Cytomegalovirus

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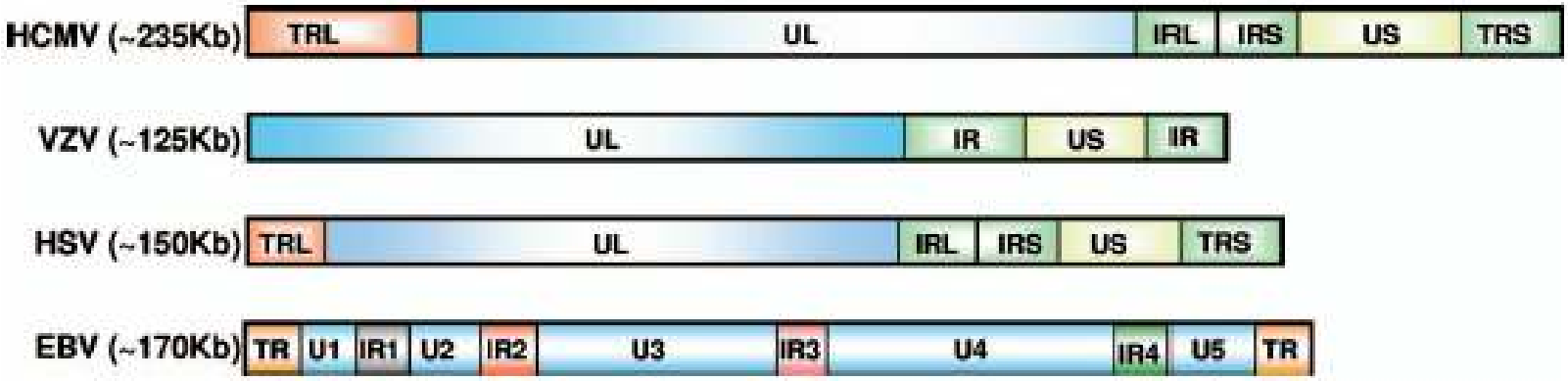
KLASİK SORULAR

- Nereden vucudumuza giriyor ?
- İlk şikayetler neler ?
- İlk nerede replike oluyor?
- Diğer dokulara nasıl yayılıyor ?
- Hangi dokulara zarar verebilir (Mİ) ?
- Viral klirens oluyor mu? Yoksa persiste mi ediyor ? Nerede latent kalıyor ?
- Başkalarına nasıl bulaşıyor ?

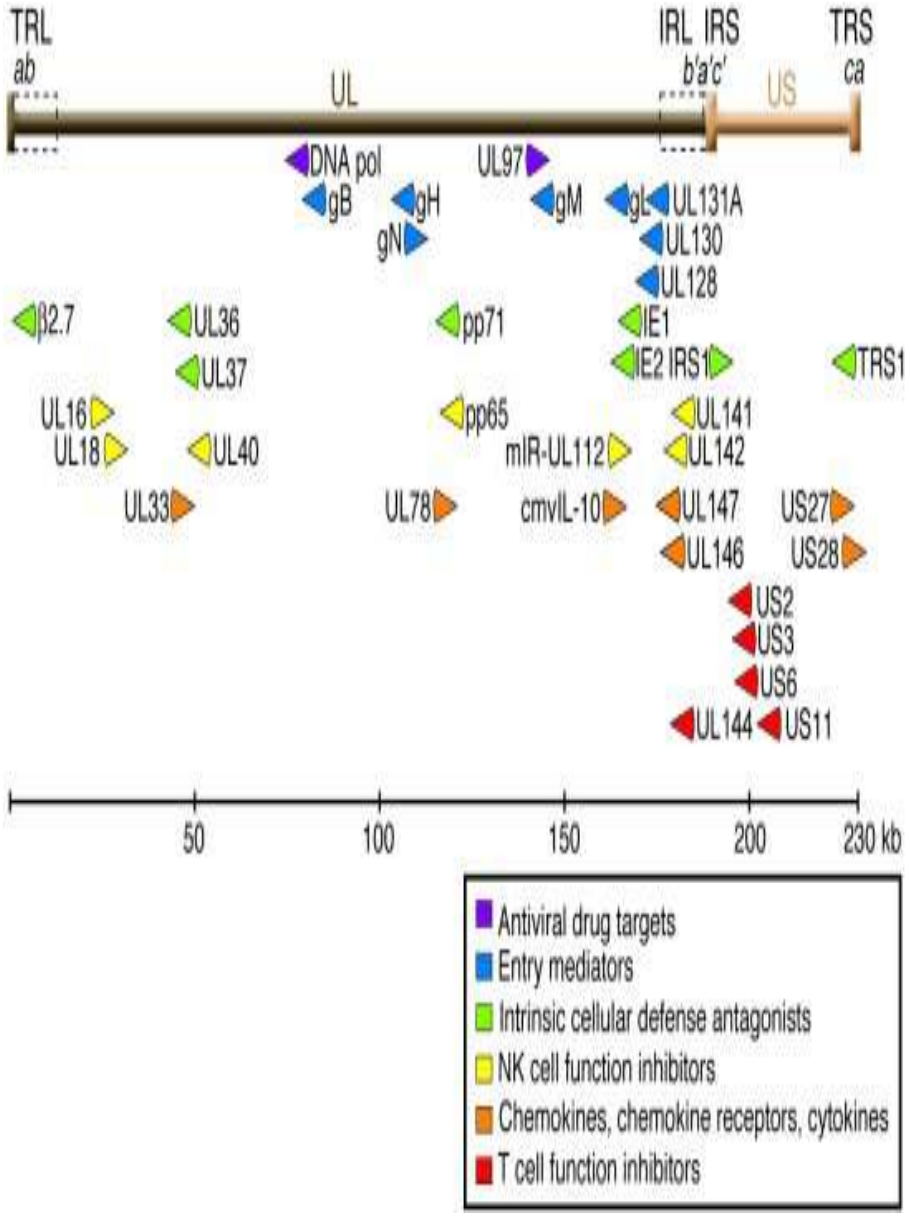
KLASİK OLMAYAN SORULAR

- Neden ikozahedral yapıda ?
- Neden çok fazla protein kodlayan gen taşıyor?
- İnterhost ve intrahost variety ne demek ?
- Kompartmanisazyon ne demek ?
- Neden zarar versin?

