

CMV-specific cell-mediated immune response: utility on management of CMV infection in Kidney transplantation



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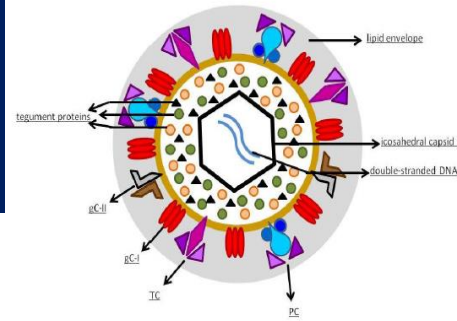
Urology & Nephrology Center

Mansoura - Egypt

Outline

- - Background, CMV infection
- - Current preventive strategies
- - CMV T-cell immunity (CMV-TCI)
 - - Mechanism
 - - Use in Prevention
 - - Use on treatment
- - Conclusions

CMV is a Herpes Virus



Human Herpes Viruses (8 types)

Neurotropic, 3 (Alpha- Herpes virus)

- HSV (HHV-1 & HHV-2 causing cold sores and genital herpes)
- HZV (HHV-3, chickenpox / shingles)

Lymphotropic, 5 (Beta and Gamma-Herpes viruses)

- Beta
 - **CMV (HHV-5)**
 - HHV-6
 - HHV-7
- Gamma
 - HHV-8 (Kaposi sarcoma)
 - EBV (HHV-4, Epstein Barr Virus-related disorders)

Methods of transmission



Exposure to maternal
blood, vaginocervical
secretions,
or breast milk



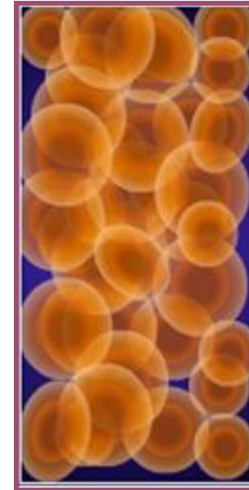
Close contact
among children
in day care
centres



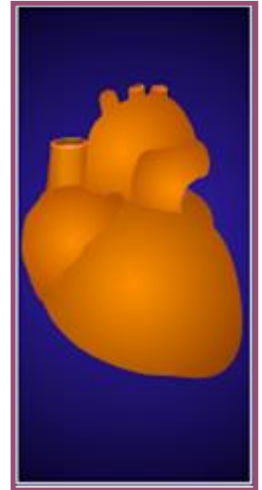
Sexual
transmission



Close contact
among adults



Blood
transfusion



Organ
transplantation

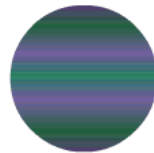
CMV has been found in:

Blood, cervical & vaginal secretions, saliva, tears, urine, faeces, semen, breast milk, transplanted donor organs

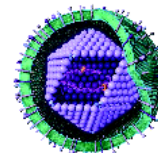
CMV and the immuno**competent** host

- The human host devotes around 10% of its T-cell immune system to the control of CMV replication
- CMV replication is effectively controlled in people with a competent immune system, and CMV and its host exist in harmony

Competent immune system



CMV



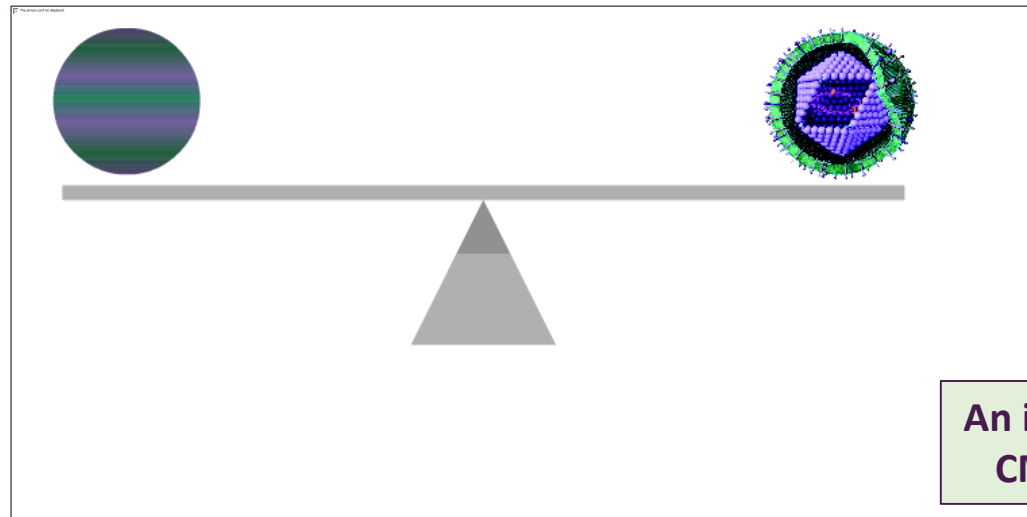
- Primary infection is generally asymptomatic although in some cases it may be associated with mononucleosis-like syndrome

1. Sylwester AW et al. J Exp Med 2005; 202: 673-685.
2. Ghandi MK and Khanna R. Lancet Infect Dis 2004; 4: 725-738.
3. Human Cytomegalovirus. Emery VC (Ed.). International Medical Press Ltd 2007.

CMV and the immuno**compromised** host

- The absence of an effective T-cell immune response is central to the pathogenesis of CMV disease
- Consequently, CMV is an important cause of morbidity and mortality in individuals whose immune system is suppressed because of immunosuppressive drugs

**Compromised
immune system**



**An increased risk of
CMV replication**

1. Pocket Reference to Cytomegalovirus. Emery VC. Current Medicines Group, 2006.
2. Gandhi MK and Khanna R. Lancet Infect Dis 2004; 4; 725-738.

CMV Transmission in Transplantation

Seropositive donor (D+)

Seronegative recipient (R-)

Risk of primary infection

Seropositive donor (D+)

Seropositive recipient (R+)

Risk of superinfection with donor virus or reactivation of recipient virus

Seronegative donor (D-)

Seropositive recipient (R+)

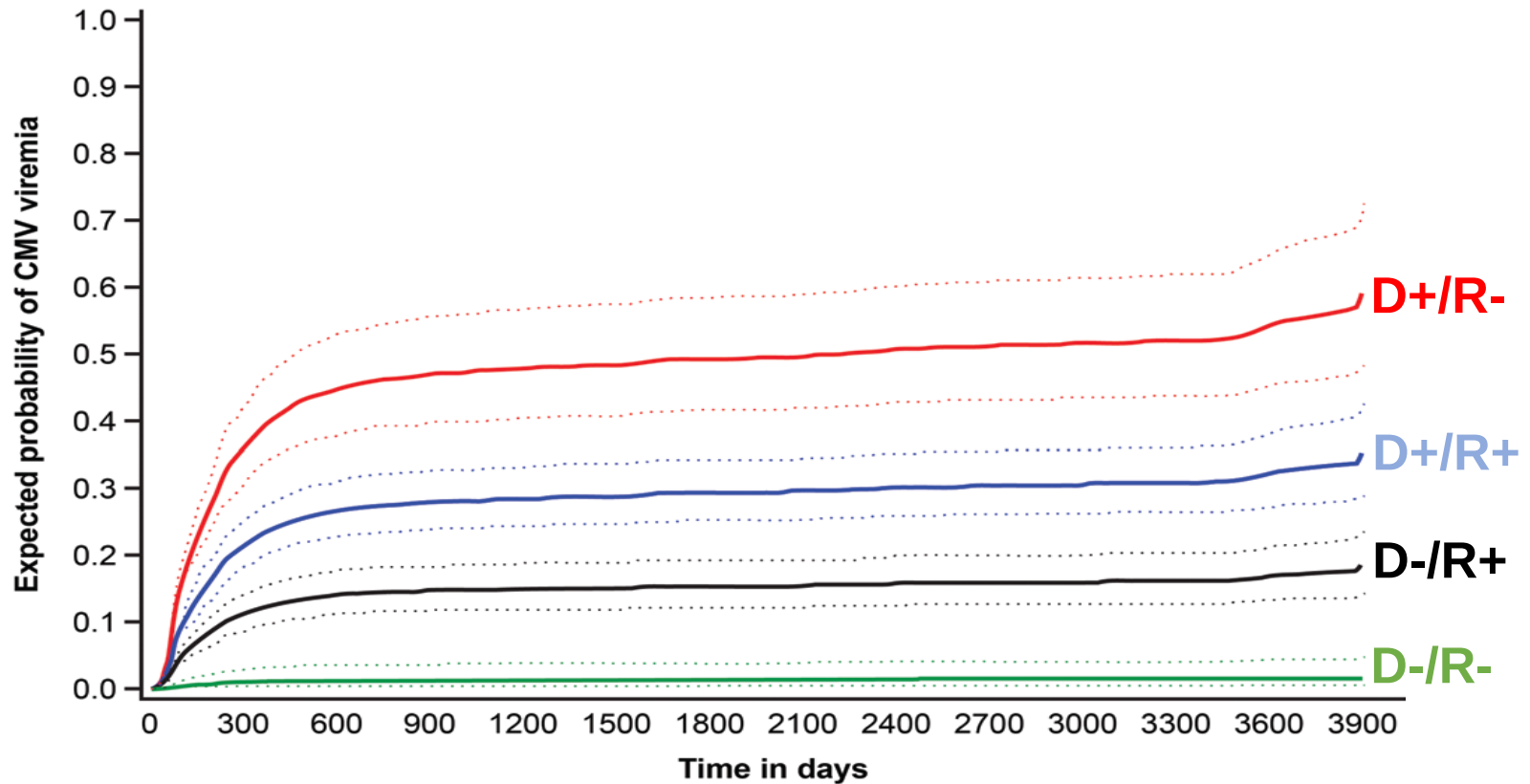
Risk of reactivation of latent infection

Seronegative donor (D-)

Seronegative recipient (R-)

