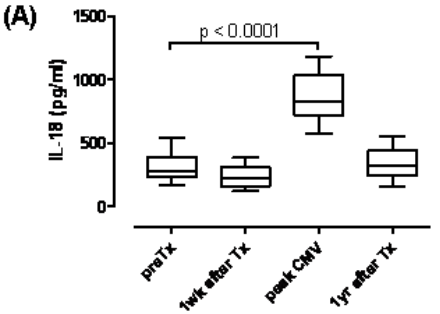
Hertoghs et al., J Clin Invest, 2010

CMV-specific CD8$^+$ T cells have an IFNγ signature

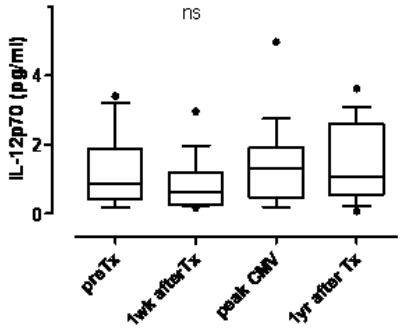
		Primary CMV infection		Healthy HCMV$^+$ donor	Healthy HCMV$^+$ donor	
Gene symbol	Accession Nr.	Peak	1 year	Latency	Effector type	Memory
IFNG	NM_000619	38,8	42,4	53,6	16,8	7,7
IFI27	NM_005532	25,3	17,3	*1,5*	*1,3*	*1,3*
IFI16	I_1997689	20,5	25,6	15,8	11,4	7,4
OAS1	NM_002534	18,2	4,7	*1,4*	*1,7*	*1,2*
IFI44L	NM_006820	11,5	-1,4	*-1,6*	*-1,3*	*-1,3*
IFI30	J03909	11,5	10,9	4,8	*-1,1*	*-1,1*
IRF4	NM_002460	10,0	5,2	4,0	5,6	2,7
ISG15	NM 005101	9,0	2,5	*1,6*	*1,6*	*1,5*
IFIT1	NM_001548	7,8	-1,2	13,7	3,9	*2,0*
IFIT3	NM_001549	7,0	1,2	24,8	5,8	2,8
MX1	NM_002462	5,3	-1,6	*-2,0*	-2,8	*-1,1*
ISG20	NM 002201	4,6	1,9	*2,0*	*1,8*	*1,8*
OASL	NM_003733	4,4	2,1	18,9	15,2	6,1
IFIT2	NM_001547	2,7	1,2	18,9	7,9	2,3
IFIT2	BC005987	2,3	1,5	20,5	17,1	4,8
IFNAR1	NM 000629	-1,6	-1,7	-2,6	*-1,4*	*1,3*
IFNGR2	NM_005534	-3,7	-4,0	-3,7	-3,0	-3,3