YAŞLI,TECRÜBELİ VE GİZEMLİ



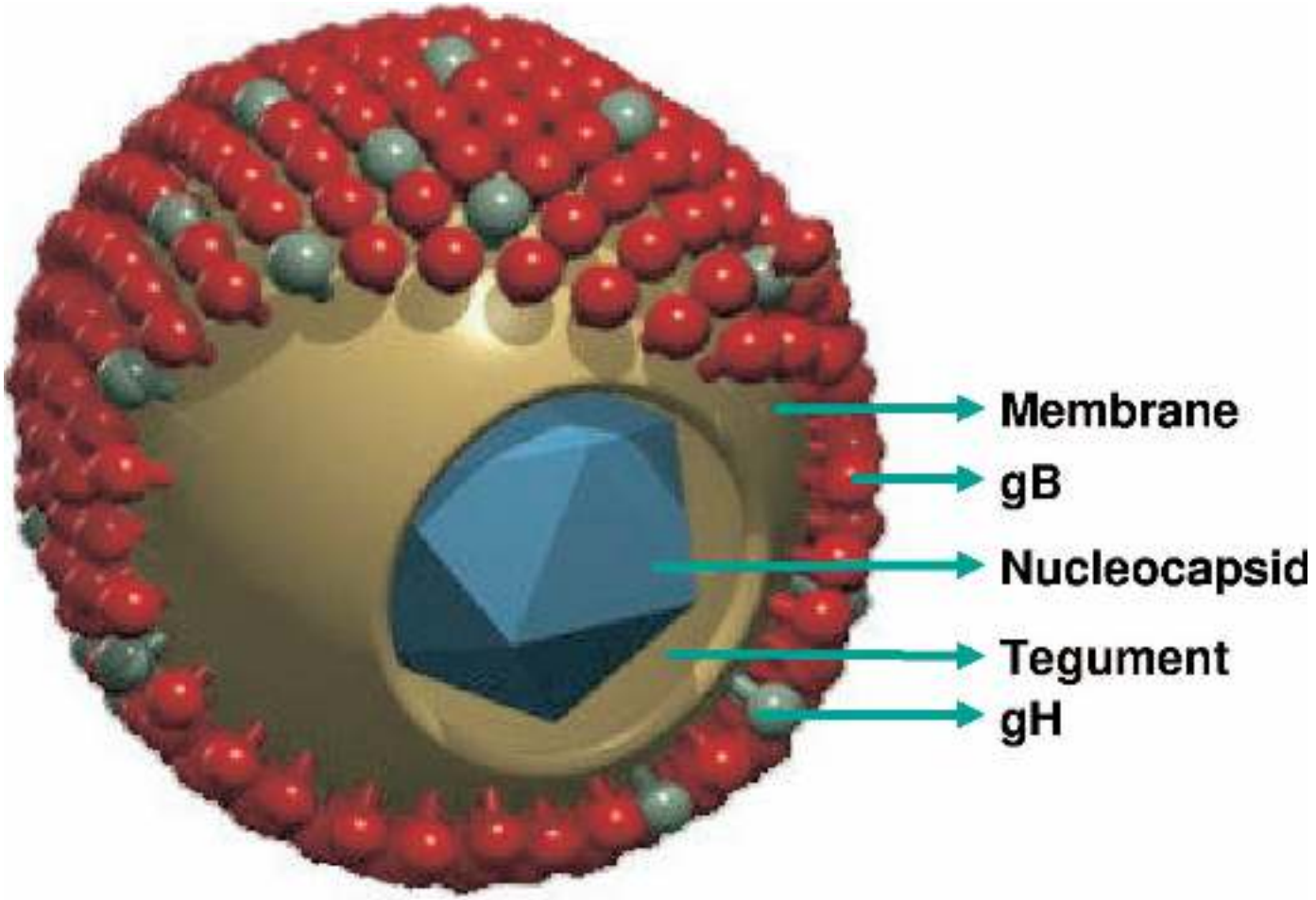
doi:10.1128/CMR.00034-08



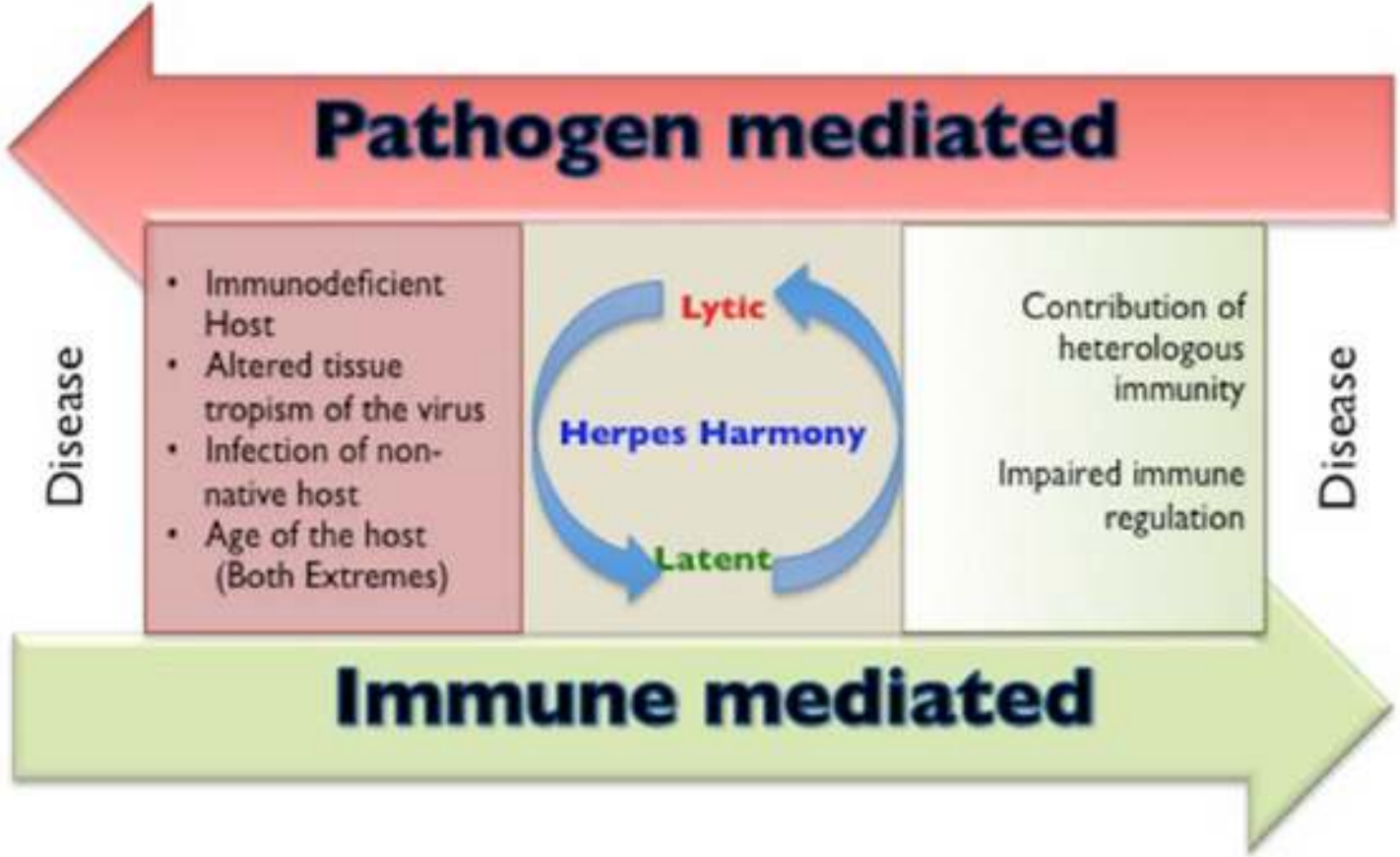
J Clin Invest DOI: 10.1172/JCI45449

UL18	Acts as a decoy for NK cell–MHCI homolog
US3, US10	Retention of MHCI in endoplasmic reticulum
US2, US11	Degradation of MHCI and MHCII
US6	Attacks the TAP complex and interfere with cytosolic peptide transport
pp65	Inhibits proteasome activity

Herpesviruses: Harmonious Pathogens but Relevant Cofactors in Other Diseases?

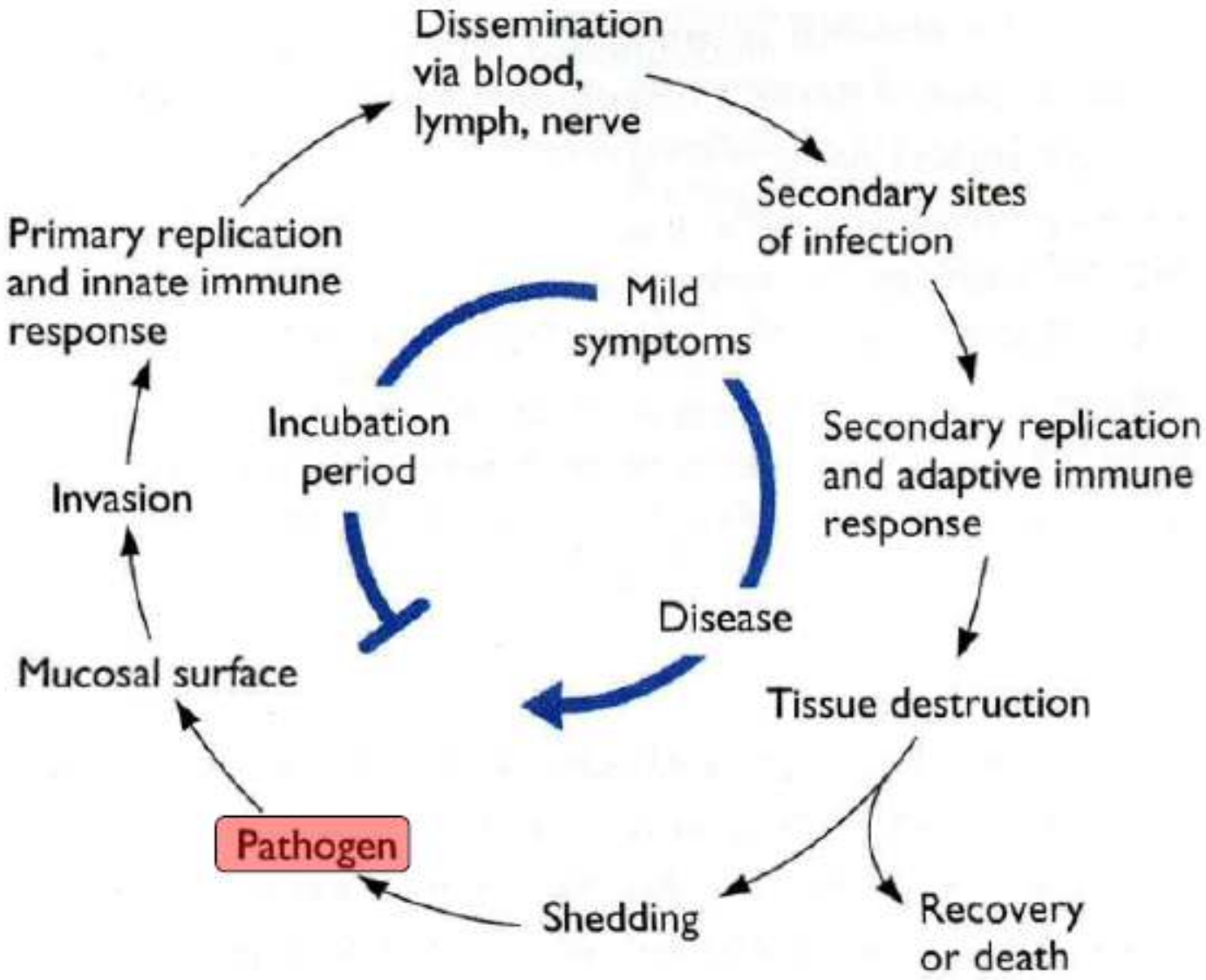


doi:10.1128/CMR.00034-08



doi: 10.3389/fcimb.2018.00177

Views of viral pathogenesis



The Journal of
Pathology and Bacteriology
Vol. LX, No. 4

616.9—022.6 (ectromelia) : 619.993.2

THE CLINICAL FEATURES AND PATHOGENESIS OF MOUSE-POX (INFECTIOUS ECTROMELIA OF MICE)

FRANK FENNER

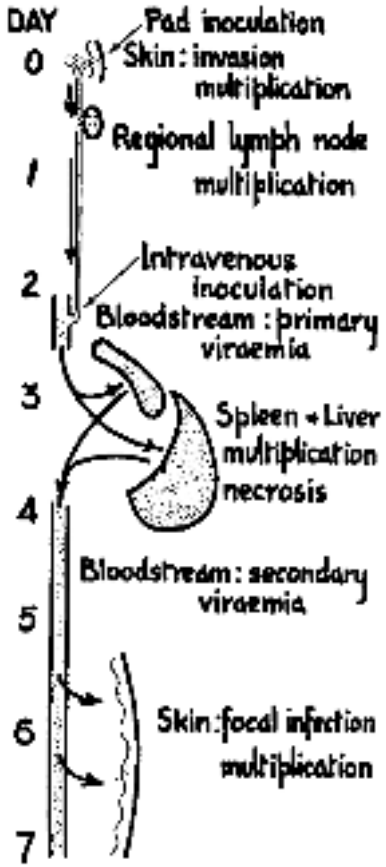
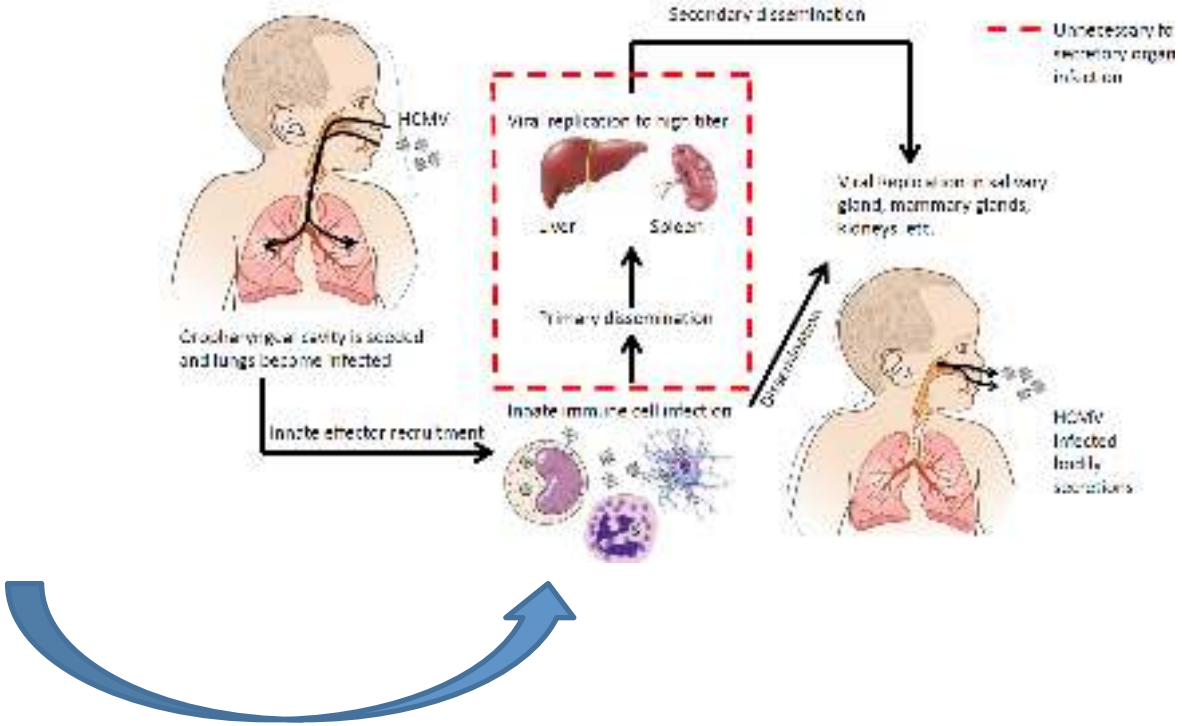
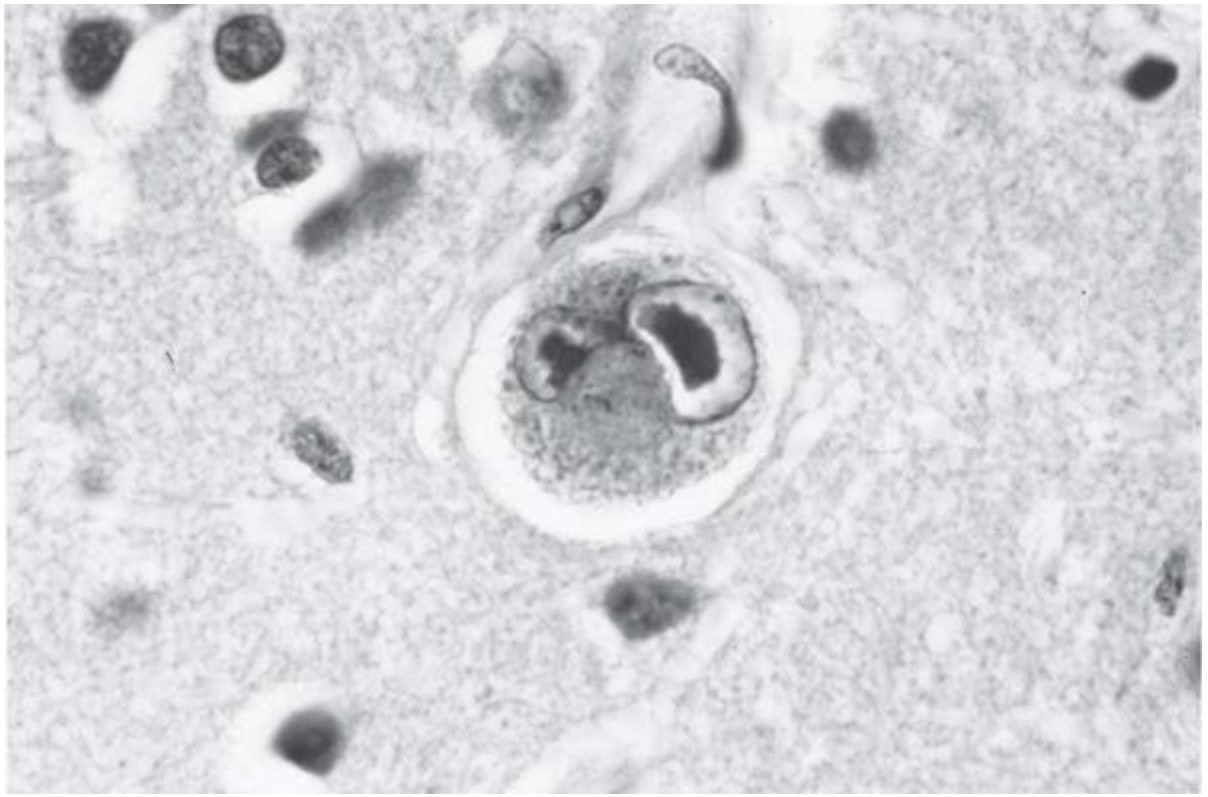


FIG. 10.—The pathogenesis of mouse-pox: a diagram illustrating the progress of infection during the incubation period.