Risk of primary infection from other source

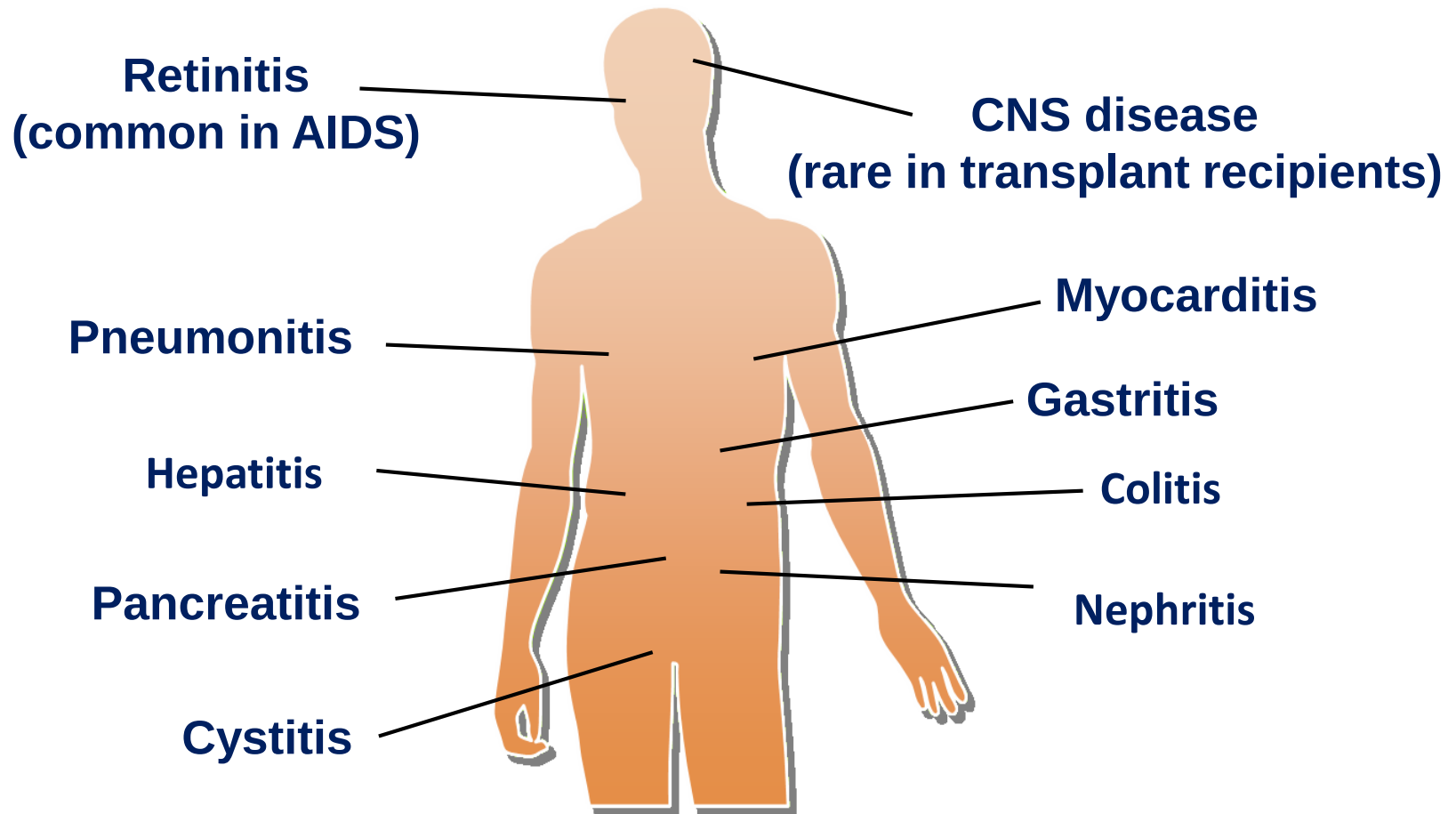
Cumulative frequency of CMV viremia by CMV D/R risk group



Risk factors for CMV associated disease in SOT

- Donor Recipient Status (D+/R-)
- CMV viral load
- Degree of MHC complex mismatch
- Amount of immunosuppression

CMV Infection: Direct effects



Rubin RH In: Rubin RH, Young LS, eds. Clinical Approach to Infection in the Compromised Host. New York, NY: Kluwer Academic/Plenum Publishers; 2002: Chapter 8.

CMV Infection: Indirect effects

- **Acute rejection rejection**

Kalil RSN et al. Am J Transpl 2003; 3: 79-81

- **Chronic allograft nephropathy**

Tong et al. Transplantation. 2002;74(4):576–8

Khan et al. J Nephropathol. 2014; 3(2): 69–79

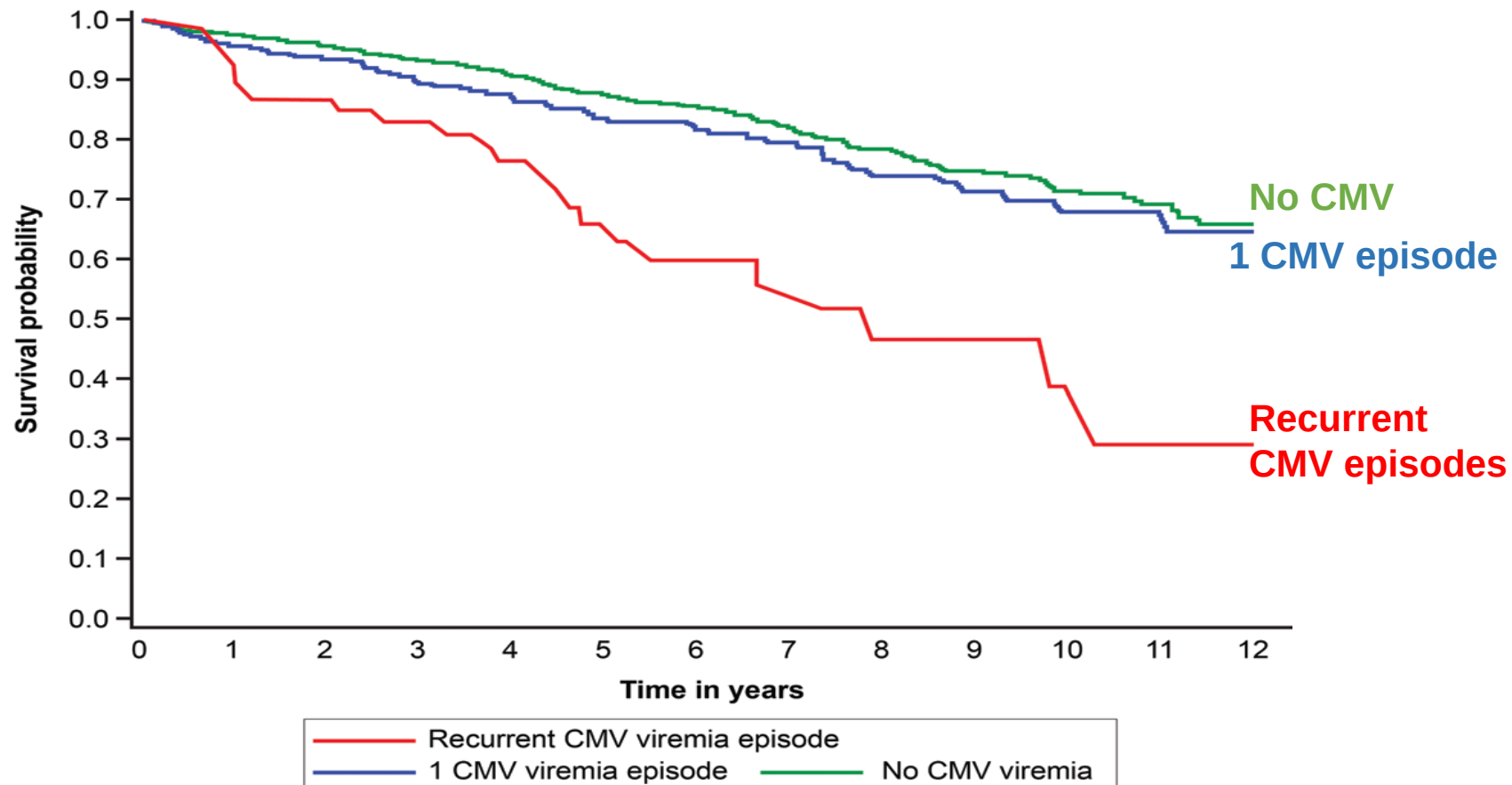
- **New-onset diabetes after renal transplantation**

Einollahi et al. J Nephropathol, 2014; 3(4):139-48

- **Cardiovascular risk after renal transplantation**

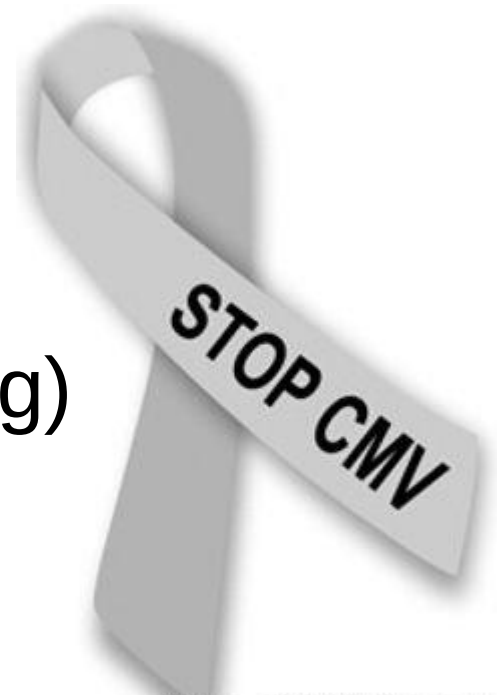
Kalil RSN et al. Am J Transpl 2003; 3: 79-81

CMV infection has deleterious impact on graft survival

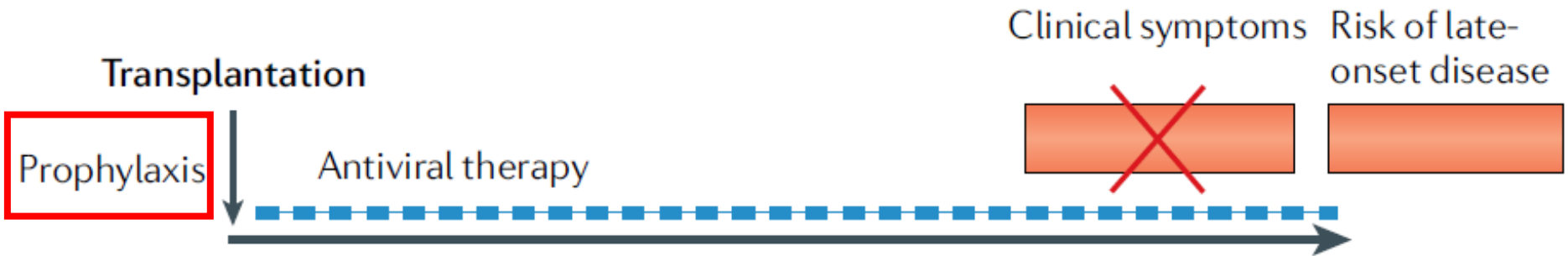


Prevention of CMV infection: strategies

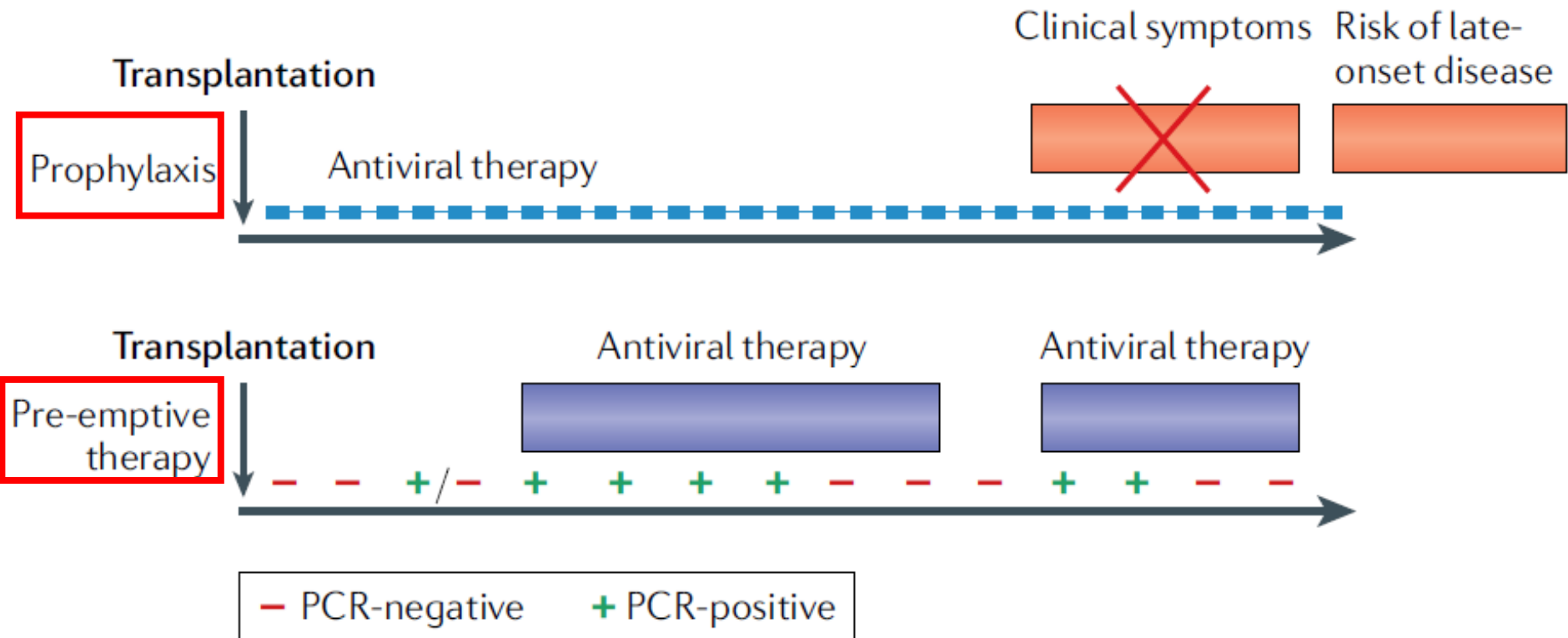
- Prophylaxis (Antivirals)
- Pre-emptive therapy (Screening)



