JNI 20es Journées Nationales d'Infectiologie
Lyon
et la région Auvergne-Rhône-Alpes
du mercredi 5 juin 2019
au vendredi 7 juin 2019

Session Infections chez les patients immunodéprimés

Cytomégalovirus en transplantation

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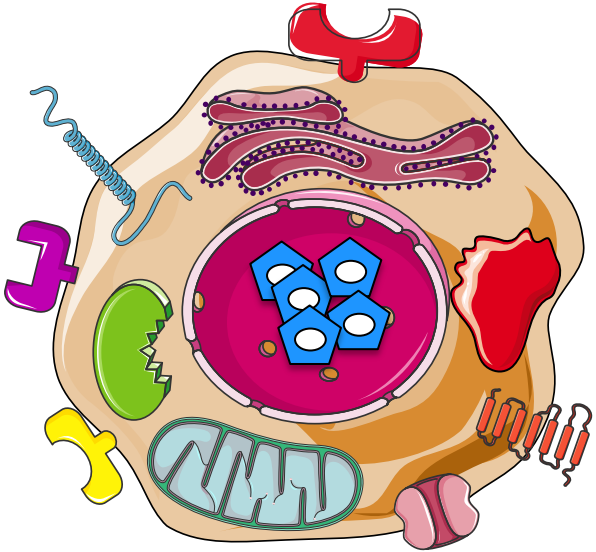
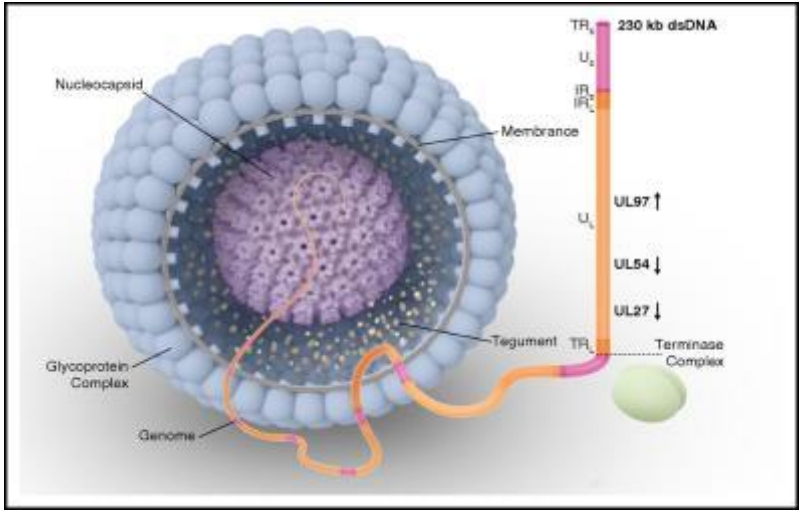
Déclaration d'intérêts de 2014 à 2018

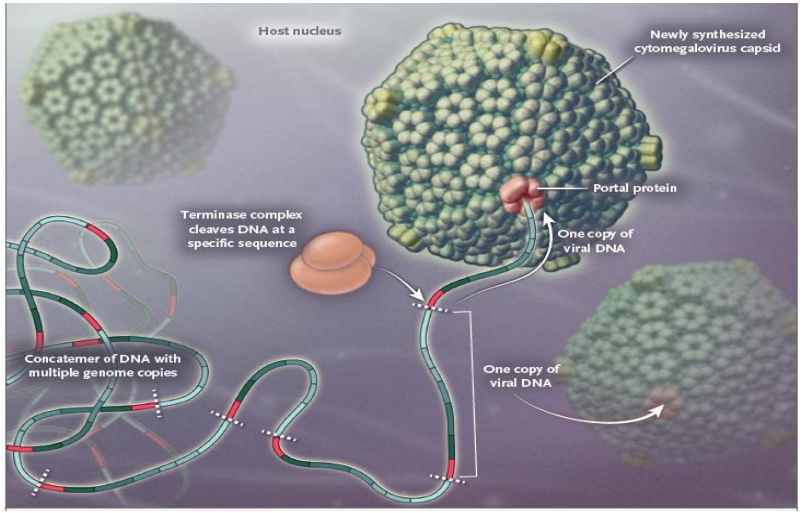
- Intérêts financiers : NON
- Liens durables ou permanents : NON
- Interventions ponctuelles : NON
- Intérêts indirects : NON