1946-2018

BU GÖZÜ BİR YERDEN TANIYORUM



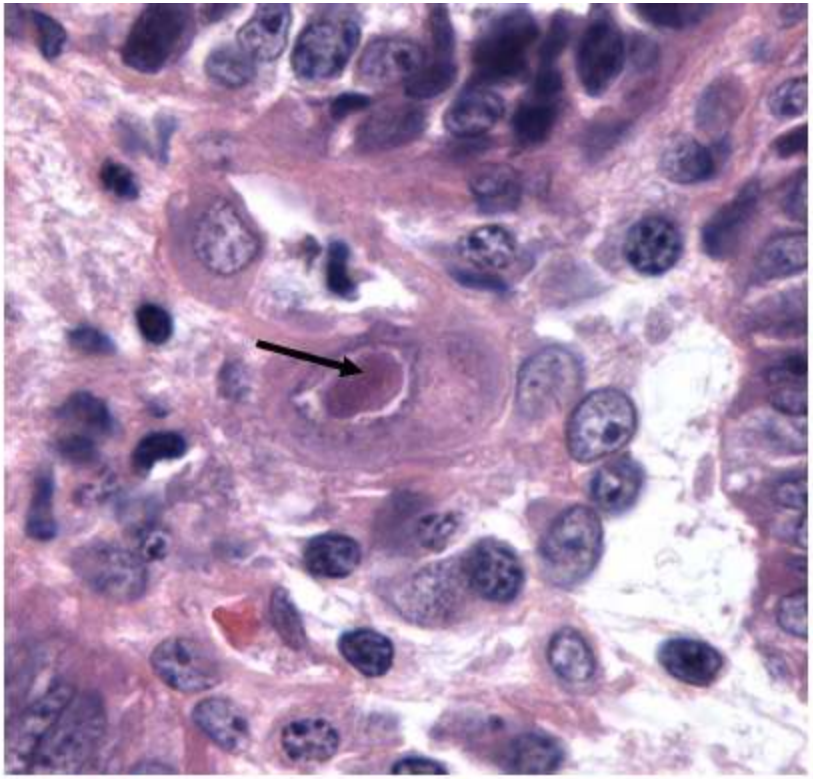
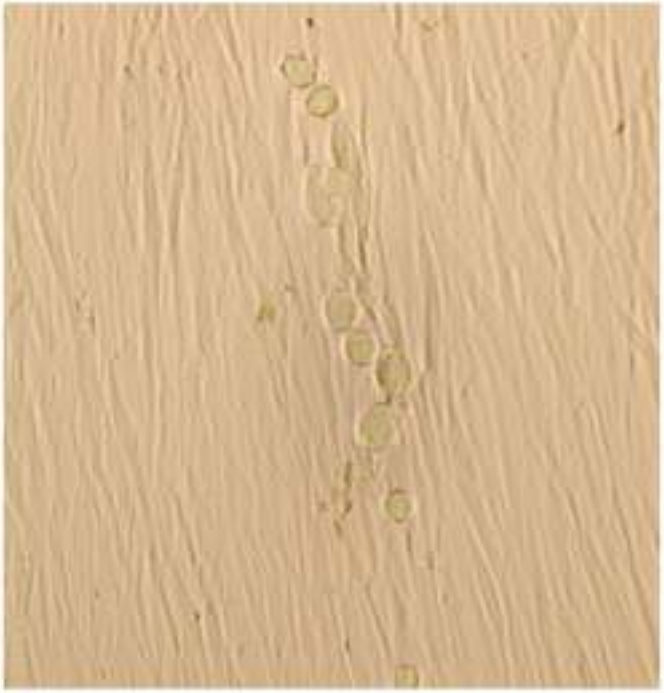


FIGURE 3 This biopsy specimen from a patient with cytomegalovirus colitis shows a classic "owl-eye" intranuclear inclusion (arrow) and intracytoplasmic inclusions. The dense intranuclear inclusion with surrounding halo is formed when the mass of viral particles shrinks away from the nuclear membrane during fixation. While herpes simplex virus intranuclear inclusions can have a similar appearance, CMV is the only member of the herpesviridae family that contains both intranuclear and intracytoplasmic inclusions. Hematoxylin and eosin stain, 1000x oil immersion.

SİTOPATİK SÜREÇ ?
Raymond Razonable
4 HAFTA
FİBROBLAST

FIGURE 1 Cytomegalovirus-induced cytopathic effects. Unstained preparation; 100X magnification.



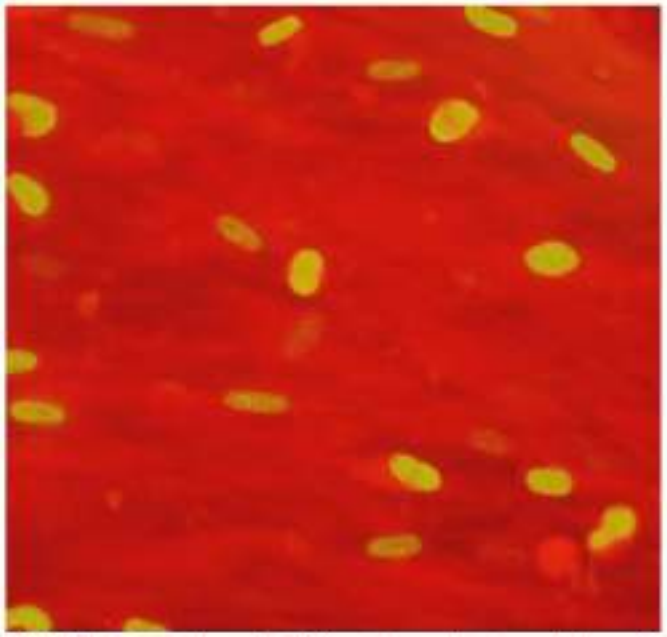


FIGURE 2 Detection of CMV antigens in the nucleic acid of infected MCR-5 cells. Following shell-vial culture, cells are stained with fluorescently-labeled antibodies which detect CMV immediate early antigen. Magnification 200X.

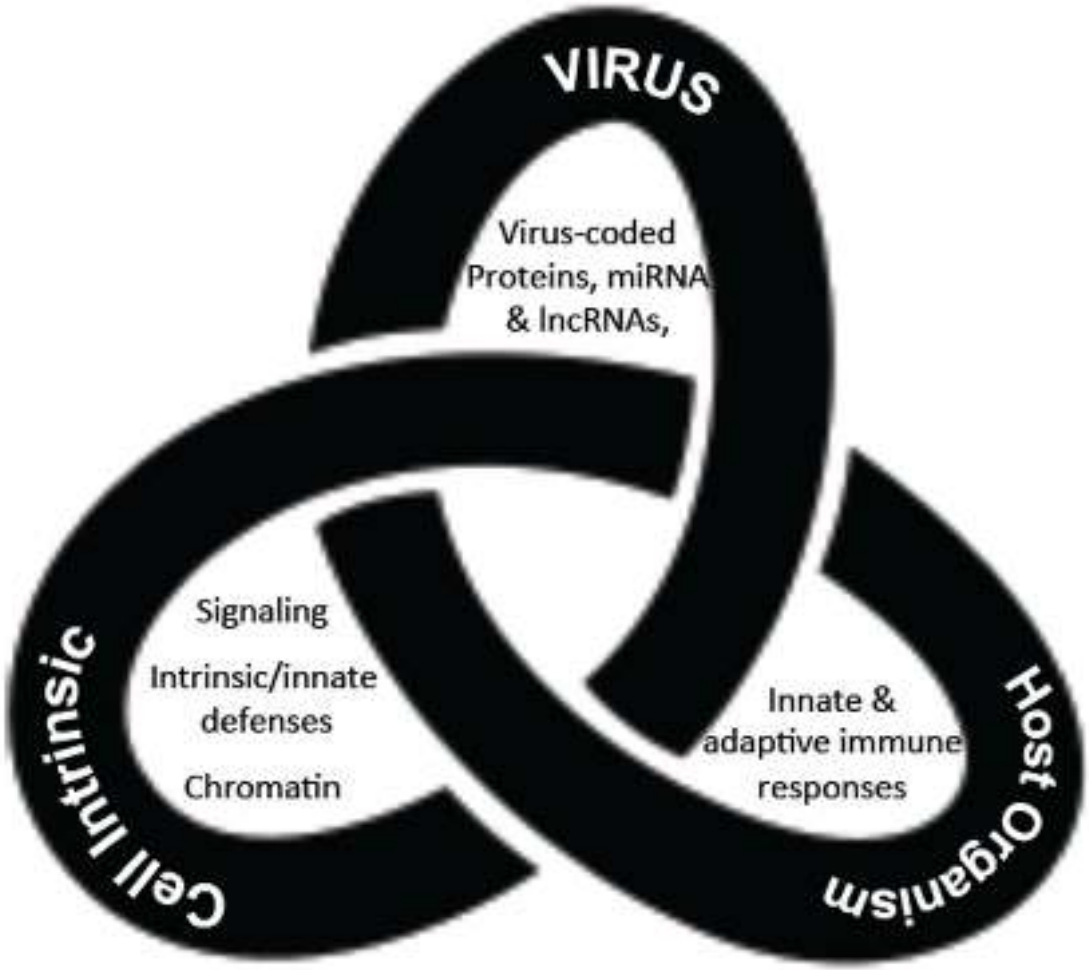
YUVALANMAK (LATENCY)

NEREDE?

- SAPTANAMAYAN VİRAL REPLİKASYON
- KAN (LÖKOSİTLER,TRANSFÜZYON)
- ORGAN PARANKİM (ORGAN NAKLİ)

  NASIL ?
- CmvIL-10 (LAcmvIL-10)

YUVALANMAK (LATENCY)



KENDİ YUVASINI YAPMAK!

nature microbiology

ARTICLES

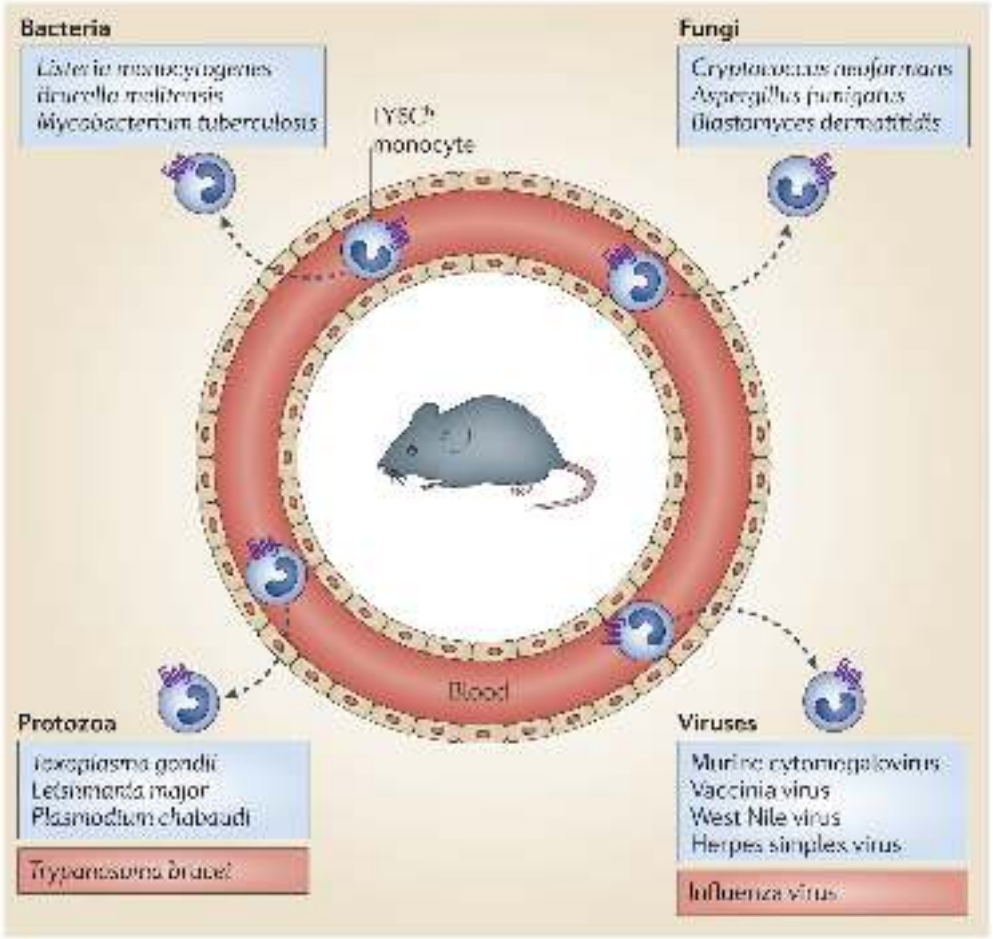
https://doi.org/10.1038/s41564-018-0131-9