CMV Prevention



CMV Prophylaxis

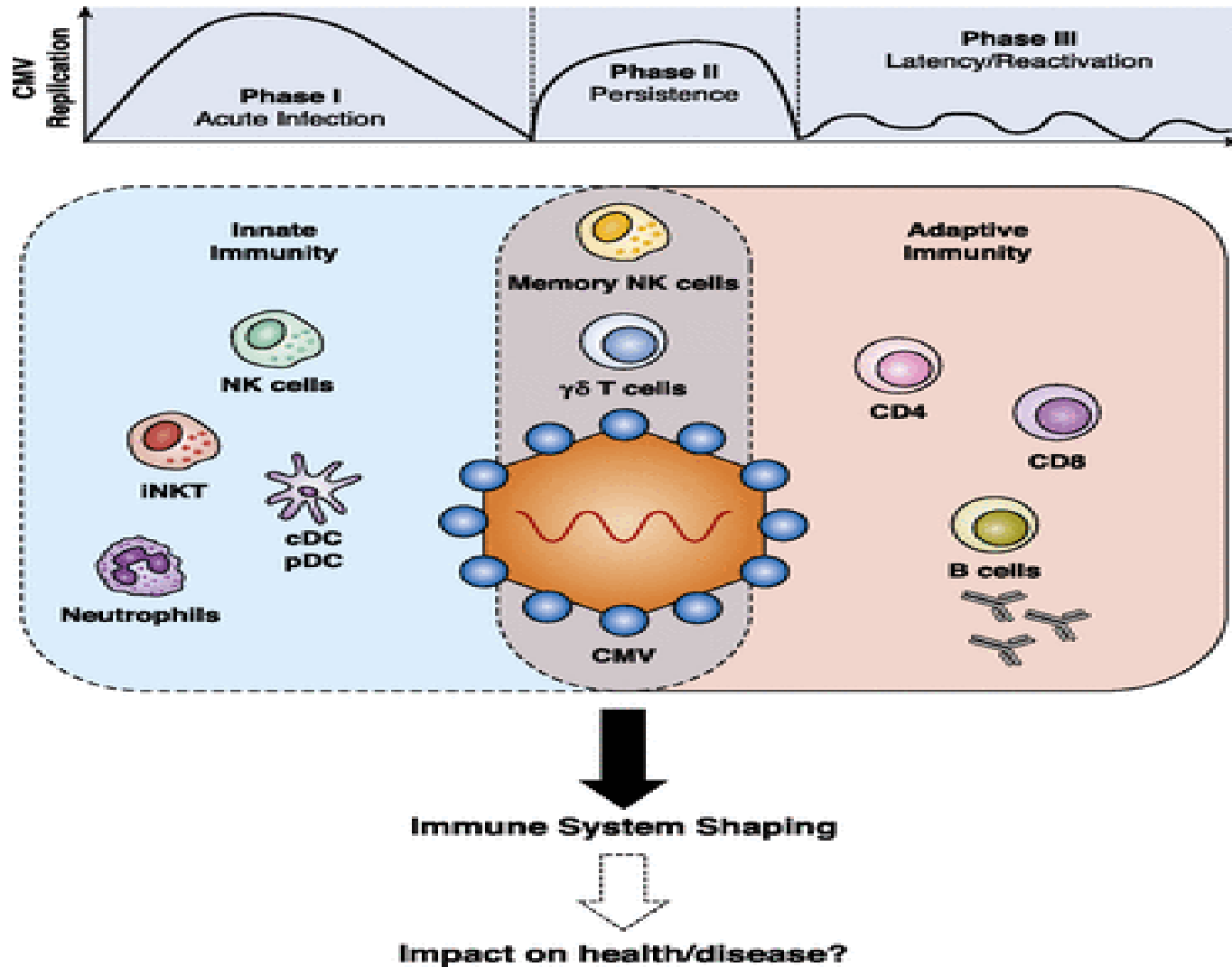


CMV and the immune response

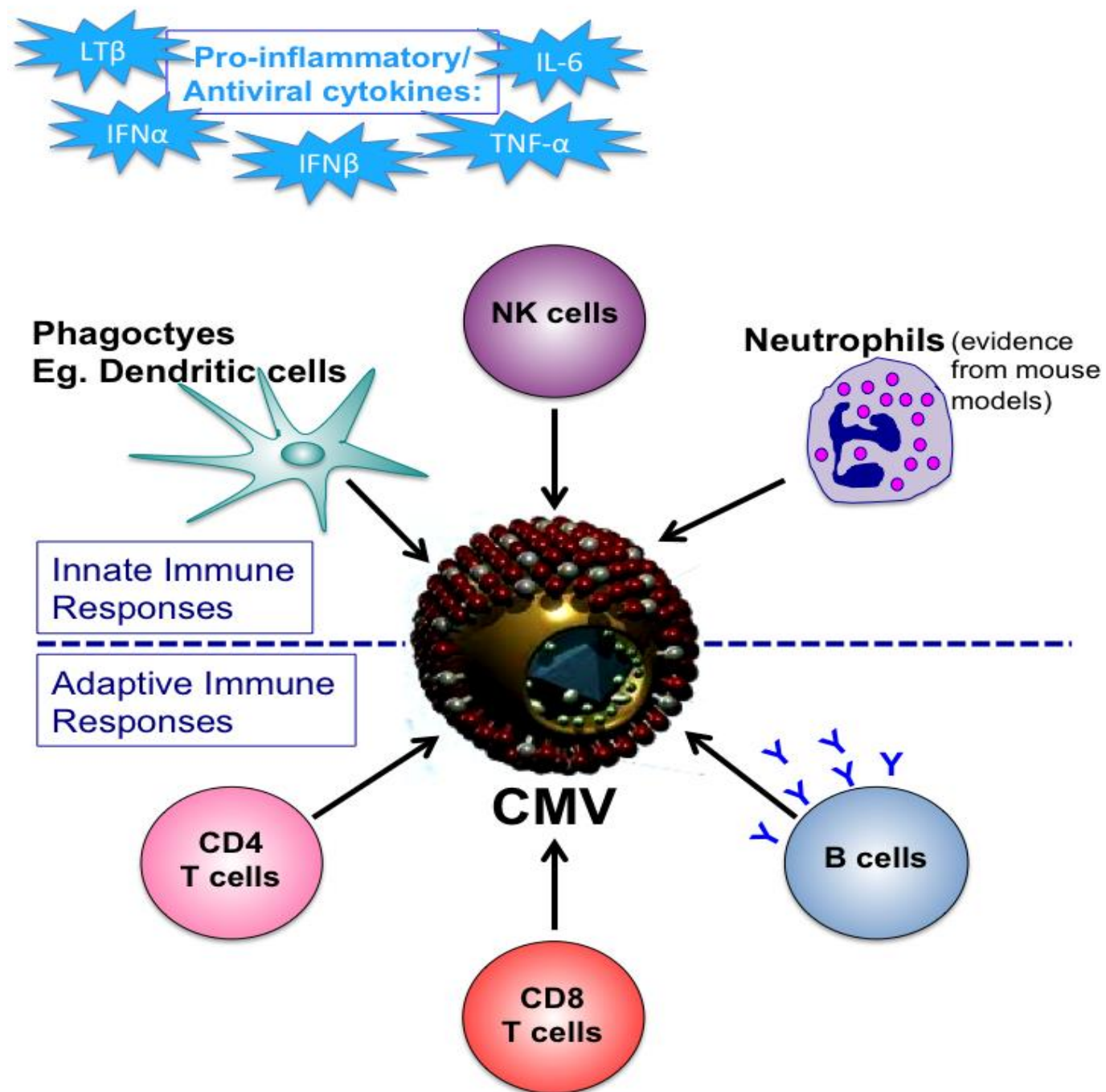
CMV and the immune response



CMV and the immune response

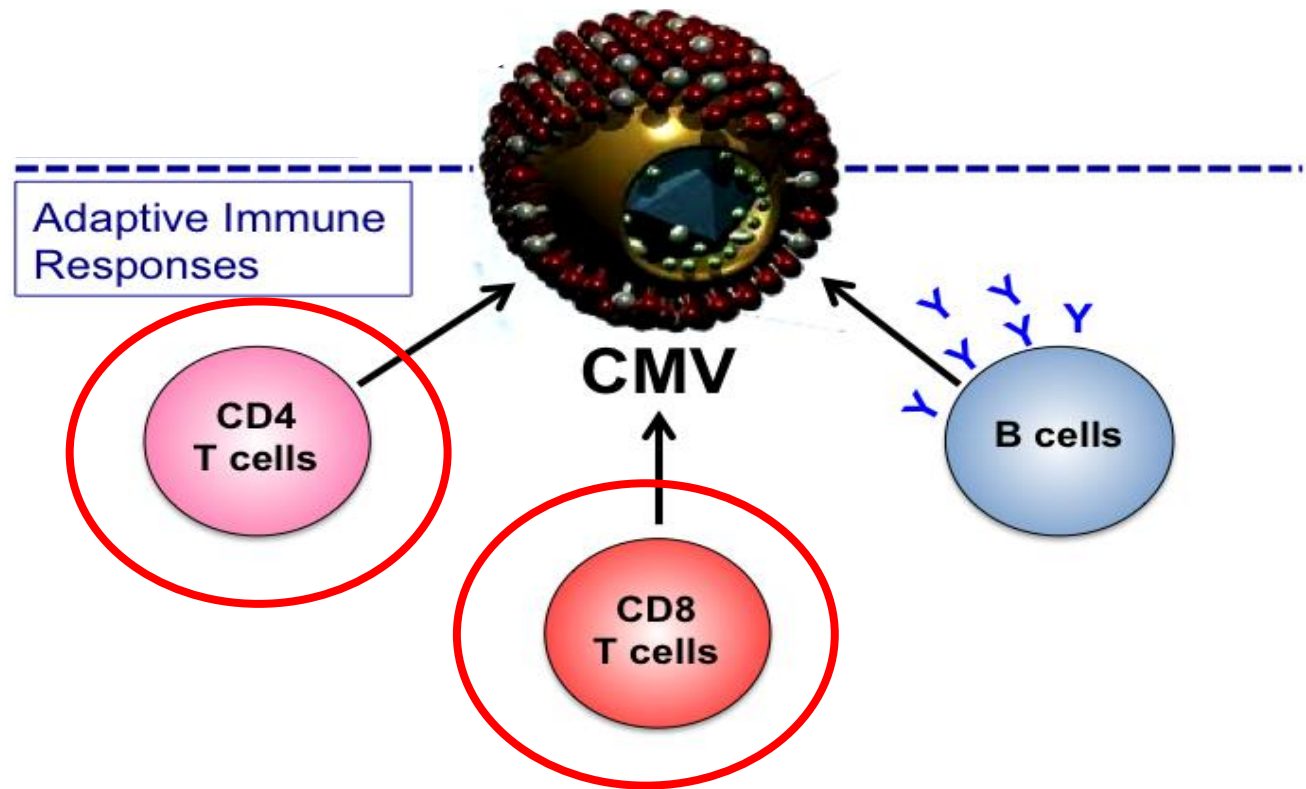


Immune responses to CMV





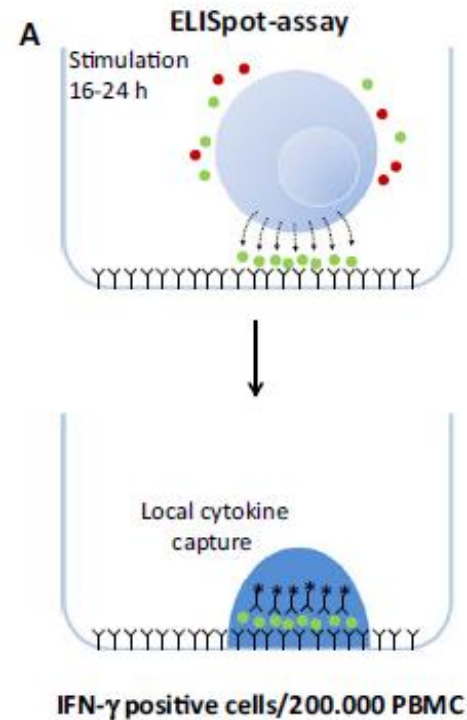
Immune responses to CMV



Techniques for detection of virus-specific T cells

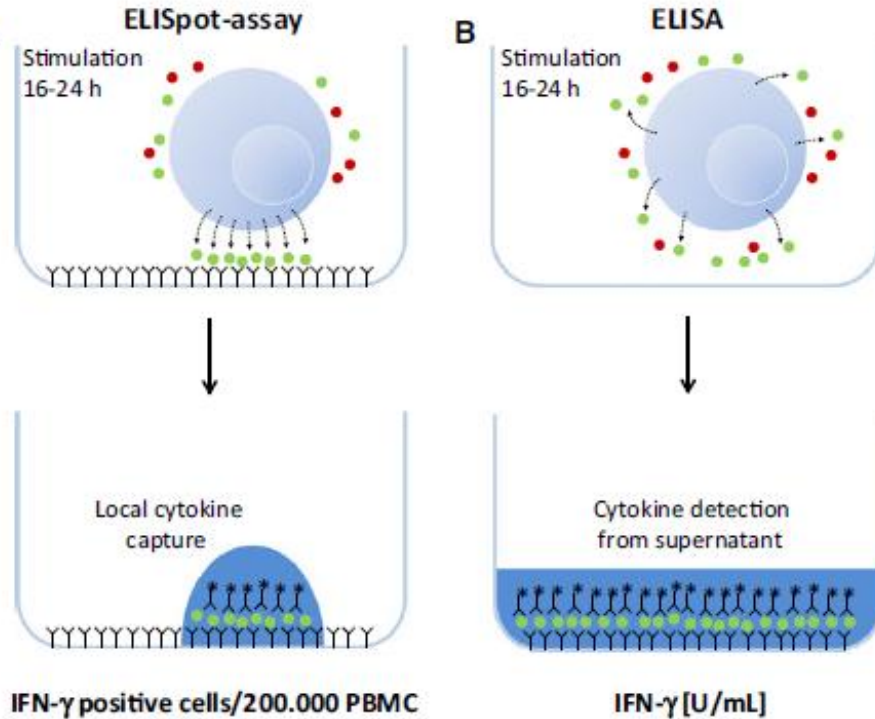
Techniques for detection of virus-specific T cells

IFN- γ