Type 1 response during primary CMV infection after renal Tx

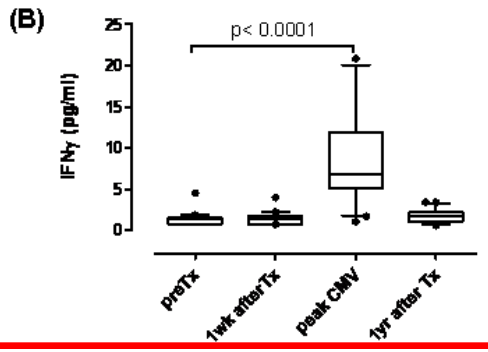
IL-18



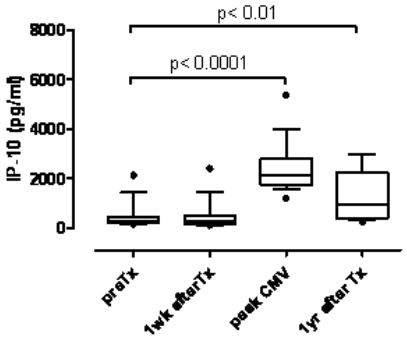
IL-12



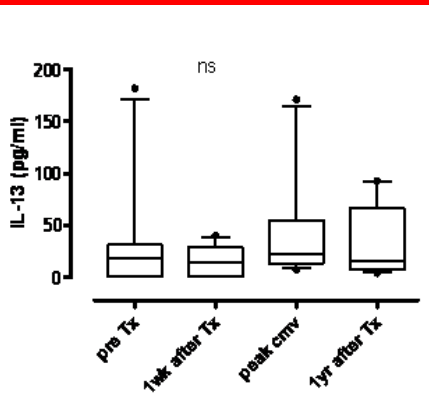
IFNγ



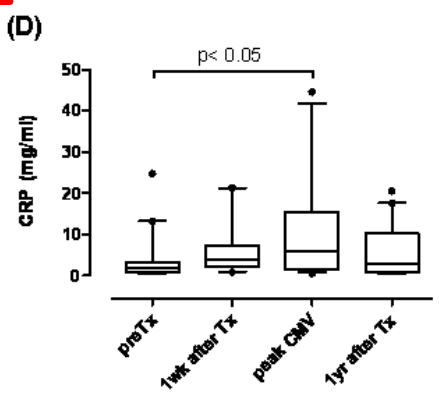
IP-10



IL-13

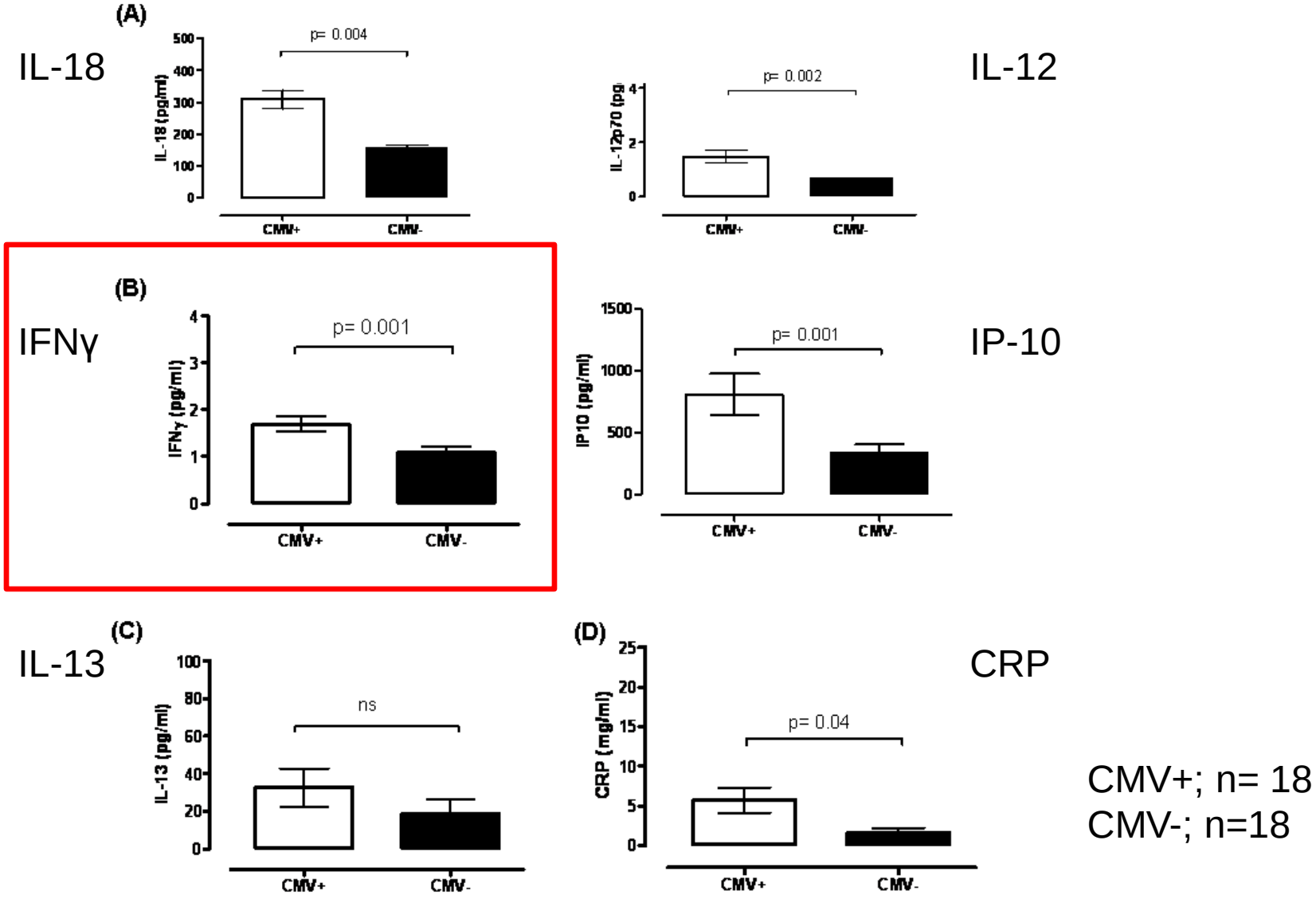