Human cytomegalovirus reprogrammes haematopoietic progenitor cells into immunosuppressive monocytes to achieve latency

Dihan Zhu[1,6], Chaoyun Pan[1,6], Jingxue Sheng[2,6], Hongwei Liang[1,3,6], Zhen Bian[1,3], Yuan Liu[3], Phong Trang[2,4], Jianguo Wu[5*], Fenyong Liu[2*], Chen-Yu Zhang[1*] and Ke Zen[1,3*]

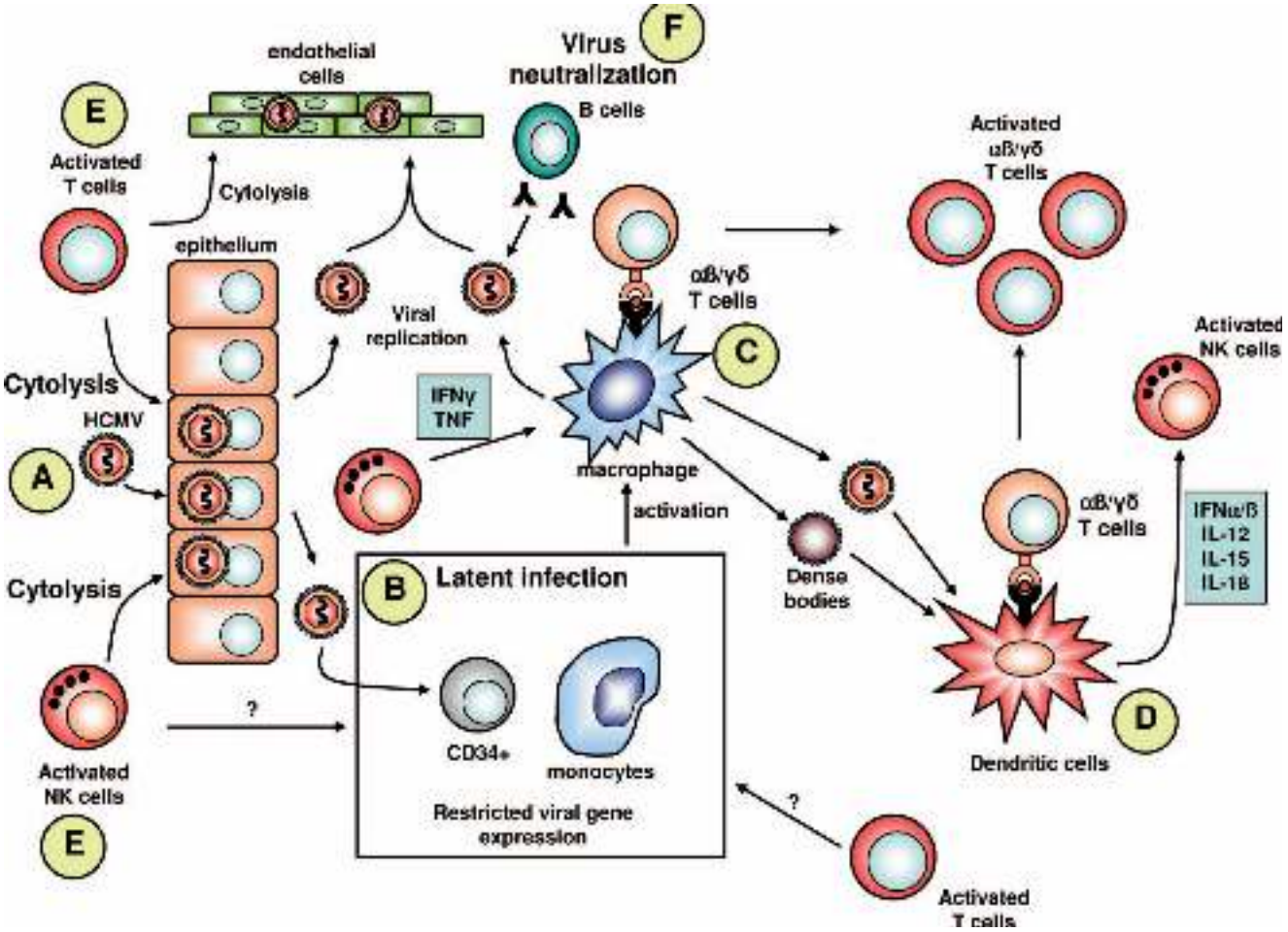
The precise cell type hosting latent human cytomegalovirus (HCMV) remains elusive. Here, we report that HCMV reprogrammes human haematopoietic progenitor cells (HPCs) into a unique monocyte subset to achieve latency. Unlike conventional monocytes, this monocyte subset possesses higher levels of B7-H4, IL-10 and inducible nitric oxide synthase (iNOS), a longer lifespan and strong immunosuppressive capacity. Cell sorting of peripheral blood from latently infected human donors confirms that only this monocyte subset, representing less than 0.1% of peripheral mononuclear cells, is HCMV genome-positive but *immediate-early*-negative. Mechanistic studies demonstrate that HCMV promotes the differentiation of HPCs into this monocyte subset by activating cellular signal transducer and activator of transcription 3 (STAT3). In turn, this monocyte subset generates a high level of nitric oxide (NO) to silence HCMV *immediate-early* transcription and promote viral latency. By contrast, the *US28*-knockout HCMV mutant, which is incapable of activating STAT3, fails to reprogramme the HPCs and achieve latency. Our findings reveal that via activating the STAT3–iNOS–NO axis, HCMV differentiates human HPCs into a longevous, immunosuppressive monocyte subset for viral latency.

Otonomi ?



Nat Rev Immunol. ; 11(11): 762–774. doi: 10.1038/nri3070.

Doğal ve edinsel immunite işbirliği



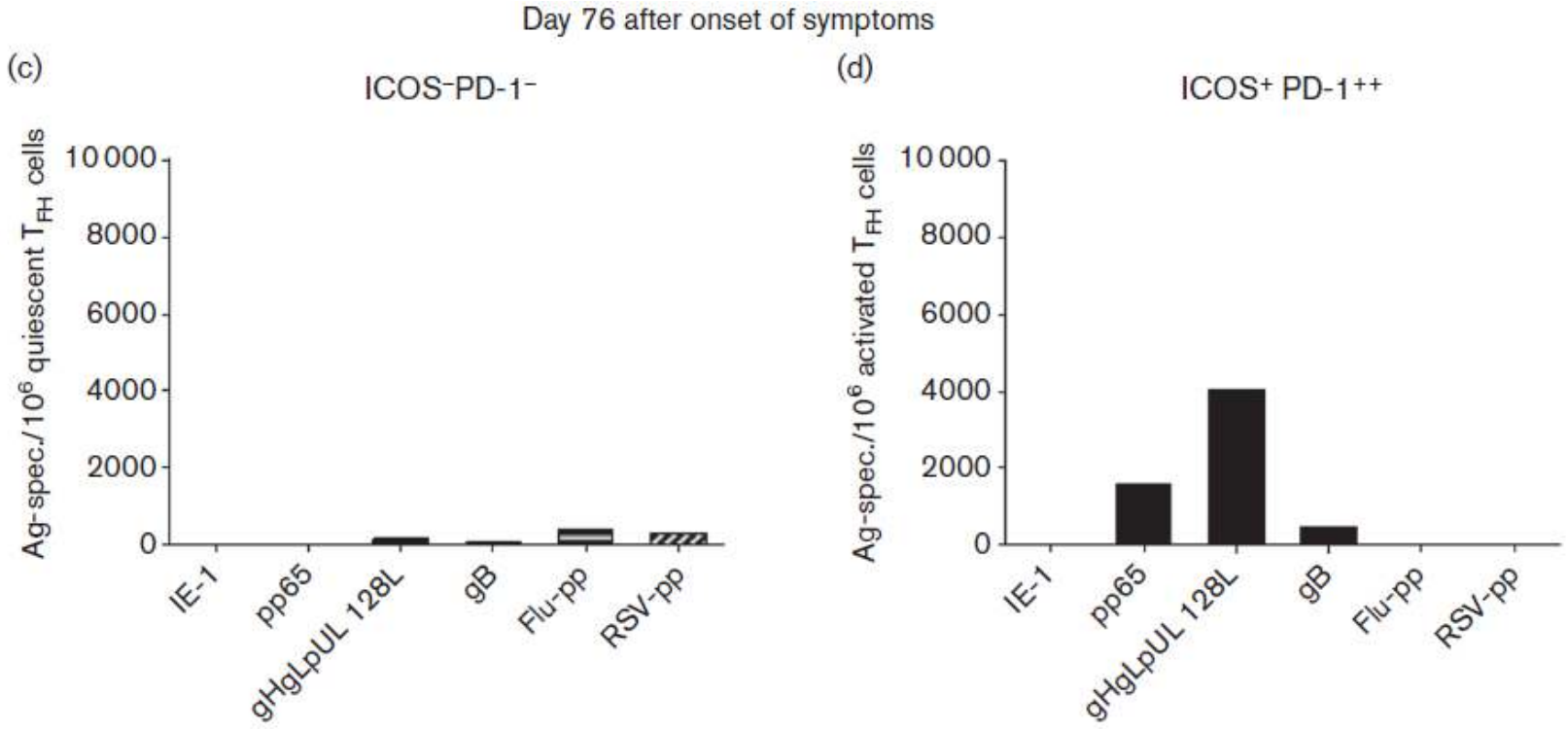
CLINICAL MICROBIOLOGY REVIEWS, Jan. 2009, p. 76–98
0893-8512/09/$08.00+0 doi:10.1128/CMR.00034-08