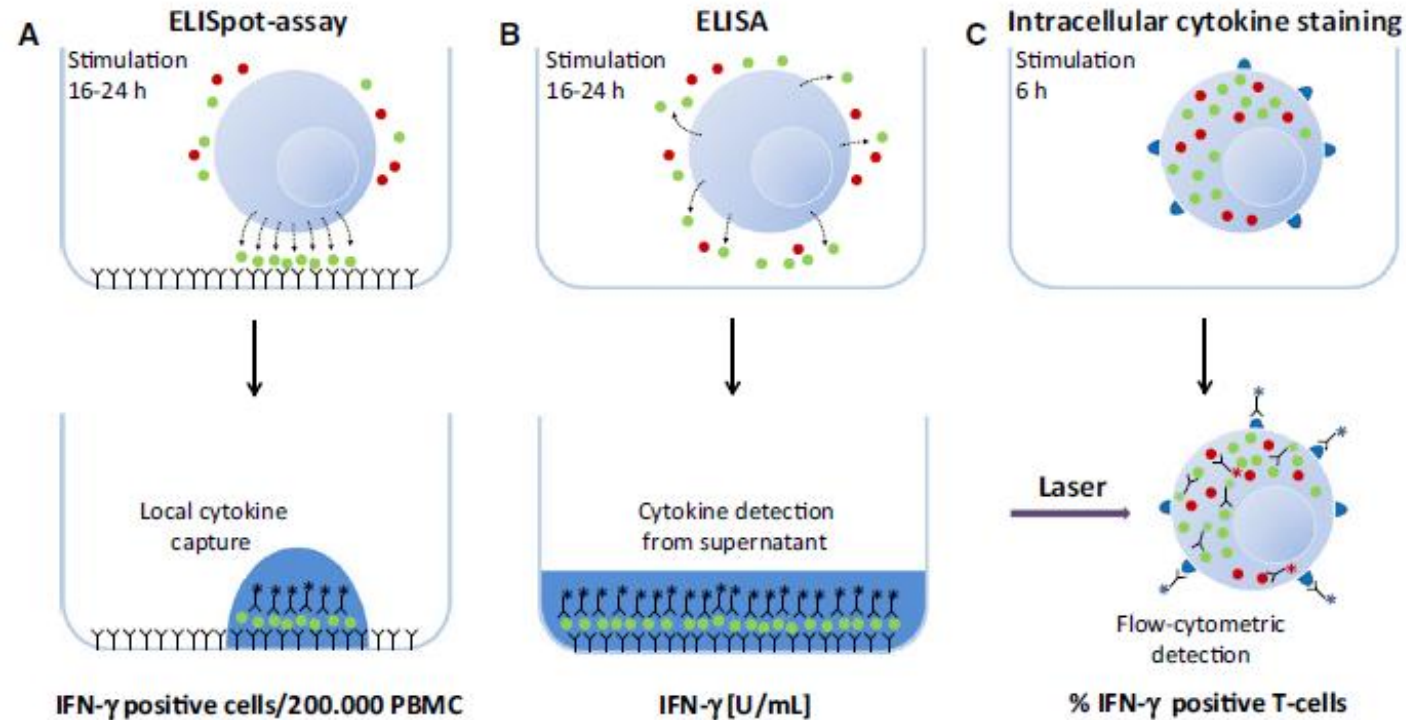
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IFN- γ



Techniques for detection of virus-specific T cells

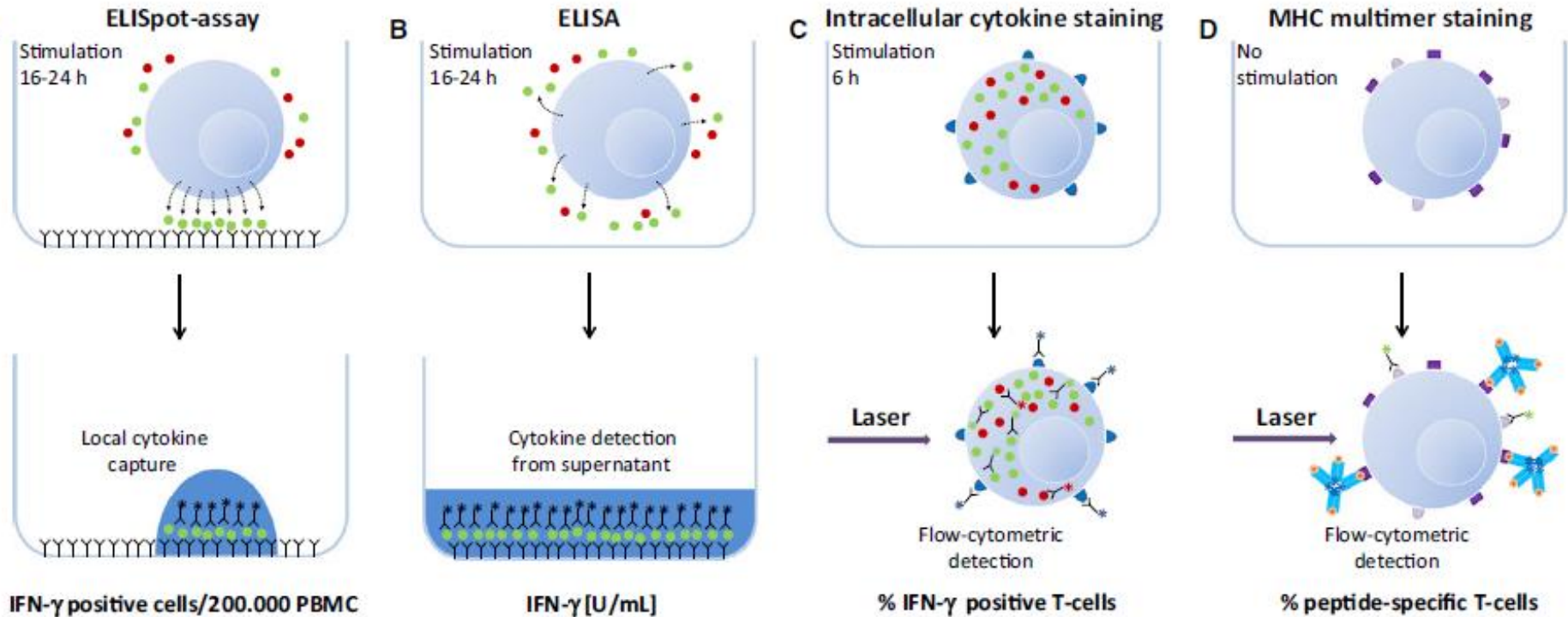
IFN- γ



Techniques for detection of virus-specific T cells

IFN- γ

T cells



CMV-CMI assays

- **QuantiFERON-CMV®**
- **ELISPOT-based CMV-CMI assays**
 - * T-Track CMV®
 - * T-SPOT®-CMV
- **Viracor CMV T cell Immunity Panel (TCIP)**

What is the role of cell-mediated immunity in the control of CMV infection?