CMV exponential phase replication



Target cell

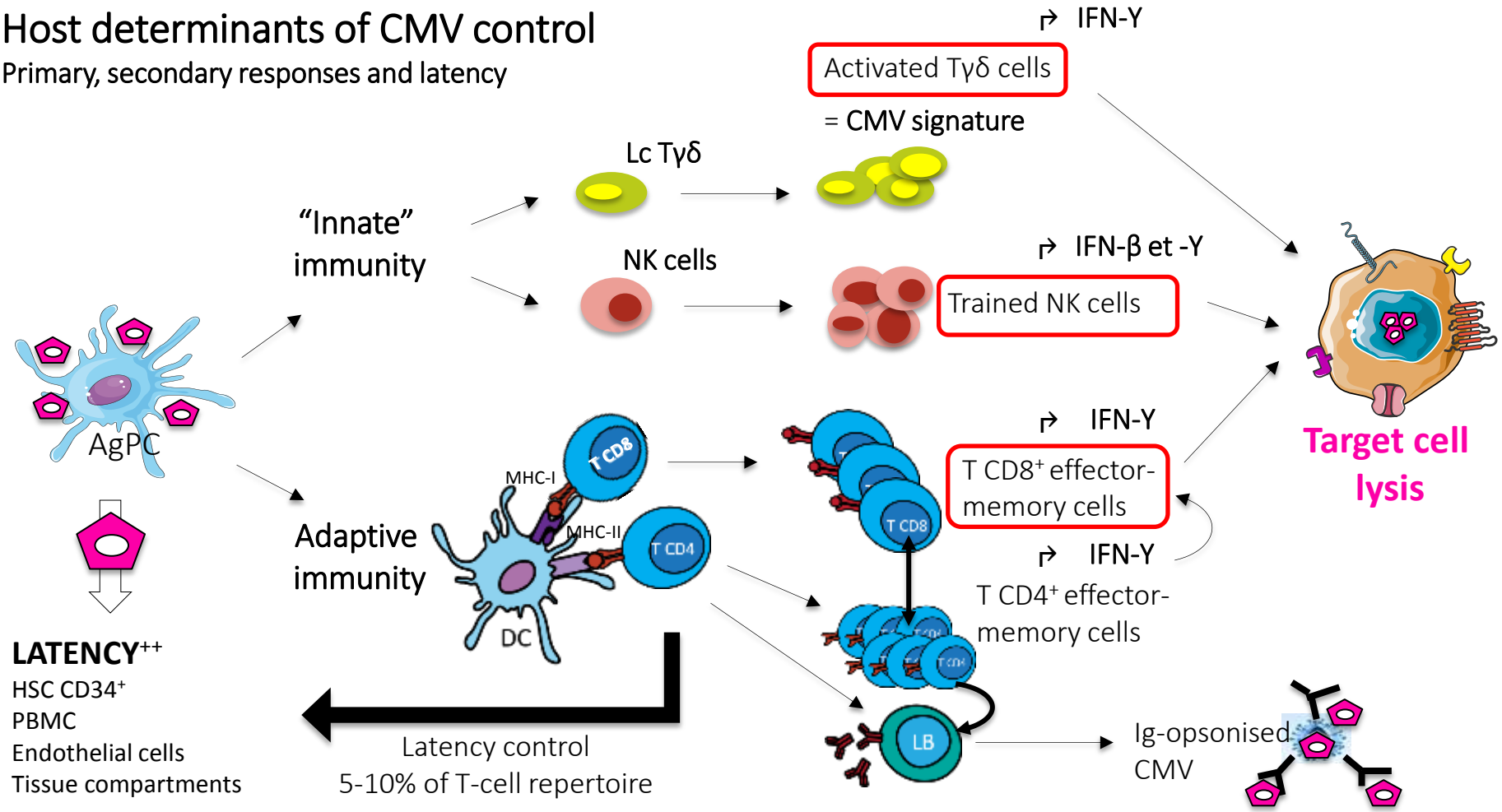




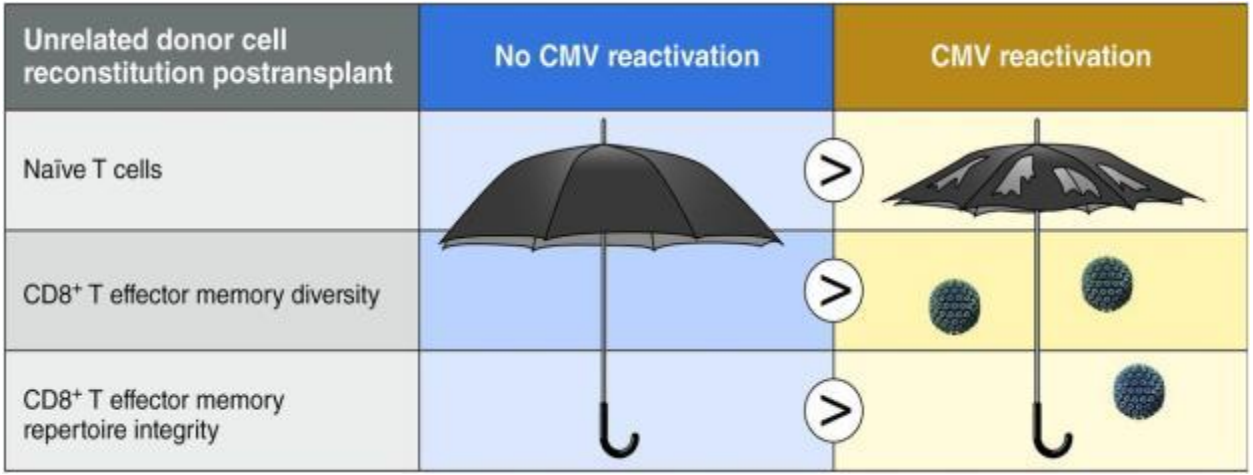
Firas El Chaer et al. Blood 2016;128:2624-2636
Griffiths, PD. NEJM 2014;370:1844