CRP



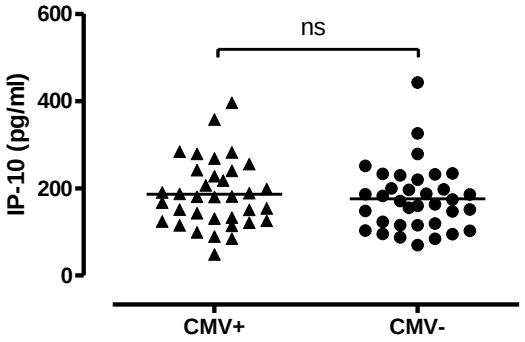
n= 18

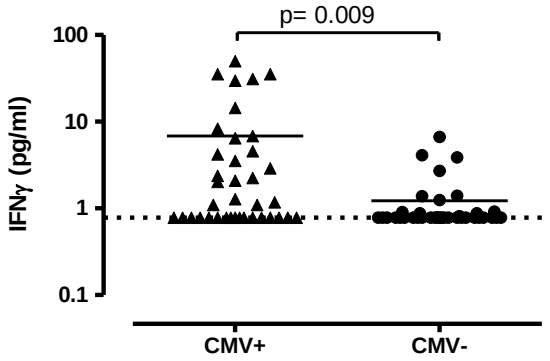
Type 1 responses during latent CMV after Tx

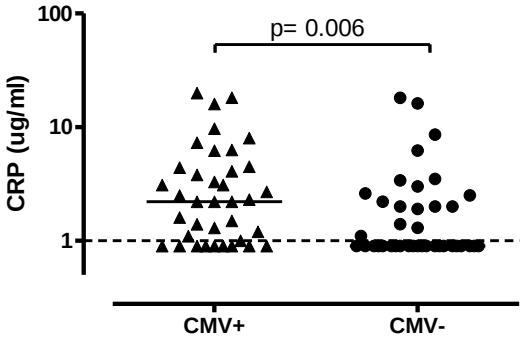


CMV+; n= 18
CMV-; n=18

CMV also induces systemic type 1 cytokine response in a subset of healthy individuals