Diagnostics **2021**, *11*, 875.



diagnostics

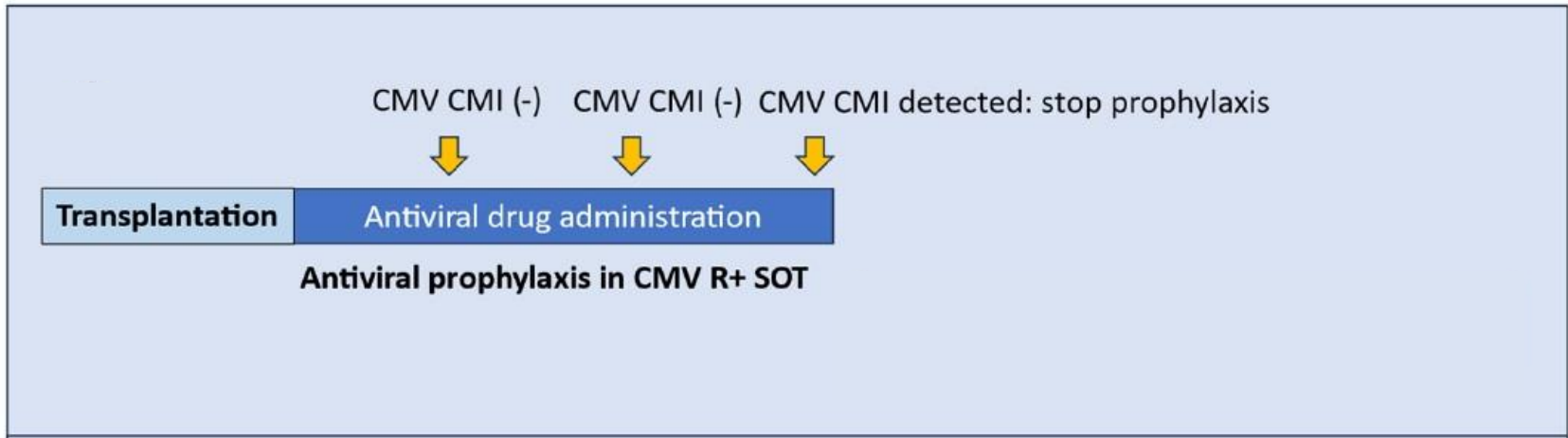


Review

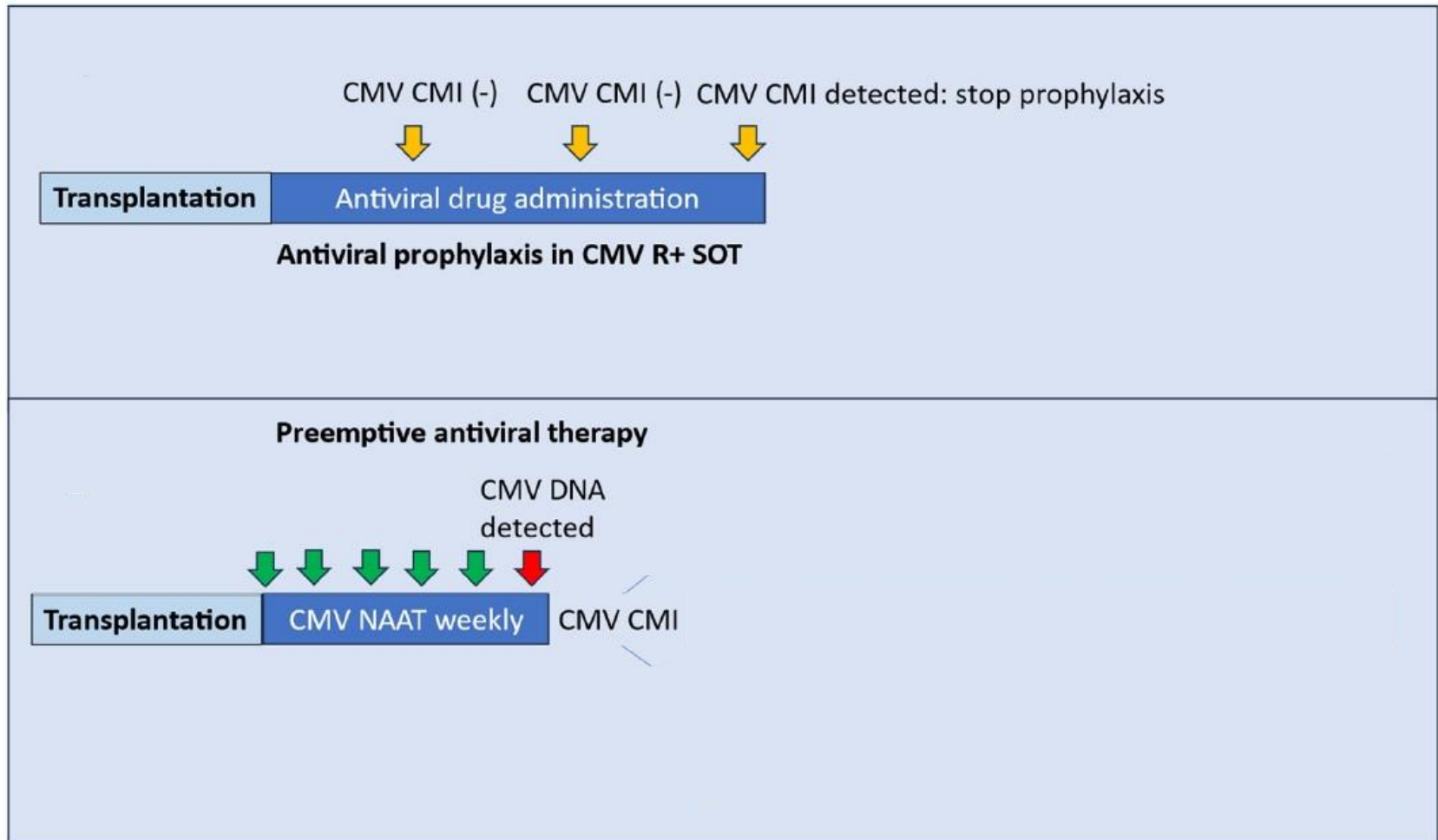
Utility of CMV-Specific Immune Monitoring for the Management of CMV in Solid Organ Transplant Recipients: A Clinical Update

Katya Prakash ¹, Aditya Chandorkar ² and Kapil K. Saharia ^{1,*}

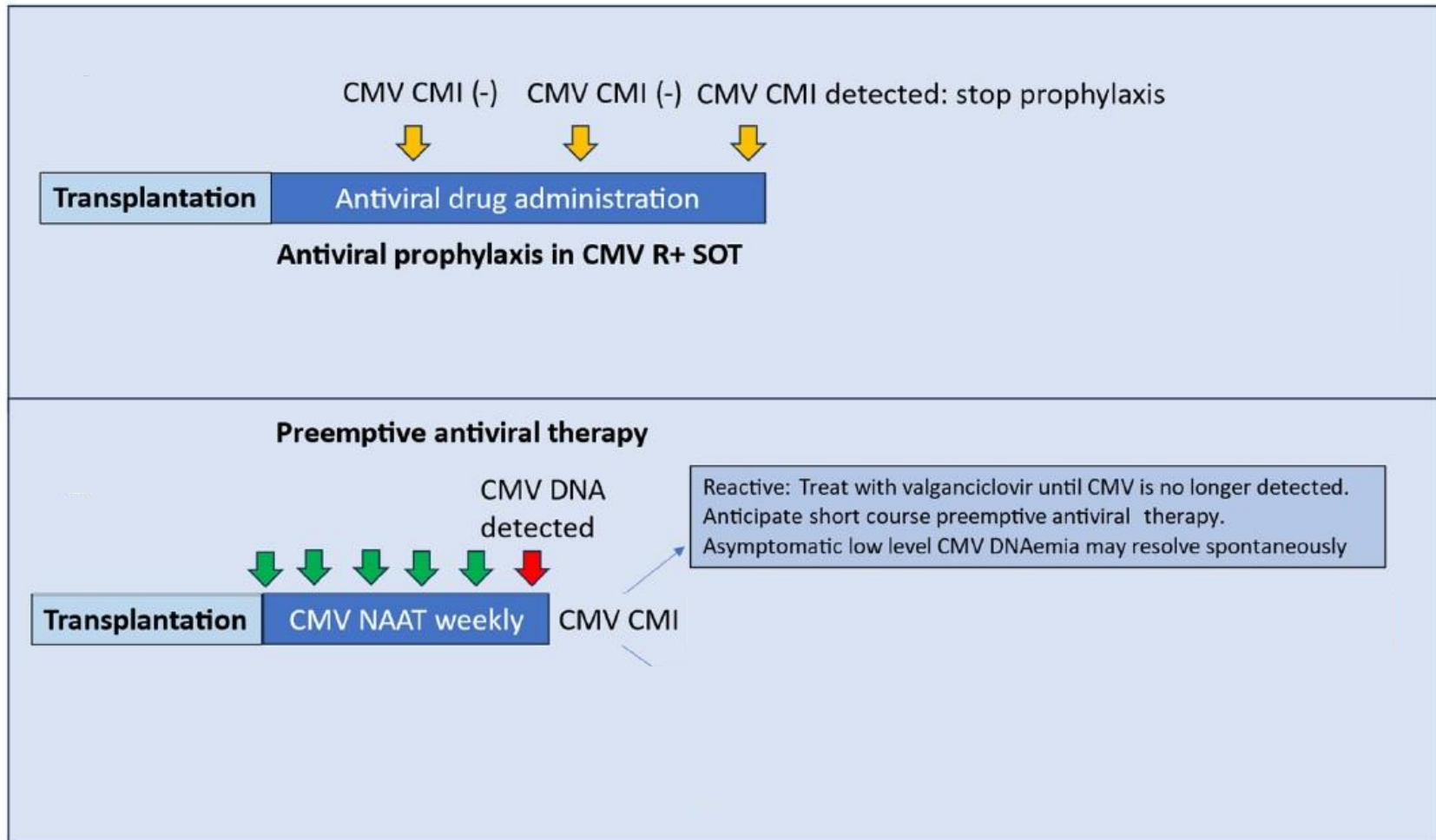
Strategies for CMV disease **prevention** that incorporates CMV-specific cell-mediated immunity