Host determinants of CMV control

Primary, secondary responses and latency



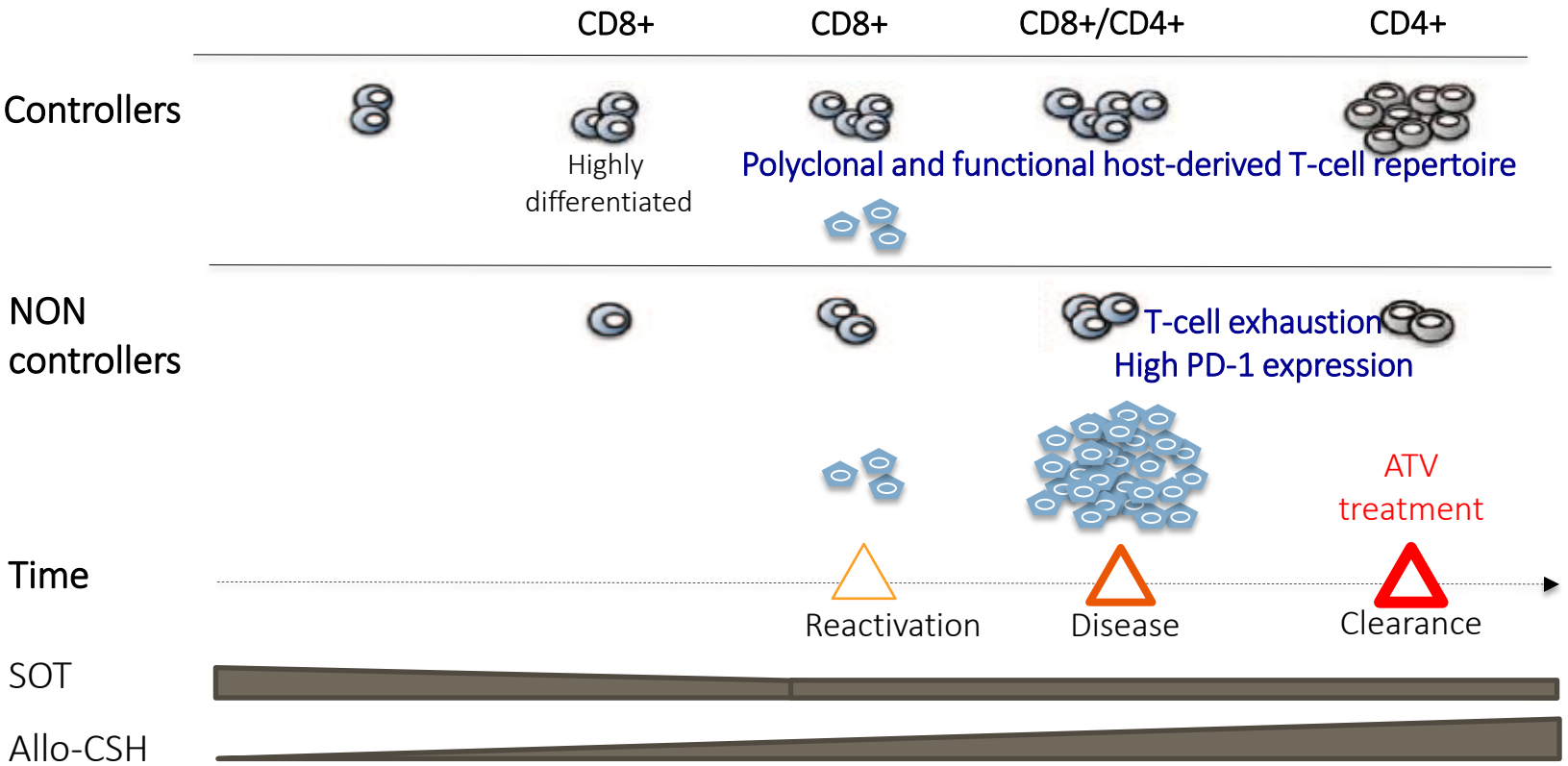
Difference between CMV controllers and non controllers at 12 months after allogeneic HSCT recipients : **defect in T cell effector/memory T CD8⁺ cells**



Everett Meyer Blood 2015;125:3827-3828

blood

T-cell phenotypes after transplantation



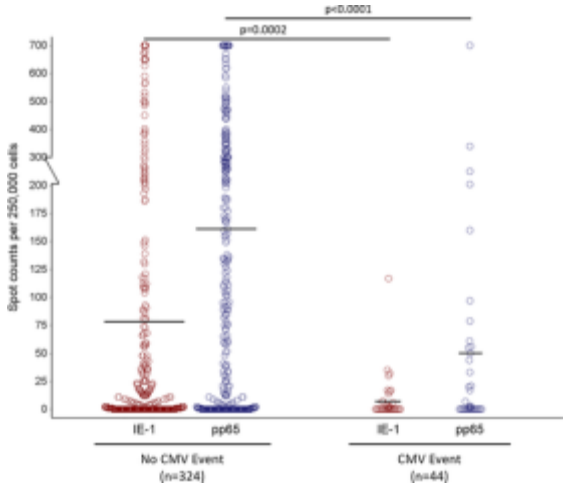
Adapted from Egli A et al. Clin Infect Dis 2012;55(12):1678–89