HÜCRE TROPİZMİ

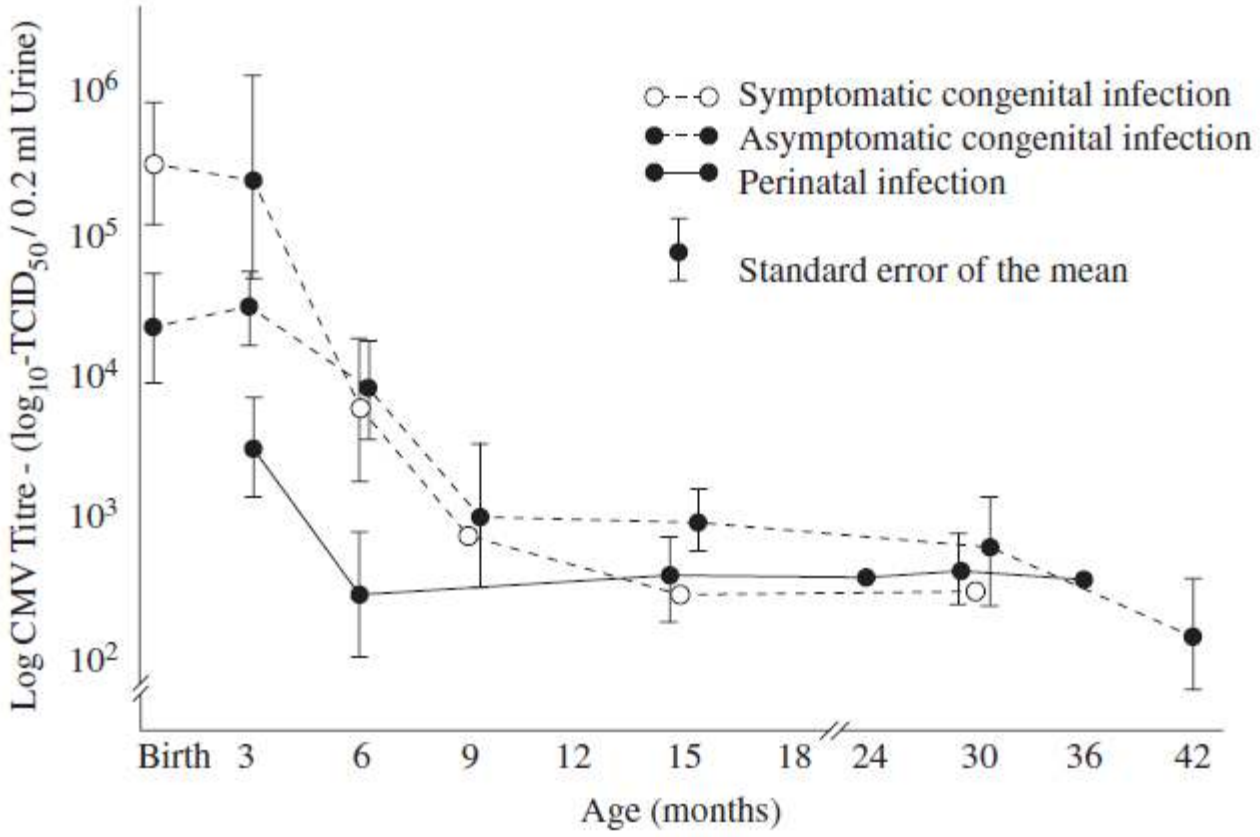
- gH/gL/pUL128-pUL130-Pul131a
- gH/gL/gO

- PDGFRα (knockout mice)

www.pnas.org/cgi/doi/10.1073/pnas.1806305115

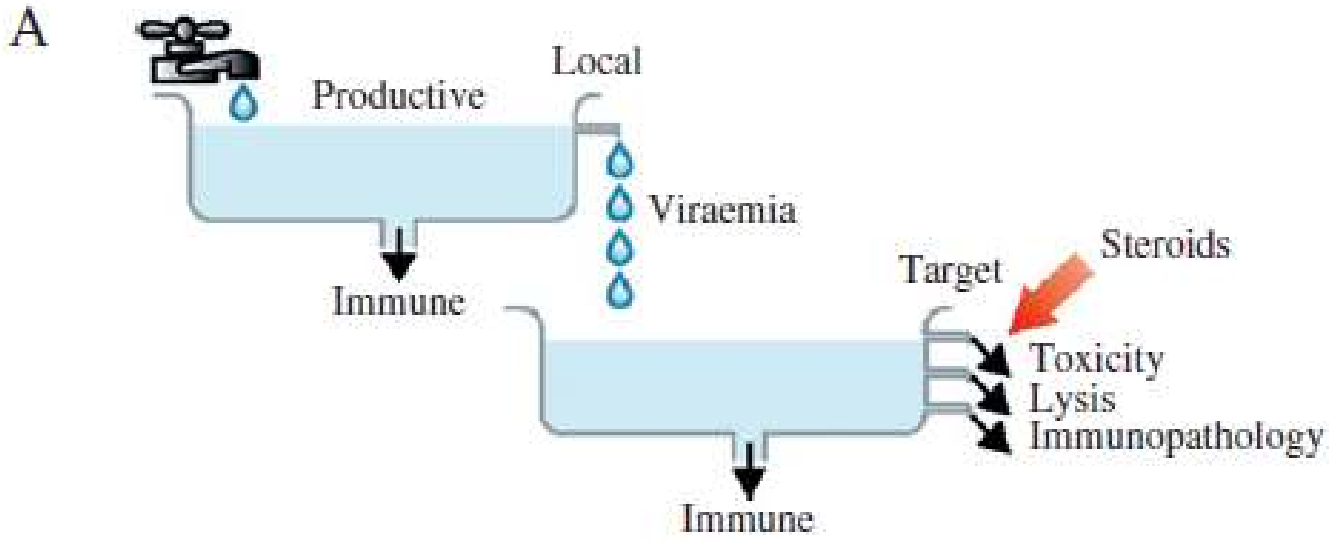

Day 76 after onset of symptoms
(c)
ICOS⁻PD-1⁻
Ag-spec./10⁶ quiescent T_FH cells
10 000
8000
6000
4000
2000
0
IE-1
pp65
gHgLpUL 128L
gB
Flu-pp
RSV-pp
(d)
ICOS⁺ PD-1⁺⁺
Ag-spec./10⁶ activated T_FH cells
10 000
8000
6000
4000
2000
0
IE-1
pp65
gHgLpUL 128L
gB
Flu-pp
RSV-pp

VİRAL YÜK

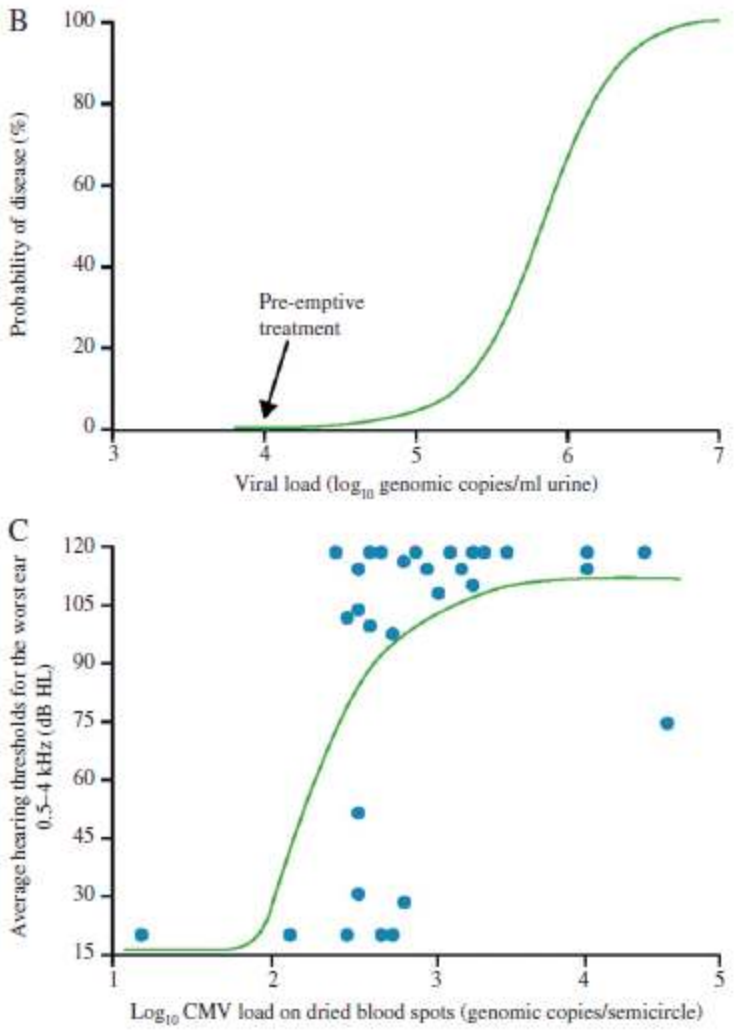


Journal of Infectious Diseases, 1975, Vol. 132, Iss.5, pages 568–577

’the wrong virus in the wrong cell line using the wrong end point



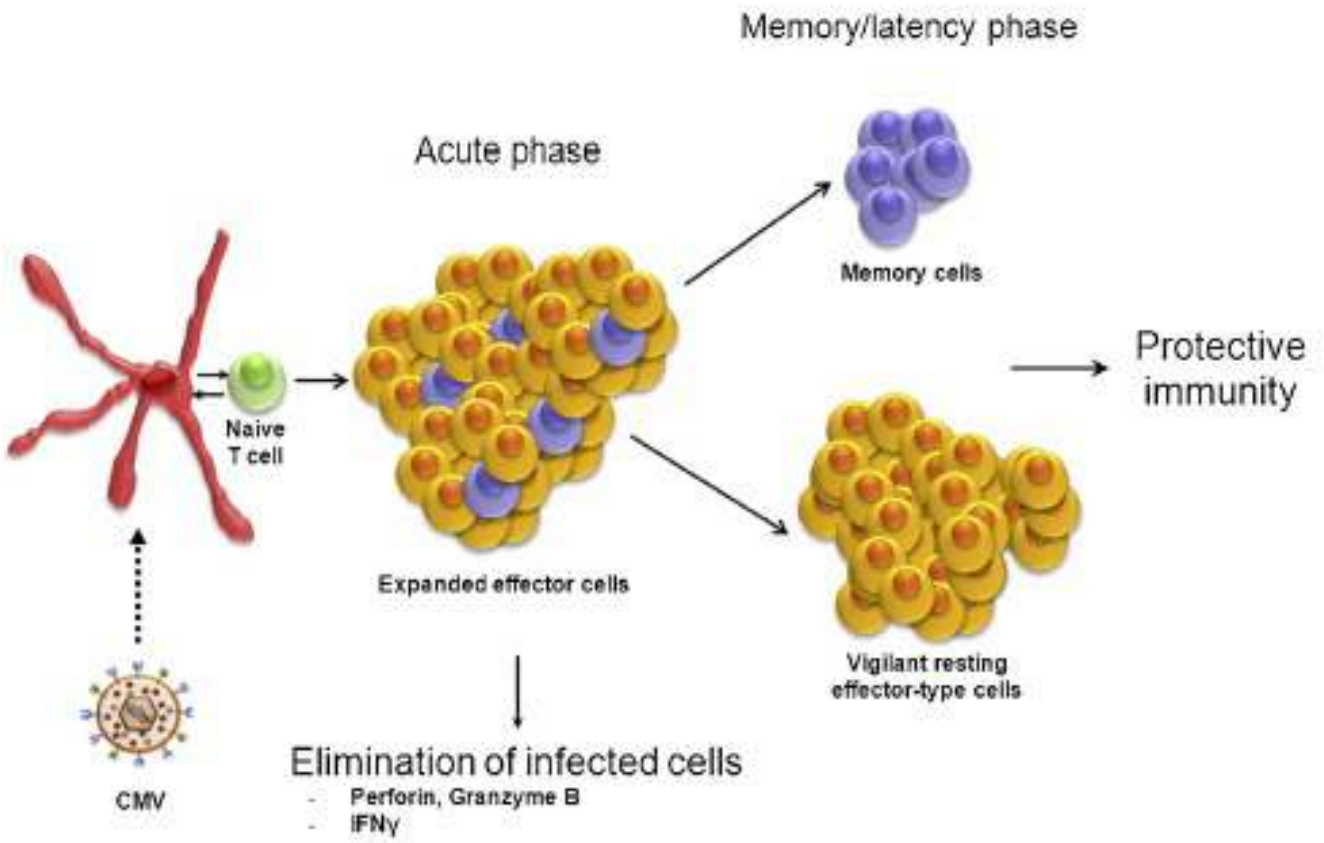
Journal of Pathology
J Pathol 2015; **235**: 288–297