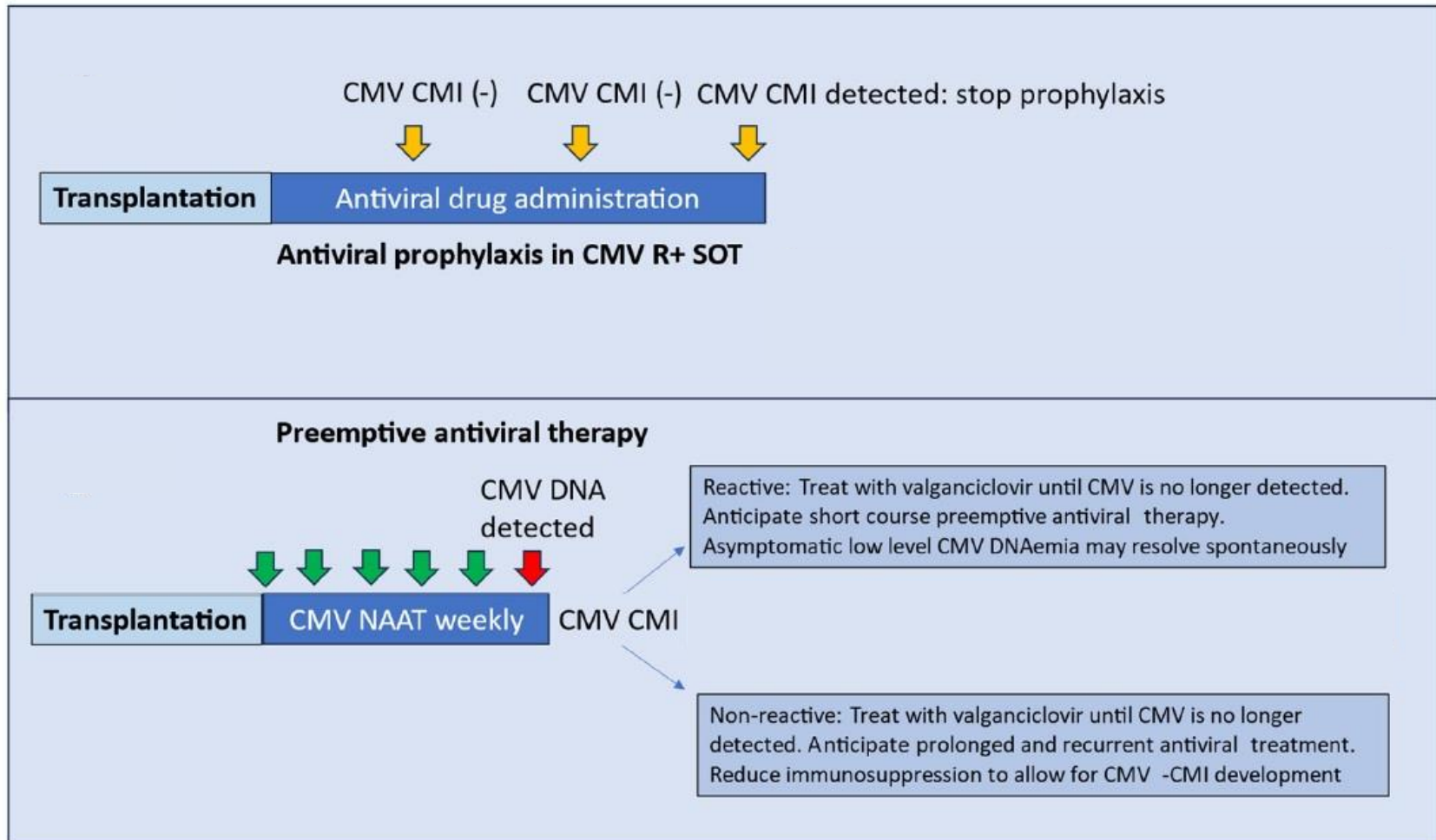
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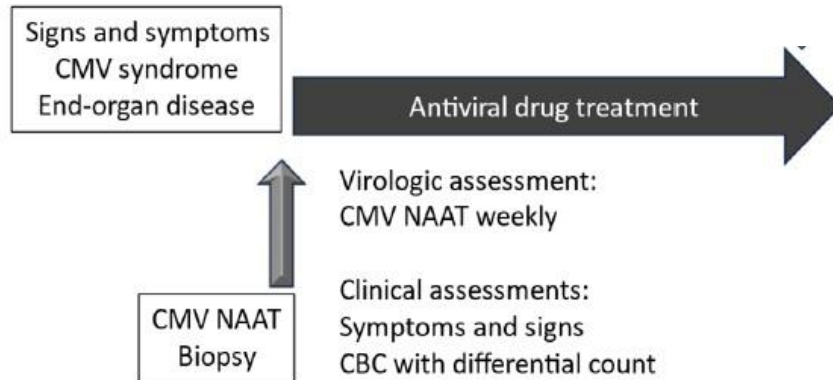
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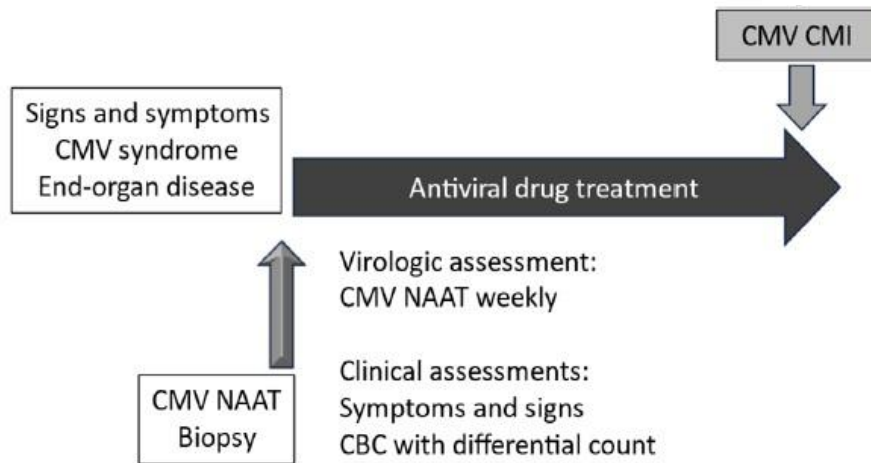
Strategies for CMV disease **prevention** that incorporates CMV-specific cell-mediated immunity



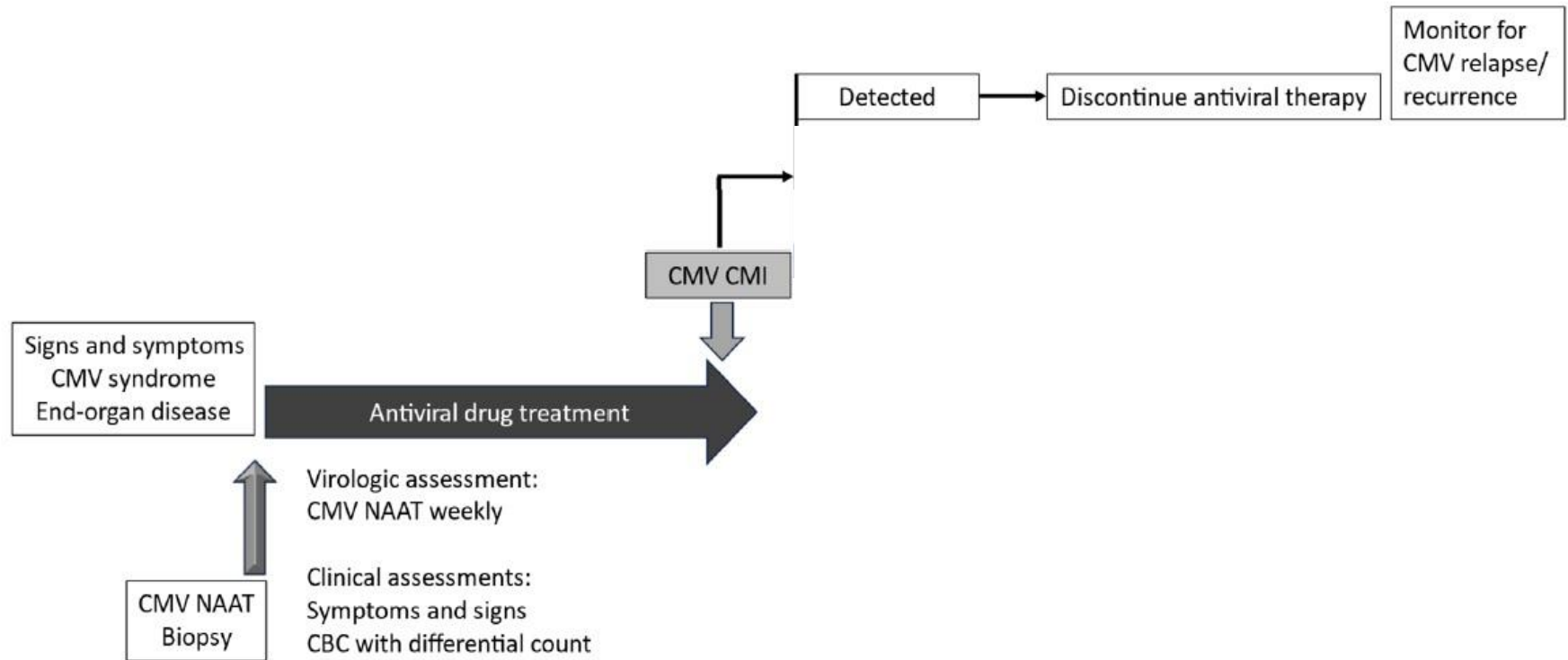
Strategies for CMV disease **treatment** that incorporates CMV-specific cell-mediated immunity



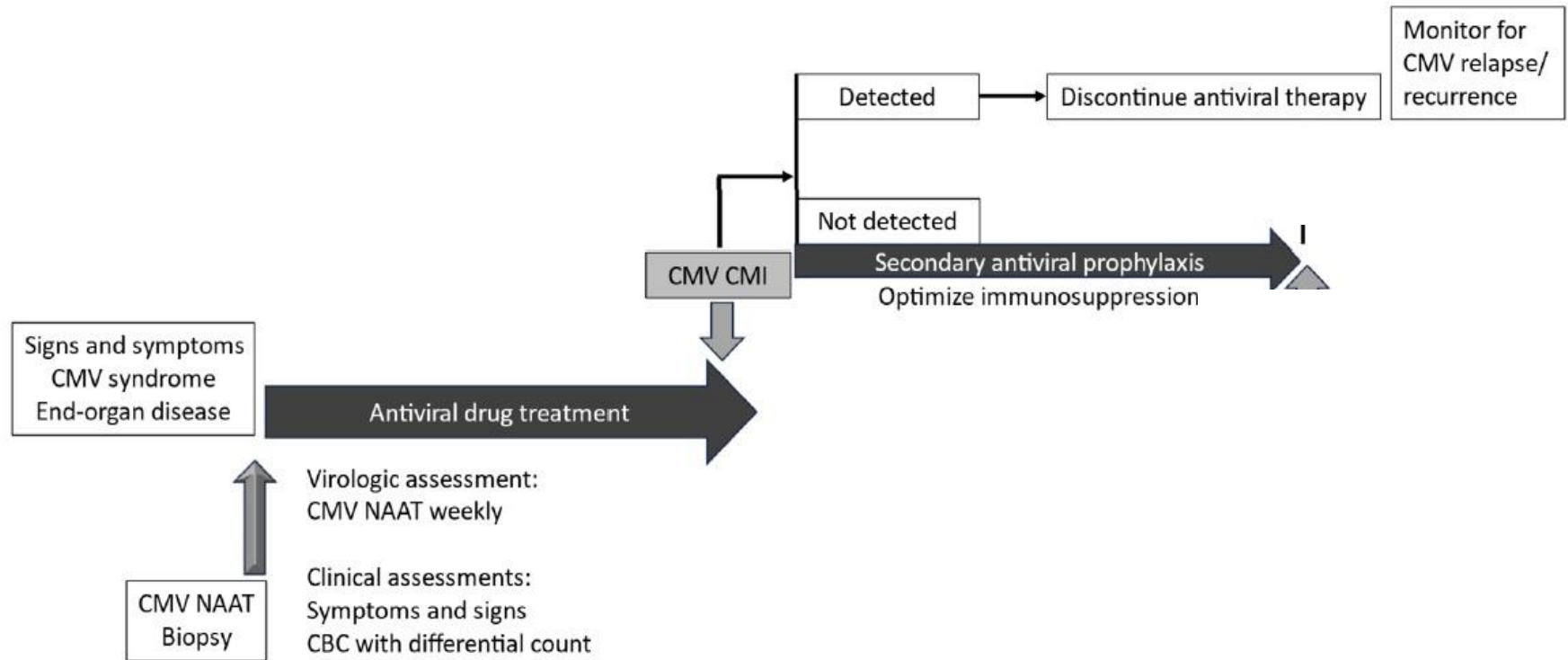
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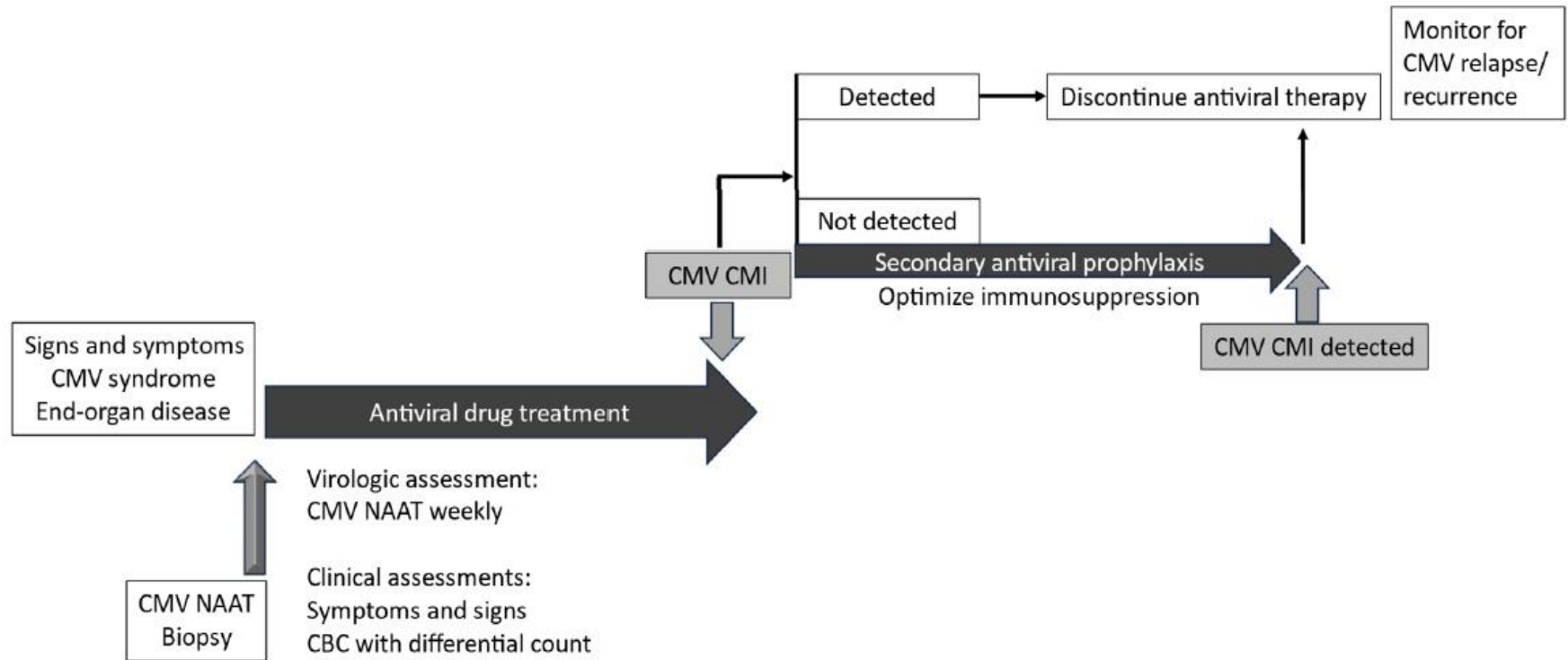
Strategies for CMV disease **treatment** that incorporates CMV-specific cell-mediated immunity