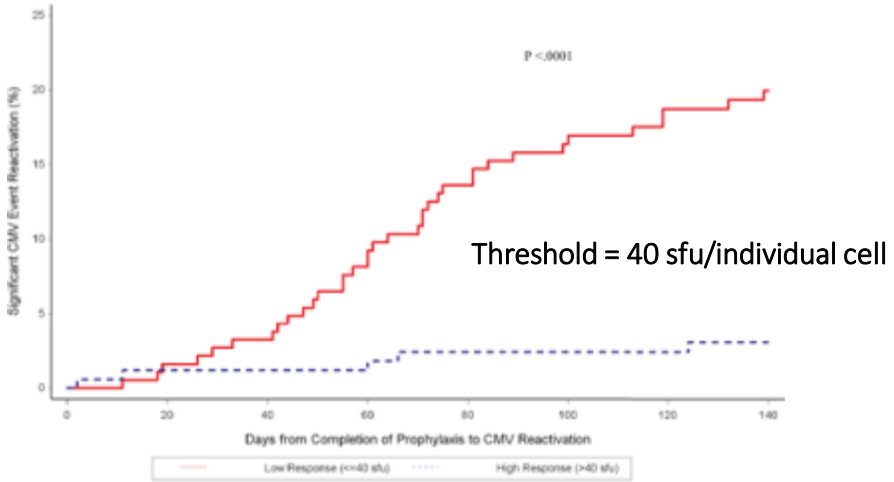
The ability of a CMV ELISPOT assay to predict outcome of low-level CMV reactivation in hematopoietic cell transplant recipients.

El Haddad et al., J Infect Dis 2018; doi: 10.1093/infdis/ jiy592

A prospective multicenter observational study of cell-mediated immunity as a predictor for CMV infection in kidney transplant recipients

Inclusion centers (US, UK, Can), n=43; patients eligible for analysis, n=368; follow-up 12 months



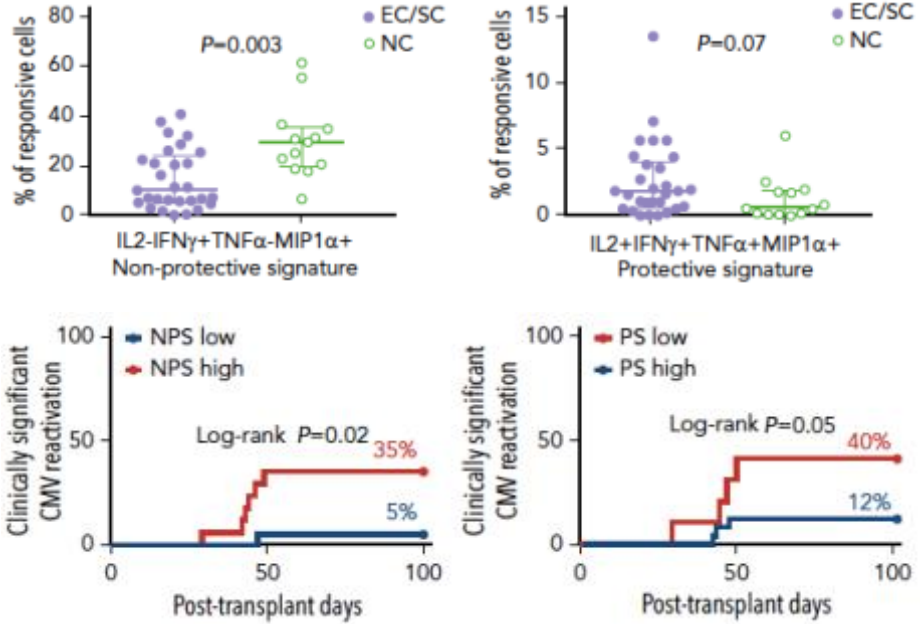


Kumar et al., Am J Transplant 2019, doi: 10.1111/ajt.15315

Deep functional immunophenotyping predicts risk of CMV reactivation after hematopoietic cell transplantation

Single center (US),
n=56 allo-HSCT, CMV-seropositive patients,
Ex vivo $CD8^+$ T-cell cytokine production in response to CMV-pp65 peptides (13-color flow cytometry):

EC: elite controllers (n=19)
SC: spontaneous controllers (n=16)
NC: non controllers (n=21)



Camargo et al., Blood 2019;133(8):867-877

Future directions and challenges of predictive biomarkers of CMV immune status

Composite biomarker signature

In healthy control CVM-positive population and in transplant recipients

e-CRF: demographics, underlying disease, transplant-related characteristics, IS drugs, transplant-related complications, outcome

Blood

Null PHA

NULL pp65 EI-1

SEROLOGY screening
IGRA
IMMUNOPHENOTYPING
Lc proliferation assay + flow cytometry
Composite **CYTOKINE** panel

Blood

Null SEB

CMV epitope(s) ?