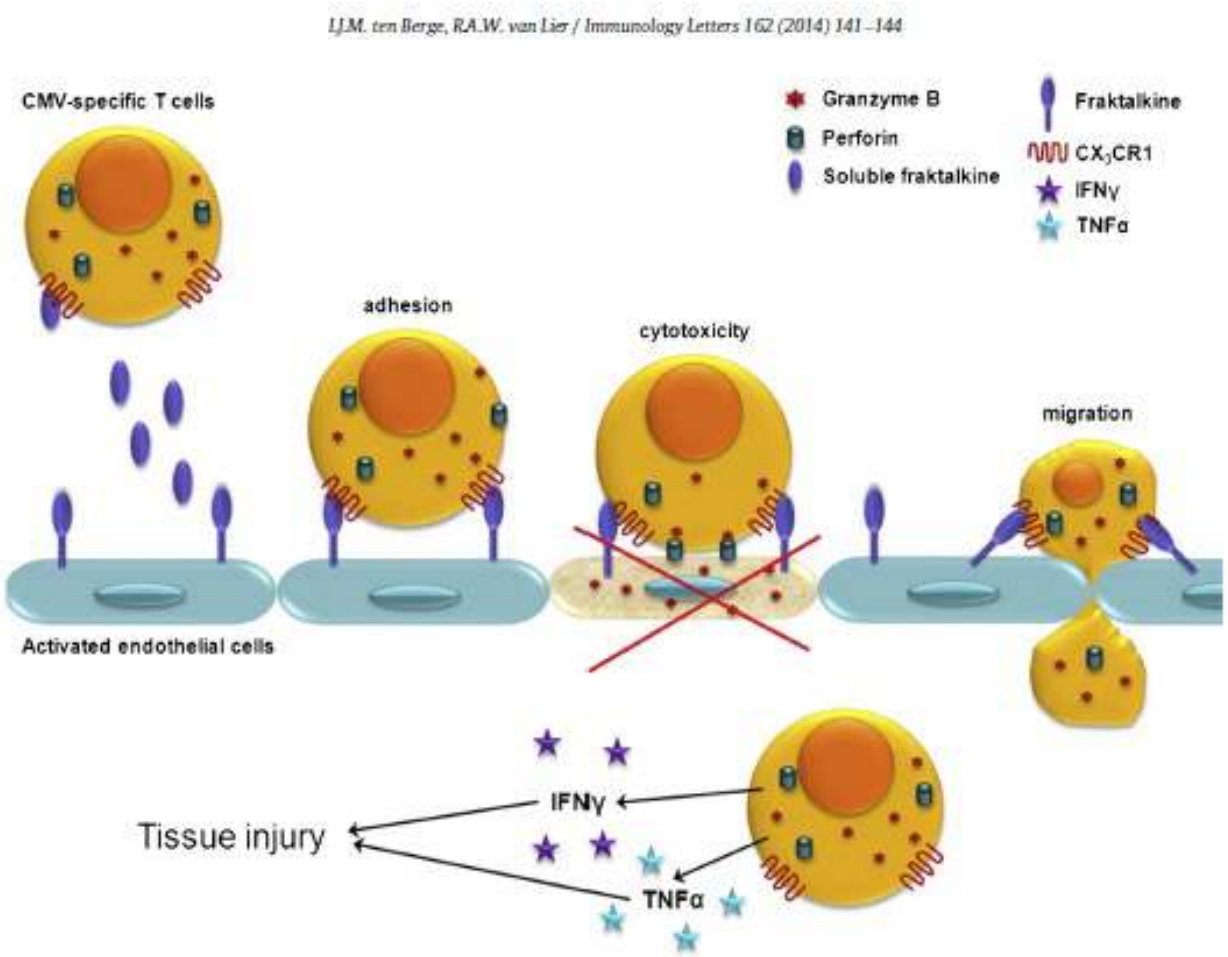
Journal of Pathology
J Pathol 2015; **235**: 288–297

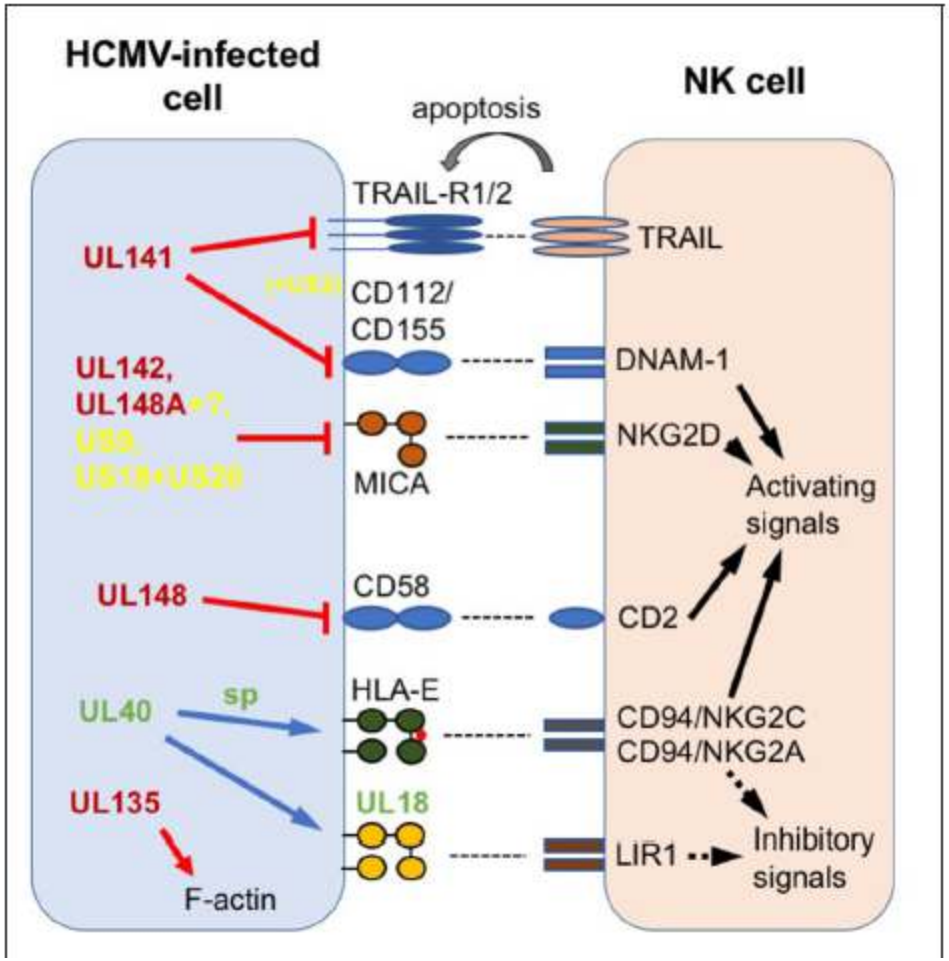
Kafa karışıklığı (koruyuculuk)

I.J.M. ten Berge, R.A.W. van Lier / Immunology Letters 162 (2014) 141–144



Kafa karışıklığı (Hasar)

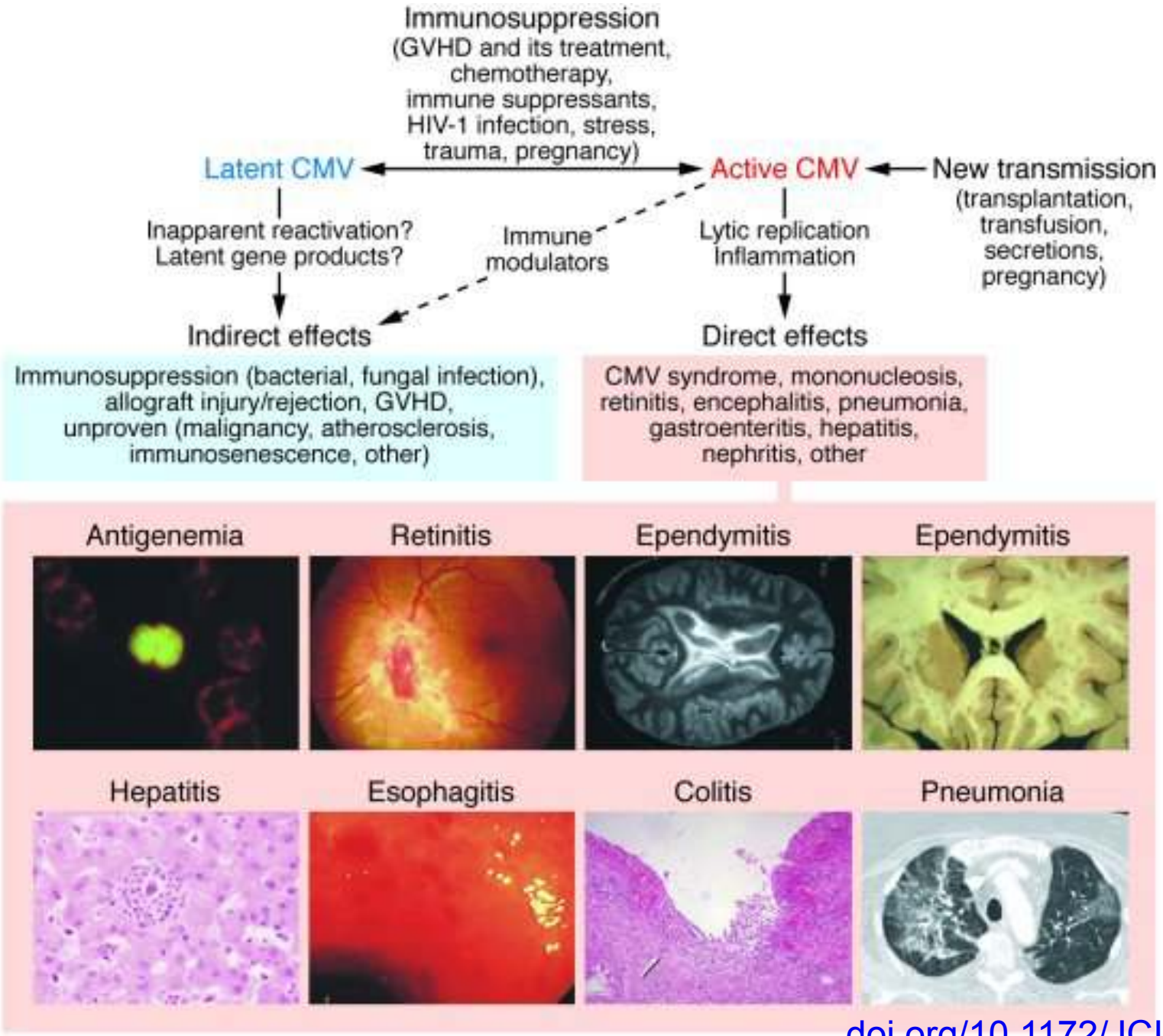




HCMV-Encoded NK Modulators: Lessons From *in vitro* and *in vivo* Genetic Variation

KLİNİK BAŞLIKLAR

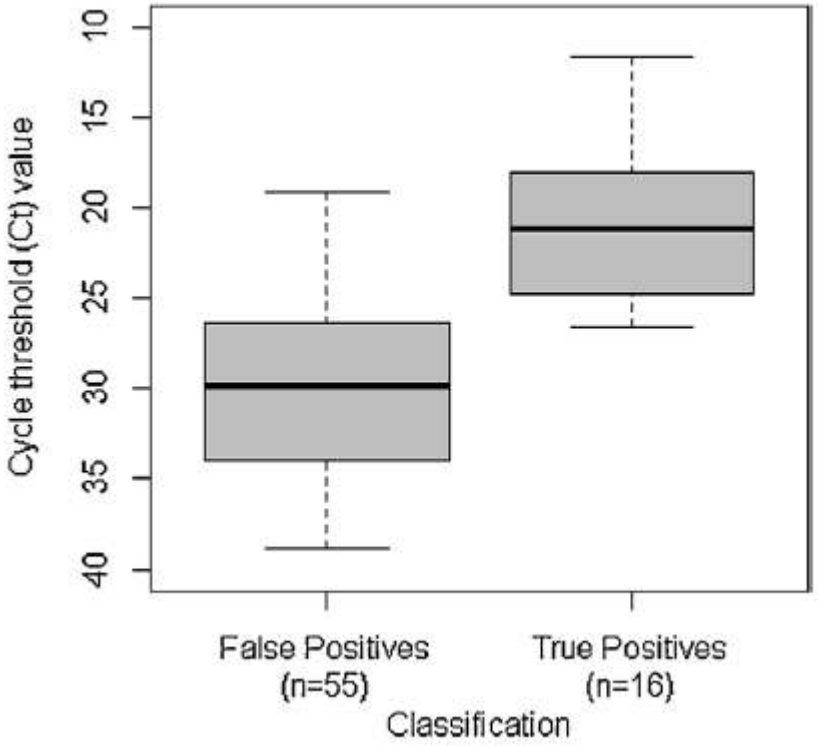
- Mononükleoz sendrom
- Konjenital enfeksiyon (edinsel immunite ?)
- HIV
- SOT
- HSCT
- Gebelik (kondisyon değişikliği)
- Sepsis (kondisyon değişikliği)
- YBÜ’ ne yatış (kondisyon değişikliği)



doi.org/10.1172/JCI45449.