Strategies for CMV disease **treatment** that incorporates CMV-specific cell-mediated immunity



Strategies for CMV disease **treatment** that incorporates CMV-specific cell-mediated immunity



Utility of CMV-Specific Immune Monitoring

1. **Prior to transplantation:** to predict risk of CMV infection post-transplantation
2. **In patients with asymptomatic CMV DNAemia:** to determine if antiviral treatment is truly indicated
3. **At the end of primary prophylaxis:** to determine if extended prophylaxis or close viral load monitoring might be of benefit
4. **At the end of treatment of CMV infection:** to support the need for secondary prophylaxis



Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com



Original article

Regular monitoring of cytomegalovirus-specific cell-mediated immunity in intermediate-risk kidney transplant recipients: predictive value of the immediate post-transplant assessment

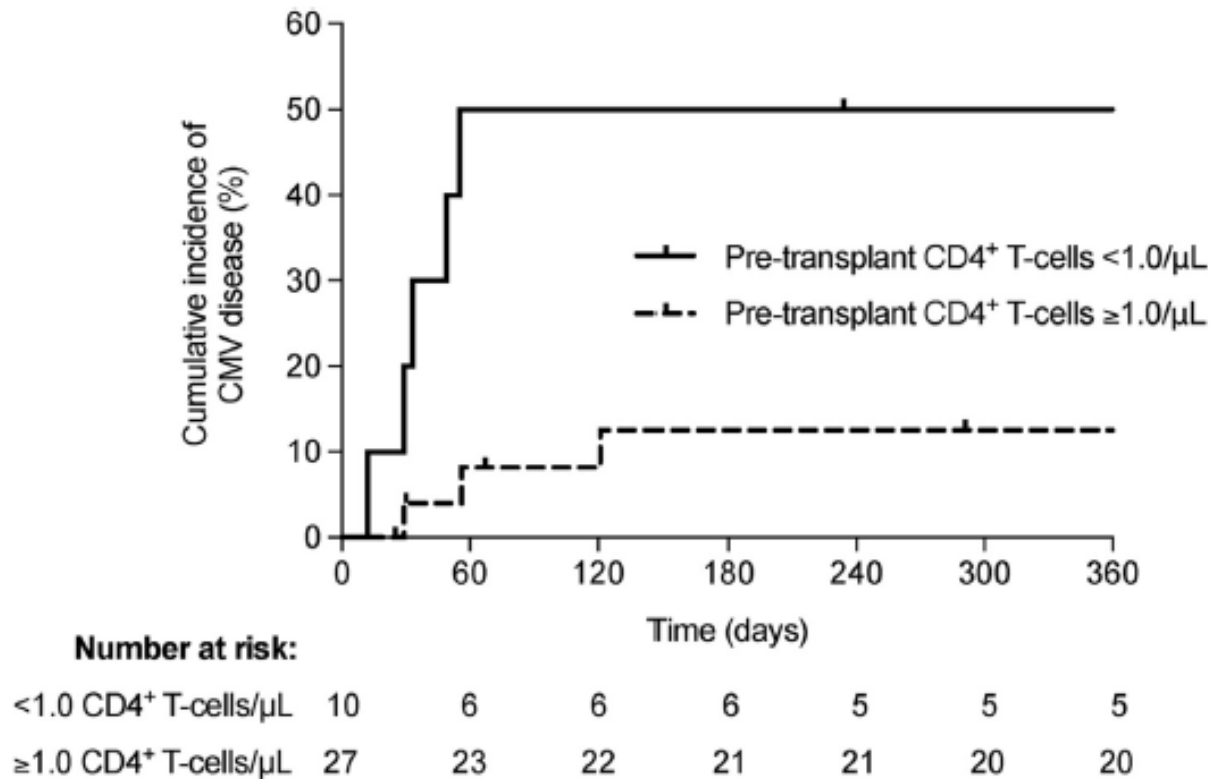
M. Fernández-Ruiz ^{1,*}, E. Giménez ², V. Vinuesa ², T. Ruiz-Merlo ¹, P. Parra ¹, P. Amat ³, M. Montejo ⁴, A. Paez-Vega ⁵, S. Cantisán ⁵, J. Torre-Cisneros ⁵, J. Fortún ⁶, A. Andrés ⁷, R. San Juan ¹, F. López-Medrano ¹, D. Navarro ², J.M. Aguado ¹,
for the Group for Study of Infection in Transplantation of the Spanish Society of Infectious Diseases and Clinical Microbiology (GESITRA-SEIMC) and the Spanish Network for Research in Infectious Diseases (REIPI)[†]

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²) Department of Microbiology, Hospital Clínico Universitario, Instituto de Investigación Sanitaria INCLIVA, School of Medicine, Universidad de Valencia, Valencia, Spain

**124 CMV-seropositive KT recipients
four Spanish institutions**

Cumulative incidence of CMV disease during the first year after transplantation according to the CMV-specific CD4 T-cell count at the pre-transplant assessment





Cytomegalovirus Cell-mediated Immunity Assays in Pediatric Transplantation

William R. Otto,^{1,2}  Surabhi B. Vora,^{3,4} and Daniel E. Dulek^{5,6}

¹Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA, ²Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio, USA, ³Division of Infectious Diseases, Seattle Children's Hospital, Seattle, Washington, USA, ⁴Department of Pediatrics, University of Washington, Seattle, Washington, USA, ⁵Division of Pediatric Infectious Diseases, Monroe Carell Jr Children's Hospital at Vanderbilt, Nashville, Tennessee, USA, and ⁶Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, USA

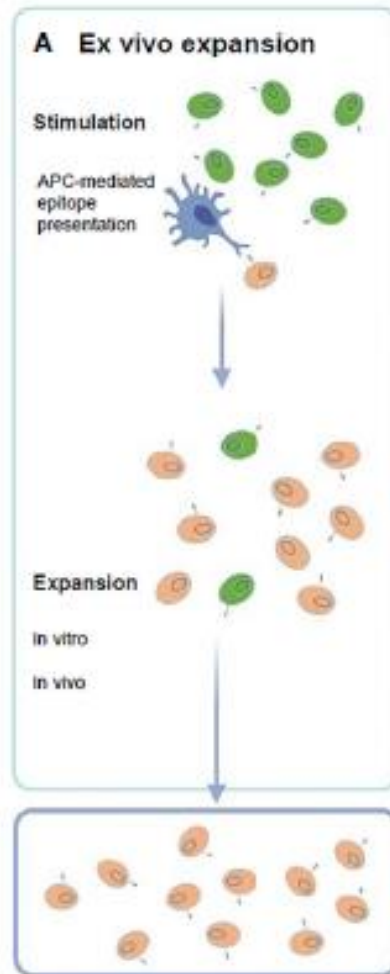


Is It Feasible to Use CMV-Specific T-Cell Adoptive Transfer as Treatment Against Infection in SOT Recipients?