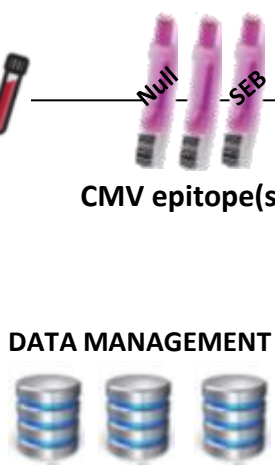
PROTEOMIC
Cytokine panel

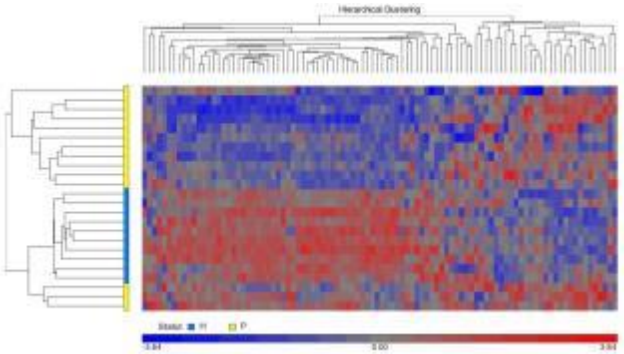
TRANSCRIPTOMIC

nanoString TECHNOLOGIES

"omics"

DATA MANAGEMENT





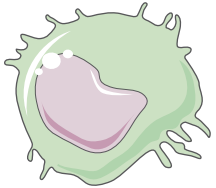
Factors influencing the burden of CMV

VIRAL FACTORS

Replication dynamics
Immune evasion
Viral heterogeneity
Co-infections

HOST FACTORS

D/R immune status
T-cell repertoire
NK cells
Exogenous immunosuppression



CMV prevention

TRENDS

Decrease in incidence of symptomatic disease
Asymptomatic or mildly symptomatic viremia
Fewer cases of tissue invasive disease