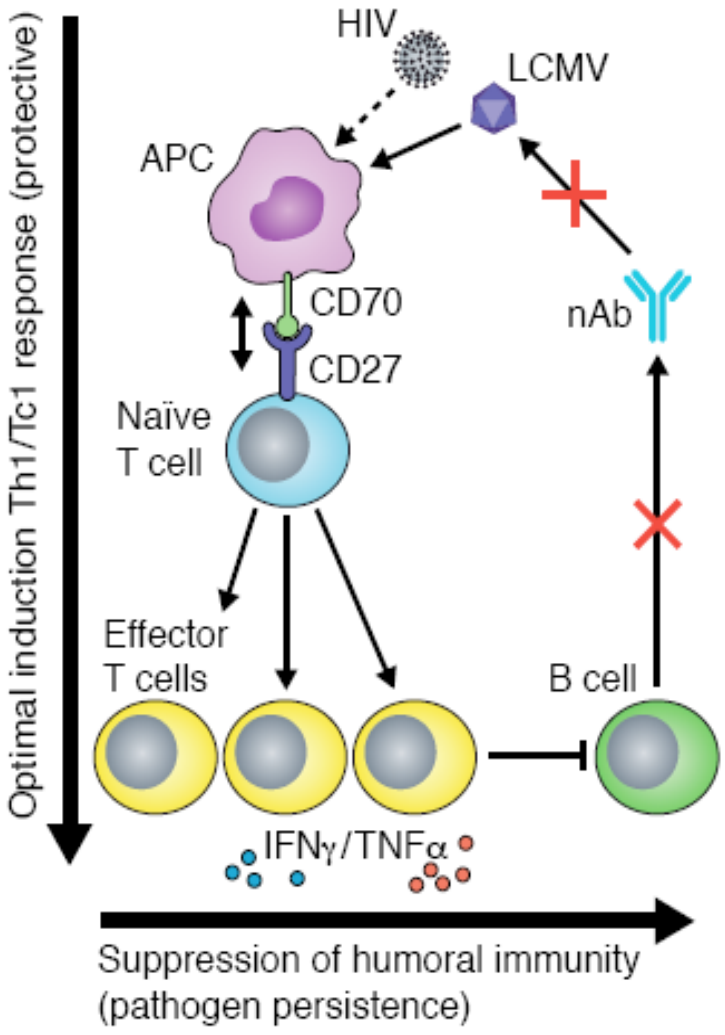




CMV+; n= 37
CMV-; n= 37

Van de Berg et al., J Inf Dis, 2010

You can’t have it all?



Nolte and van Lier, J.Exp.Med., 2006

Conclusions

- **The strong immune response to CMV is unlikely to restrict immunological space for naïve cells and memory cells in lymph nodes.**
  - ***Spleen, Bone Marrow?***

- **In mice (Vezys et al., *Nature,* 2009) hyperimmunization strongly increased vaccin-specific $CD8^+$ T cell numbers but preserved immunological memory and CD4, B and naïve CD8 numbers.**

- **Possibly, factors produced by cells specific for latent viruses (i.e. CMV) may downregulate immune responses (IFNγ)**

➢ **Is this good news for vaccination strategies in the CMV-infected elderly?**
  ➢ ***Adjuvants?***

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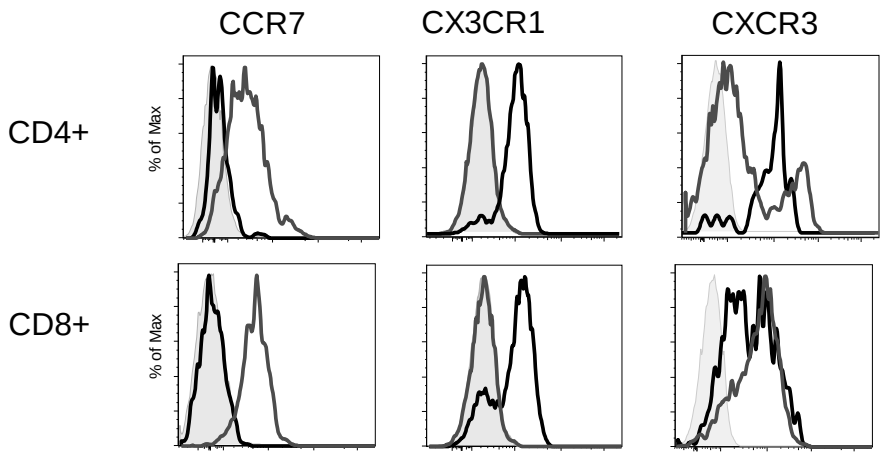
CMV-induced, effector type T cells also express CXCR3 (= IP10 receptor)



Grey= naive
Black= effector-type

> CMV-induced effector-type CD4+ and CD8+ T cells have chemokine receptors that allow them to migrate to stimulated endothelium