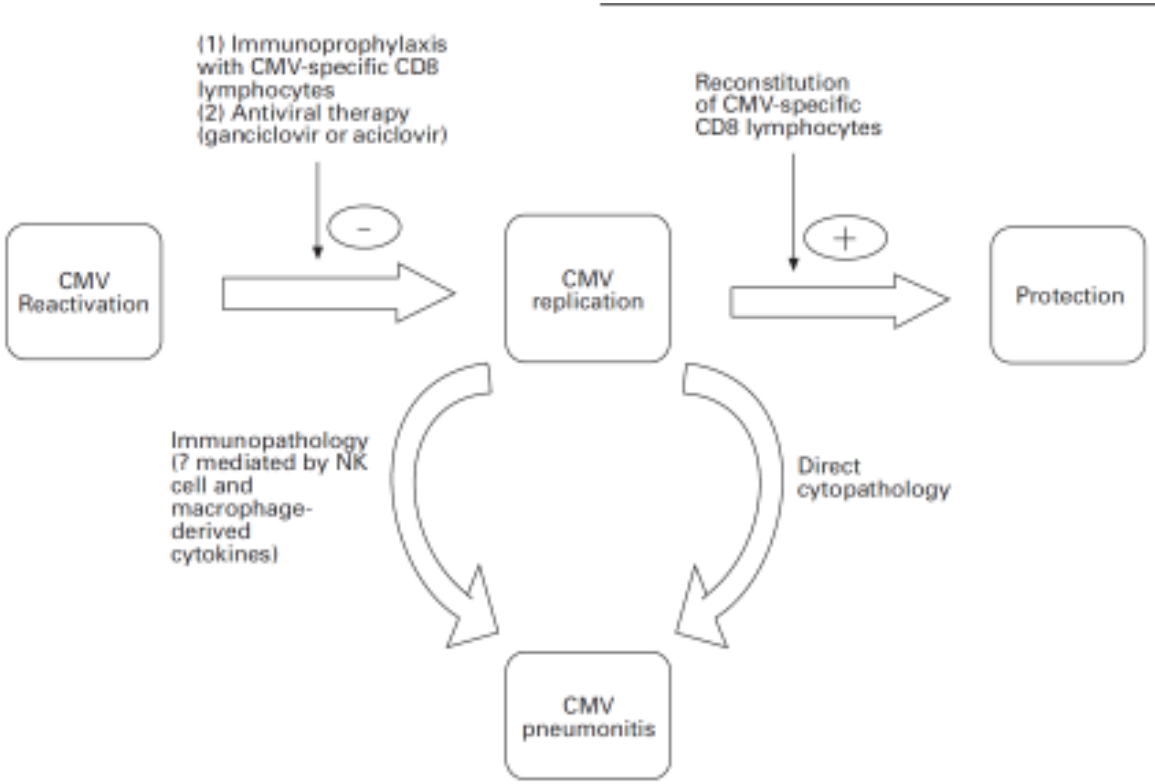
NE KAN NE DOKU da CMV DNA (emi)?

Inclusions or bystanders? CMV PCR sensitivity and specificity in tissue samples



Review

Cytopathology or immunopathology? The puzzle of cytomegalovirus pneumonitis revisited



10.1111/j.1469-0691.2008.02106.x

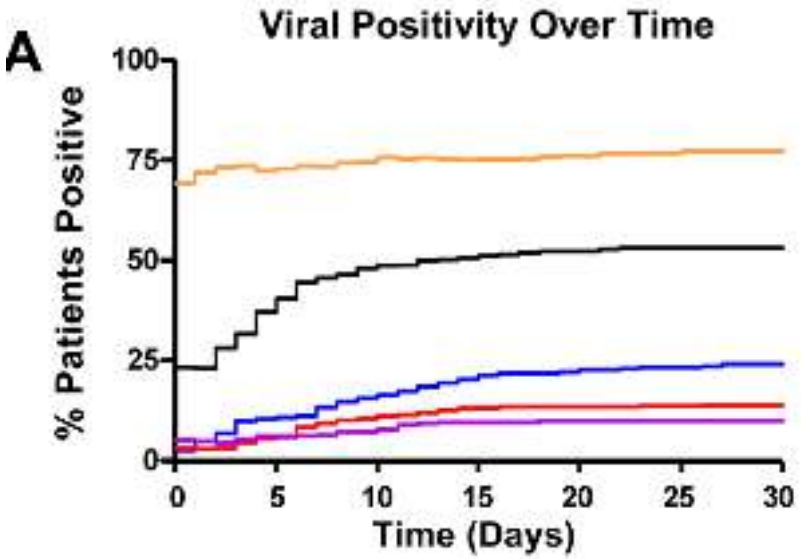
Fatal cytomegalovirus pneumonia in patients with haematological malignancies: an autopsy-based case–control study

H. A. Torres[1], E. Aguilera[1], A. Safdar[1], N. Rohatgi[1], I. I. Raad[1], C. Sepulveda[1], M. Luna[2], D. P. Kontoyiannis[1] and R. F. Chemaly[1]

[1]Department of Infectious Diseases, Infection Control, and Employee Health and [2]Department of Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

Co-infections within 1 month of autopsy	22/25 (88)	26/34 (76)	0.3	
Fungal co-infections[b]	6/25 (24)	13/34 (38)	0.2	
Pneumocystis jiroveci	1/25 (4)	0/34 (0)	0.4	
Other moulds	3/25 (12)	3/34 (9)	0.6	
Bacterial co-infections[b]	15/25 (60)	19/34 (56)	0.7	
Viral co-infections[b,c]	9/25 (36)	2/34 (6)	0.005	
Herpes simplex virus	7/25 (28)	2/34 (6)	0.02	0.1
Co-infections at autopsy	14/25 (56)	23/34 (68)	0.3	
Fungal co-infections[b]	10/25 (40)	16/34 (47)	0.5	
Pneumocystis jiroveci	2/25 (8)	0/34 (0)	0.1	
Other moulds	6/25 (24)	9/34 (27)	0.8	
Bacterial co-infections[b]	5/25 (20)	11/34 (32)	0.2	
Viral co-infections[b,c]	1/25 (4)	2/34 (6)	1.0	

Reactivation of Multiple Viruses in Patients with Sepsis



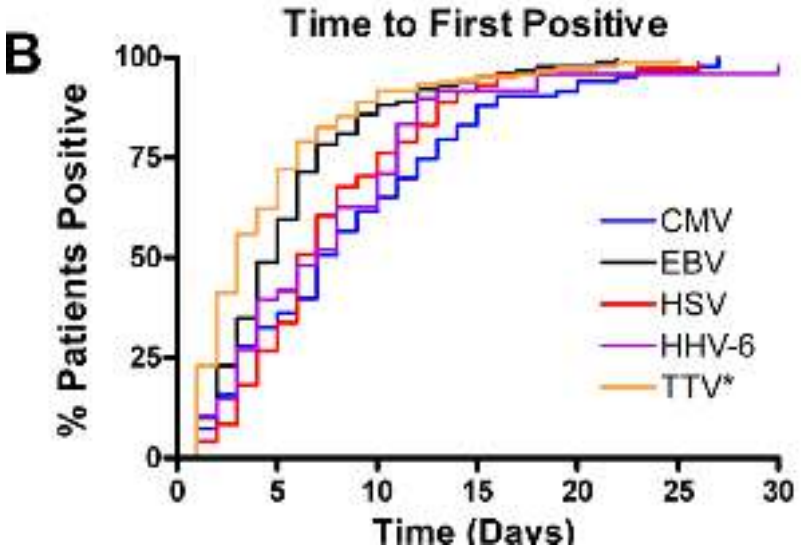


Table 3. [illegible]

Virus	Sepsis		Critically Ill Non-Sepsis		Healthy Control	
	Blood	Plasma	Blood	Plasma	Blood	Plasma
	[illegible]					
CMV*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
EBV	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
HSV	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
HHV-6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TTV		[illegible]		[illegible]		[illegible]
Any Virus	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Ganciclovir/Valganciclovir for Prevention of CMV Reactivation in Acute Injury of the Lung and Respiratory Failure (GRAIL)

Measured Values

	IV Ganciclovir	Placebo
Participants Analyzed	84	72
Number of Days Alive and Not in the ICU [Units: Days] Mean (Standard Deviation)	10.02 (6.84)	10.97 (8.23)

Measured Values

	IV Ganciclovir	Placebo
Participants Analyzed	84	72
CMV Disease [Units: Participants] Count of Participants		
Biopsy proven CMV disease	0 0.0%	0 0.0%
No Biopsy proven CMV disease	84 100.0%	72 100.0%

ClinicalTrials.gov Identifier: NCT01335932

Lifelong CMV infection improves immune defense in old mice by broadening the mobilized TCR repertoire against third-party infection

Megan J. Smithey[a,b], Vanessa Venturi[c], Miles P. Davenport[c], Adam S. Buntzman[d], Benjamin G. Vincent[e], Jeffrey A. Frelinger[a], and Janko Nikolich-Žugich[a,b,1]

Lifelong interactions between host and the ubiquitous and persistent cytomegalovirus (CMV) have been proposed to contribute to the age-related decline in immunity. Prior work from us and others found some support to increased vulnerability t Moreover, evidence has ac beneficial to immune defer dominantly via enhanced ir unexpected impact of mu response of old mice to *Li* model antigen, OVA (Lm- OVA-specific CD8 T cell rec demonstrated that old MC verse clonotypes that affo recognition of antigenic pe to old control mice, which e: enization of the elicited re of the total naïve CD8 TCRβ diverse OVA-specific clon CD8 repertoire of mice in a MCMV^{-}) yet were only recruited into the Lm-OVA response in MCMV^{+} old mice. These results have profound implications for our understanding of T cell immunity over a life span and suggest that our coevolution with CMV may include surprising, potentially positive impacts on adaptive heterologous immunity in late life.

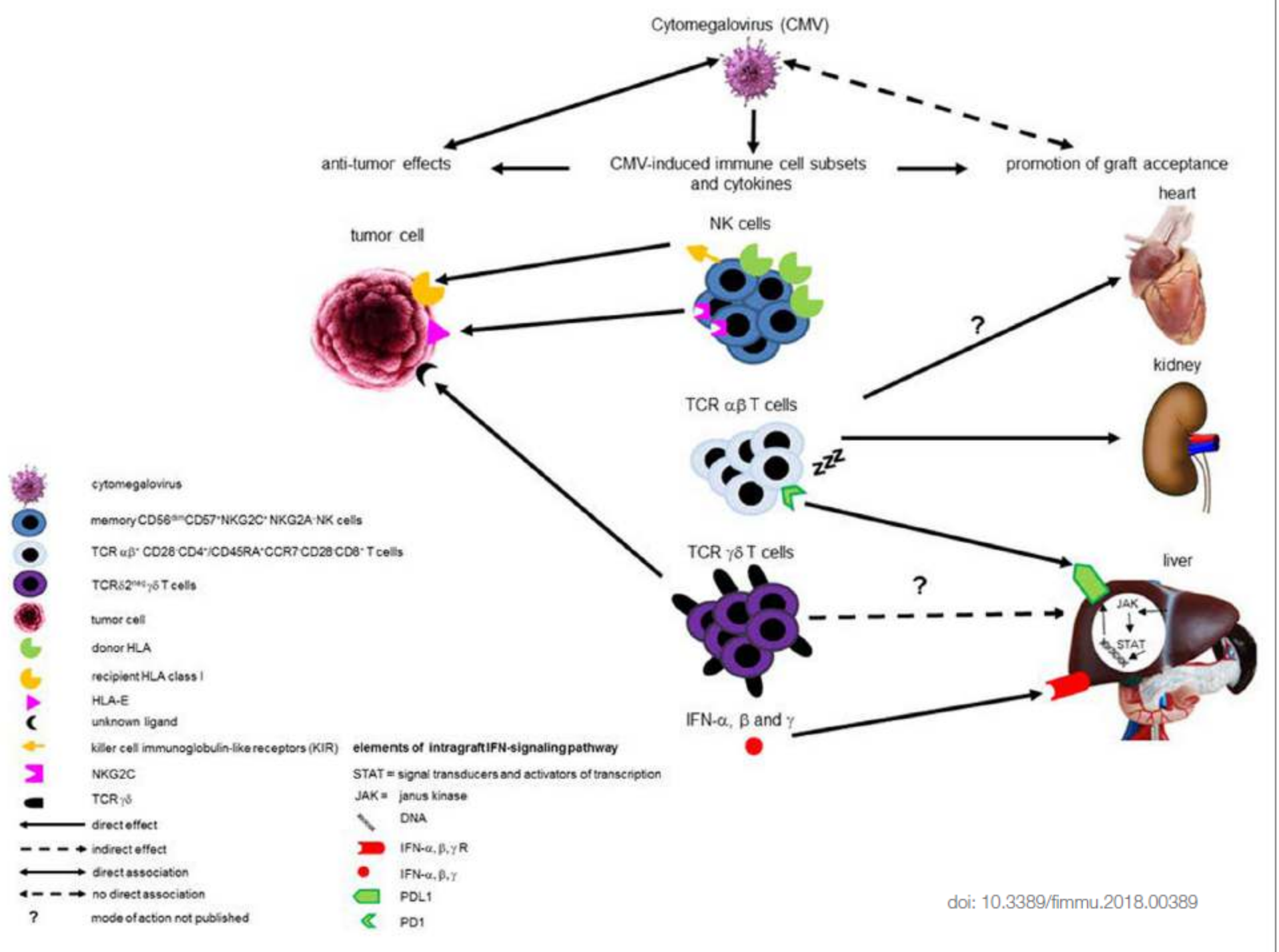
Significance

Epidemiological studies have shown a correlation between CMV infection and immune system aging, especially in elderly populations. It remains unclear whether CMV infection is a key driver of, or simply a factor associated with, aging of the immune system. We show that aging in the presence of lifelong CMV infection improves T cell immunity in old animals by broadening the immune response to a different pathogen. Animals that have aged with CMV are able to recruit novel T cells into these immune responses that are present in, but not utilized in, animals aging without CMV. These data squarely challenge the premise that CMV is solely detrimental to the aging of the adaptive immune system.