ValGCV → GCV

MBV

GCV-P

UL97

GCV-PP

GCV-PPP

Kinases C

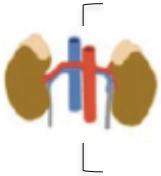
UL27

UL54

CDV-PP

CDV/BCDV

Kinases C



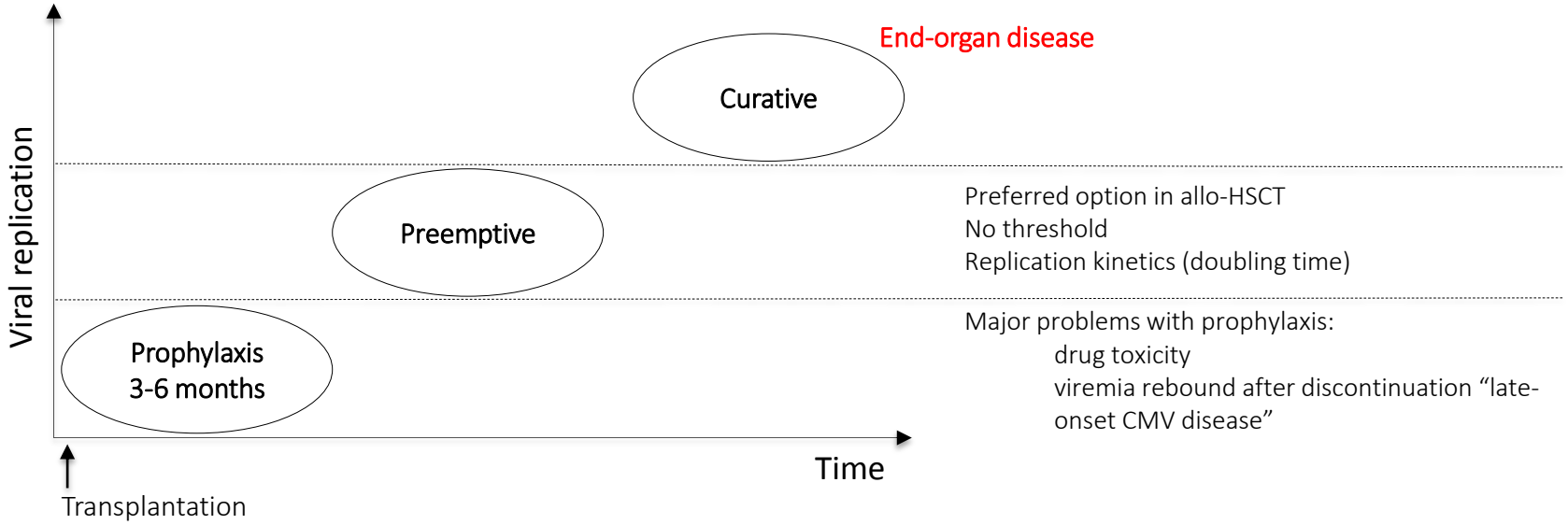
PFA

LTV

UL51/
56/89

- viral phosphotransferase
- DNA polymerase
- cell cycle regulation protein
- terminase complex kinases

Antiviral strategies



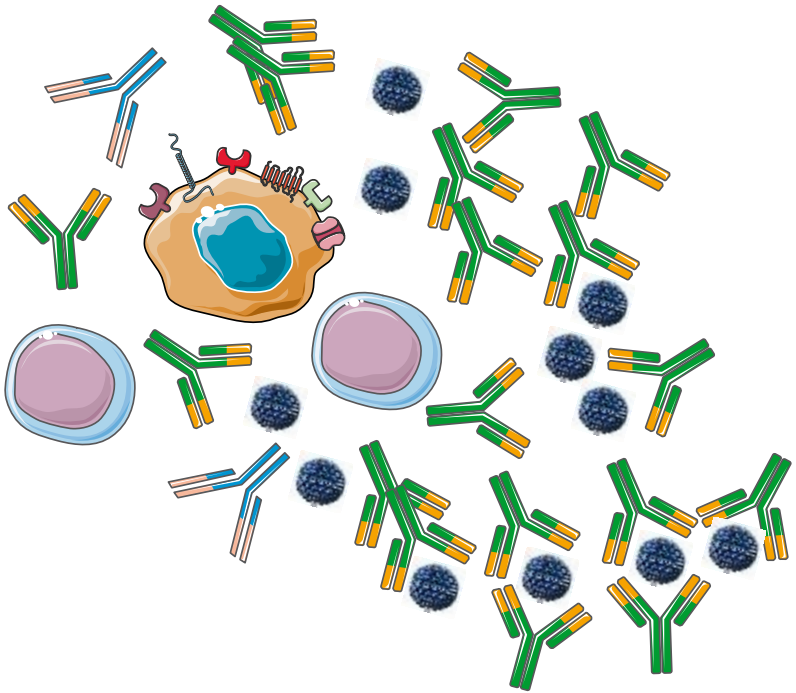
Kotton CN et al. Transplantation 2013 & 2018

Anti-CMV treatment : subsets of suboptimal outcomes