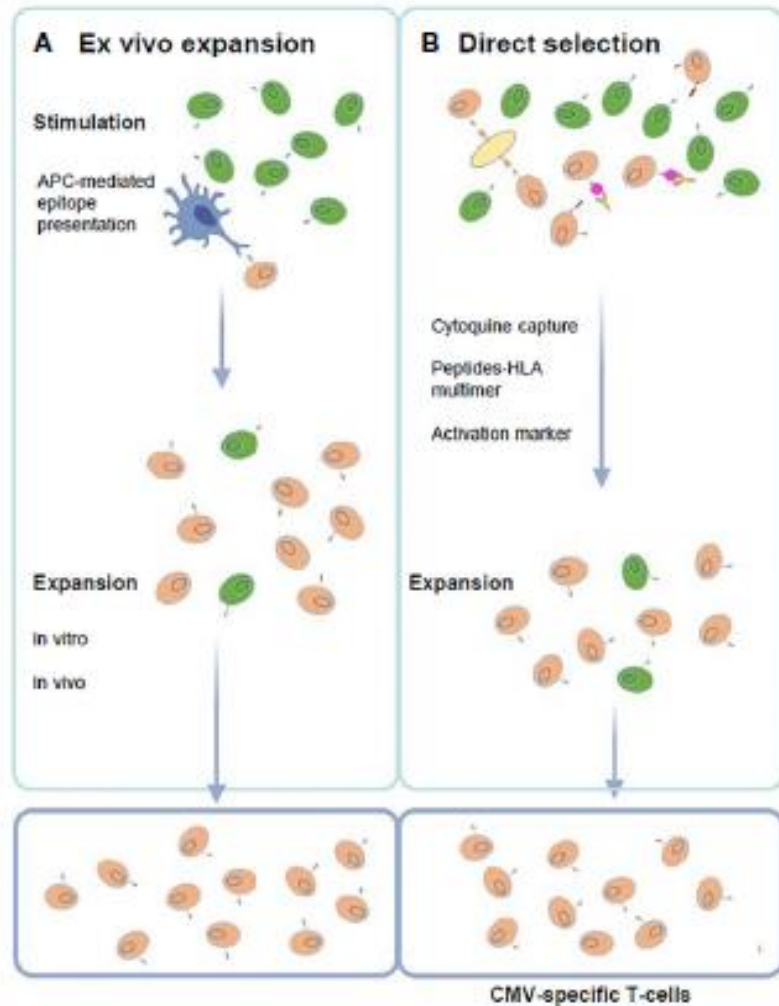
*Estéfani García-Ríos, Marcos Nuévalos, Francisco J. Mancebo and Pilar Pérez-Romero**

National Center for Microbiology, Instituto de Salud Carlos III, Majadahonda, Spain

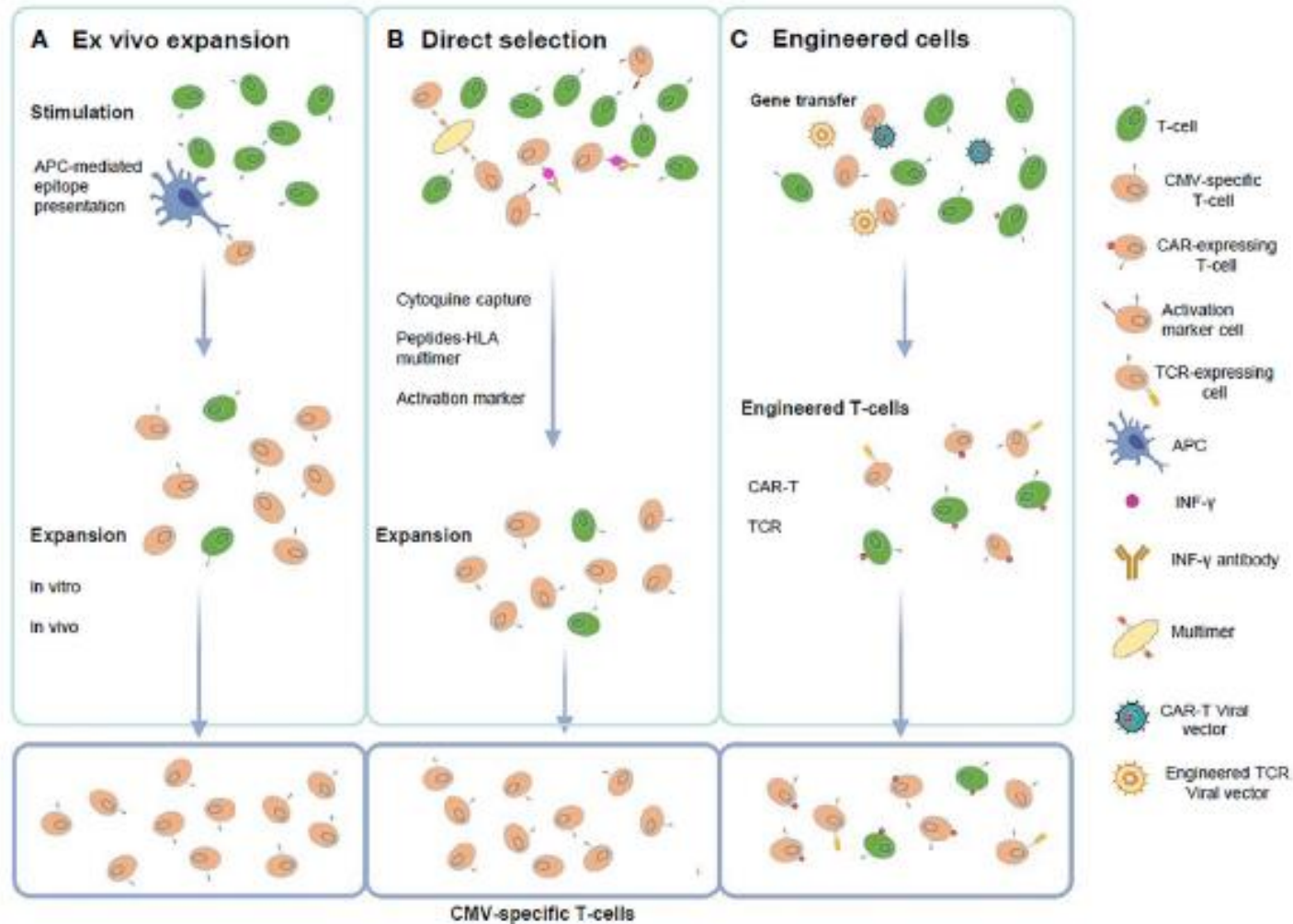
Strategies for the generation of CMV-specific T-cells



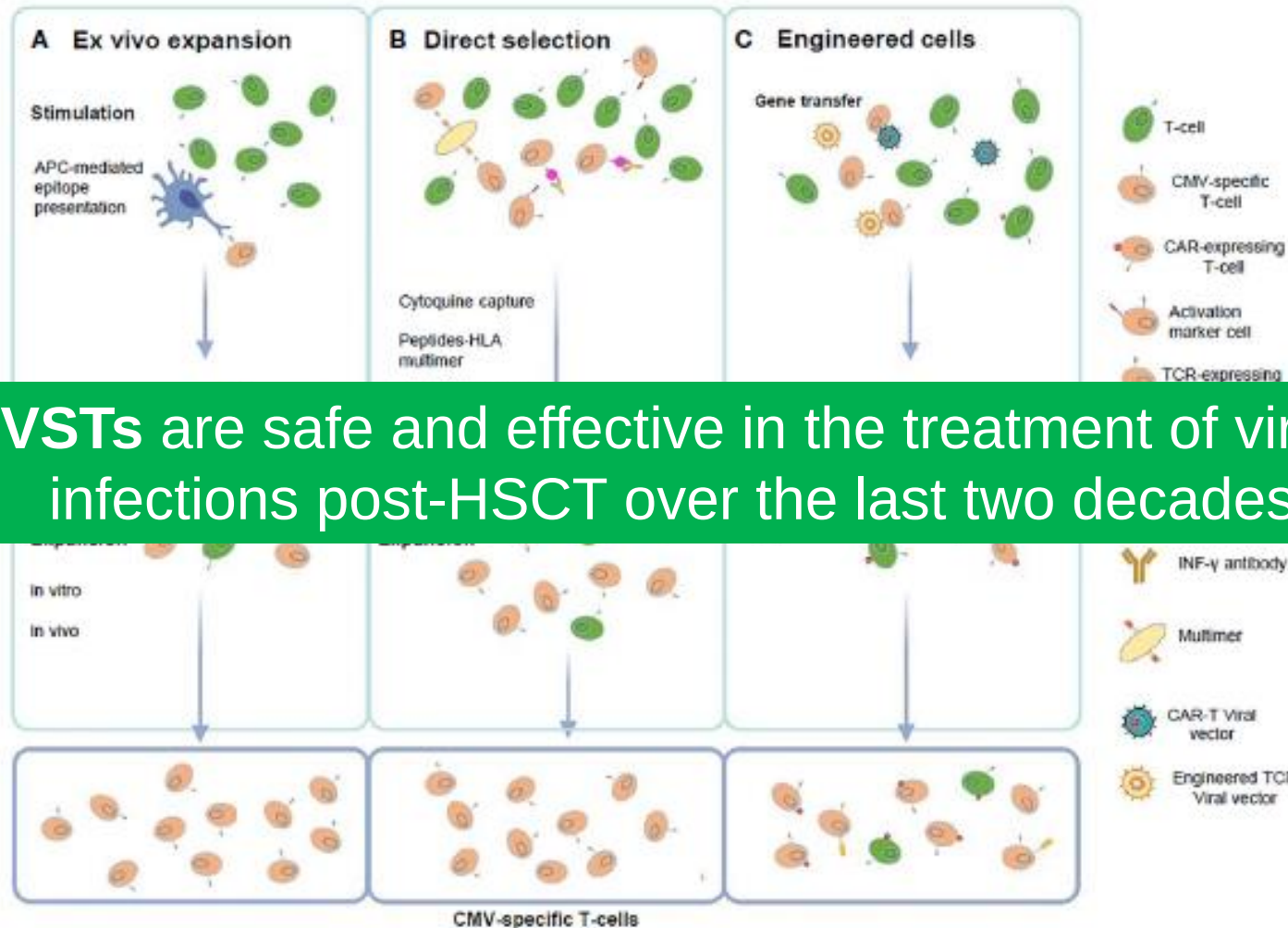
Strategies for the generation of CMV-specific T-cells



Strategies for the generation of CMV-specific T-cells



Strategies for the generation of CMV-specific T-cells



VSTs are safe and effective in the treatment of viral infections post-HSCT over the last two decades

Role of Virus-Specific T Cell Therapy for Cytomegalovirus and BK Infections in Kidney Transplant Recipients

Sandesh Parajuli ¹, Margaret Jorgenson,² Ross O. Meyers,^{3,4} Arjang Djamali,¹ and Jacques Galipeau^{4,5,6}

Registered clinical trials of virus-specific T cells in solid organ transplantation

ID	Cell Therapy	Targets	Indication	N	Solid organ transplant	Virus-specific T Lymphocyte Donor	Primary Endpoint	Site
NCT02779439	CTL	CMV, EBV, ADV	Resistance to Rx >2 wk	25	Any	Allogeneic	Infusion related safety at 1 wk	Sydney
NCT02532452	CTL	EBV, CMV, ADV, or BKV	Any Infection	100	Any	Allogeneic	Infusion related toxicity	Cincinnati
NCT03010332	CTL	CMV	Intolerant to or failed Rx	N/A	Any	Allogeneic (ATA230)	N/A	Atara Biotherapeutics
NCT03950414	CTL	CMV	Intolerant to or failed Rx	20	Kidney	Allogenic	Safety and tolerability	Madison, Wisconsin

CTL, cytotoxic T lymphocytes; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ADV, adenovirus.



REVIEW

published: 07 November 2023

doi: 10.3389/ti.2023.11963



Cytomegalovirus Cell-Mediated Immunity: Ready for Routine Use?

Oriol Bestard^{1,2}, Hannah Kaminski^{3,4}, Lionel Couzi^{3,4}, Mario Fernández-Ruiz^{5,6,7} and Oriol Manuel^{8}*

Conclusions

- Cell-mediated immunity is considered the most important factor in controlling CMV infection.
- Patients deficient in cell-mediated immunity are at greatest risk for CMV disease.
- CMV-specific CD4+ and CD8+ lymphocytes play an important role in immune protection after primary infection or reactivation of latent disease.

Conclusions

- CMV-specific cell-mediated immunity could provide an opportunity for implementing personalized medicine to manage CMV infection in kidney transplantation:
 - Assays to predict the risk of development of subsequent CMV disease
 - Tailoring duration of antiviral prophylaxis
- Cell therapy utilizing Virus-specific T cell therapy offers an attractive alternative approach to traditional interventions in the treatment of CMV after kidney transplant.

WELCOME



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