Potential Beneficial Effects of Cytomegalovirus Infection after Transplantation

*Nicolle H. R. Litjens[1], Lotte van der Wagen[2], Jurgen Kuball[2] and Jaap Kwekkeboom[3]**

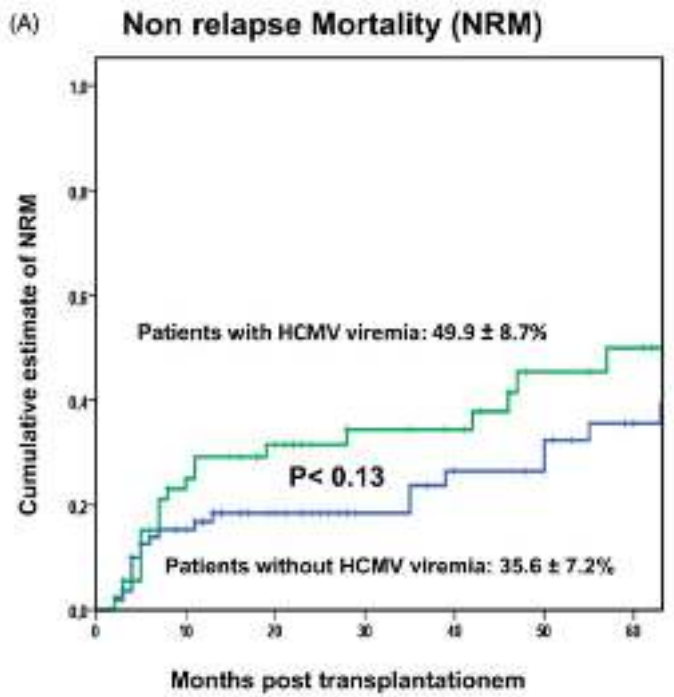
[1]Department of Internal Medicine, Nephrology and Transplantation, Erasmus MC, University Medical Center, Erasmus University Rotterdam, Rotterdam, Netherlands, [2]Laboratory of Translational Immunology, Department of Hematology, University Medical Center Utrecht, Utrecht, Netherlands, [3]Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Erasmus University Rotterdam, Rotterdam, Netherlands

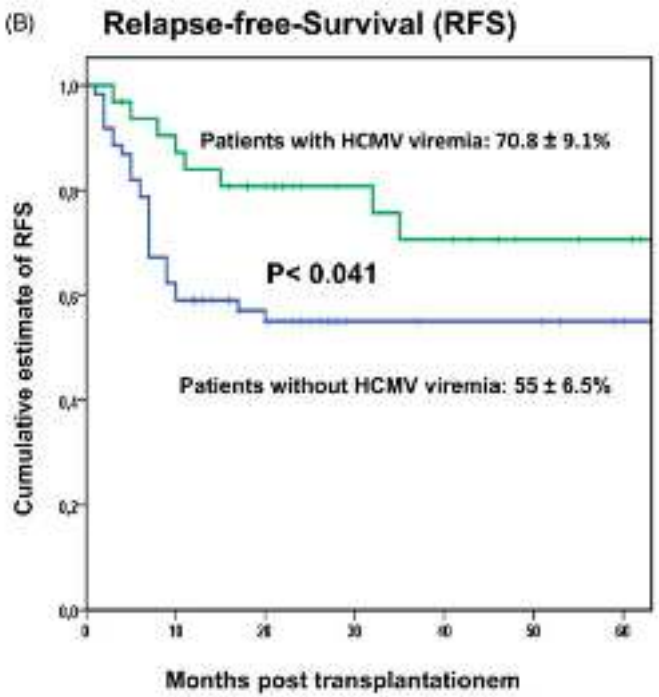


doi: 10.3389/fimmu.2018.00389

TABLE 1 | Summary of recent studies on the association of post-transplant Cytomegalovirus (CMV) replication and relapse of hematological malignancies after HSCT.

Study (Ref.)	Effect	Patients	Adults/ pediatric patients	Myeloablative pre-conditioning	T/NK-depleted graft	Antibody-based in vivo T-cell depletion	Donors	Stem cell source	CMV detection	Endpoint	Relapse rate			Effect of CMV reactivation on AML relapse	Comments
											With CMV reactivation	Without CMV reactivation	*P*-value		
Elmaagacli et al. [5]	Positive in AML	AML *n* = 286	Adults	All	No	No	Sibs 118 (44%); MUD 149 (56%)	BM 45 (17%); PBSC 221 (83%)	pp65 antigenemia	Cumulative incidence of AML relapse at 10 years after HSCT = 33% (95% CI, 27–40%)	10-year CIR AML 9%	10-year CIR AML 42%	<0.0001	*CMV infection: HR = 0.2, 95% CI = 0.1–0.4, *P* < 0.0001	
Manjappa et al. [7]	Positive in AML	AML *n* = 284	Adults	208 (76%)	no	46 (17%) ATG	MRD 108 (41%); MUD 156 (59%)	BM 23 (9%); PBSC 240 (91%)	PCR	Cumulative incidence of AML relapse at 6 years after HSCT = 43%	5-year CIR AML 38.9%	5-year CIR AML 56%	0.03	*CMV infection: HR = 0.53, 95% CI = 0.33–0.83, *P* = 0.015	Effect restricted to patients receiving myelo-ablative conditioning
Jang et al. [8]	Positive in AML	AML *n* = 74	Median age 35; range 15–59 years	68 (92%)	Not mentioned	11 (15%) ATG or alemtuzumab	MRD 31 (42%); MUD 43 (58%)	BM 5 (7%); PBSC 69 (93%)	PCR	Cumulative incidence of AML relapse at 5 years after HSCT = 31%	Patient numbers not mentioned			*CMV infection: HR = 0.21, 95% CI = 0.09–0.54, *P* = 0.001	
Green et al. [6]	Positive in AML	AML *n* = 781 ALL *n* = 322 CML *n* = 646 Lymphoma *n* = 254 MDS *n* = 371	2306 adults/ 250 children	859 (87%) of AML patients	39 (5%) of AML patients	Not mentioned	Sibs 397 (52%); MUD 351 (46%); haplo 12 (2%)	BM 301 (40%); PBSC 460 (60%)	pp65 antigenemia	Cumulative incidence of AML relapse at 1 year after HSCT = 25.2%	1-year CIR AML 26.5%	1 year CIR AML 32.7%	0.19	*CMV infection: HR = 0.66, 95% CI = 0.3–0.9, *P* = 0.02*	Effect restricted to AML patients and no effect on overall mortality
Takenaka et al. [9]	Positive in AML	AML *n* = 1836 ALL *n* = 911 CML *n* = 229 MDS *n* = 589	Median age 46; range: 16–74 years	1391 (75%) of AML patients	No	No	MRD 969 (54%); MUD 847 (46%)	BM 1287 (69%); PBSC 569 (31%)	pp65 antigenemia	Cumulative incidence of AML relapse at 5 years after HSCT = 26.5%	5 year CIR AML 22.4%	5 year CIR AML 29.6%	<0.01	*CMV infection: HR = 0.77, 95%C = 0.59–0.99, *P* = 0.04	Effect restricted to AML patients





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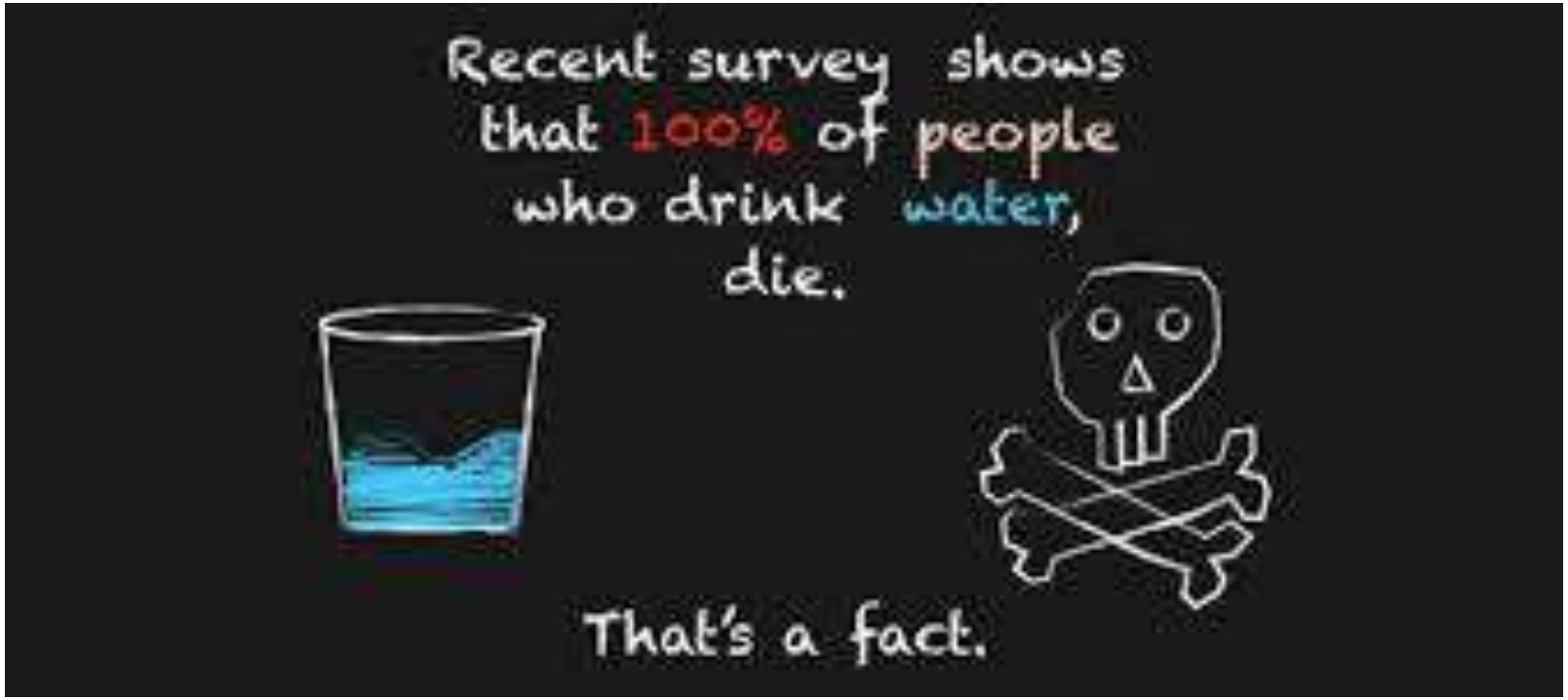
Water == CMV


Recent survey shows
that 100% of people
who drink water,
die.
That's a fact.