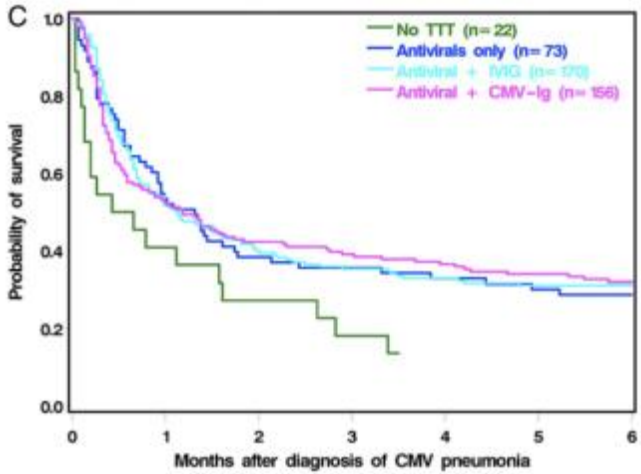
	Refractory	Resistant	Intolerant
Definition	> 1 log_{10} increase in CMV viremia > 2 w appropriately dosed ATV therapy	Viral mutation(s) ! CNR Limoges ! 	Dose-limiting adverse event(s)
Mechanism	Inadequate ATV drug delivery/dose or potency	One or several CMV gene point mutation(s)	Bone marrow toxicity Renal impairment
Consequence(s)	Persistent viral load despite ATV	Exponential increase in viral load	
Complication(s)	End-organ disease	End-organ disease	

Chemaly et al., Clin Infect Dis 2019;68(8):1420–6
for the Resistant Definitions Working Group of the Cytomegalovirus Drug Development Forum

Immunoglobulin-based treatment



IVIG or highly enriched
Free particle clearance “tip of the iceberg”
Transient effect
Cost/benefit
CMV pneumonia (?)



The addition of IV pooled or CMV-specific Igs to antiviral treatment did not improve overall or attributable mortality

Erard et al., Clin Infect Dis 2015

Overview of current developments

New drugs : MBV/LTV
Adoptive T-cell transfer

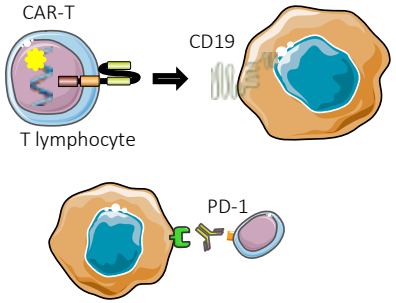
	MARIBAVIR (MBV)		LETERMOVIR (LTV)	
Drug *vs.* placebo	Lancet Infect Dis 2011	n=90, double-blind 2:1 randomization, oral MBV 100 mg twice daily	N Engl J Med 2017	n=67, double-blind, 2:1 randomization, oral or IV LTV 480 mg once daily (or 240 mg if taken with cyclosporine)
Patients		HSCT recipients		HSCT recipients
Primary end-point		Incidence of CMV disease within 6 months of transplantation		Clinically significant CMV infection through week 24 after transplant
Study outcome		CMV disease: 4.4% at month 6 (placebo 4.8%; OR 0.90) CMV infection: 34.6% at day 100 (placebo 40.5%; OR 0.77)		CMV disease: 1.5% at week 24 (placebo 1.8%) CMV infection: 37.5% at week 24 (placebo 60.6%; $p < 0.001$)
Mortality		All-cause mortality at day 100: 7% (placebo 9%)		All-cause mortality at week 24: 10.2% (placebo 15.9%; $p = 0.03$)
Most recent study	Clin Infect Dis 2019	n=120, phase II trial, randomized, double-blind, 1:1:1 twice-daily dose-ranging MBV 400, 800, or 1200 mg	Transplantation 2019	n=6, salvage therapy in refractory CMV disease
Patients		HSCT and SOT recipients		HSCT and SOT recipients
Primary end-point		Proportion of patients with confirmed undetectable plasma CMV DNA within 6 weeks of treatment		Mixed efficacy in patients with refractory CMV infection suggesting that LTV may be a useful therapeutic adjunct, potentially in combination with other ATV . RESISTANCE
Study outcome		CMV infection: 25% vs. 17.5% vs. 25% CMV disease : 15% vs. 17.5% vs. 7.5%		
Mortality		Similar across treatment		

Marty et al., Lancet Infect Dis 2011; Marty et al., N Eng J med 2014; Papanicolau et al. Clin Infect Dis 2019, Humar et al. Transplantation 2019

Adoptive immunotherapy of viral infections: should infectious disease embrace cellular immunotherapy ?

Michael Boeckh and Lawrence Corey
Editorial commentary. J Infect Dis 2017; 926-928

Immunotherapy of cancer



Combined approaches including active immunotherapy

Immunotherapy of CMV infection

Issues and limits

- timely production of T-cells,
- donor product issues (matching, donor seropositivity),
- exposure of products to CST and IS drugs,
- no controlled trials (non-inferiority),
- management of cytokine release Sd,
- cost/benefit

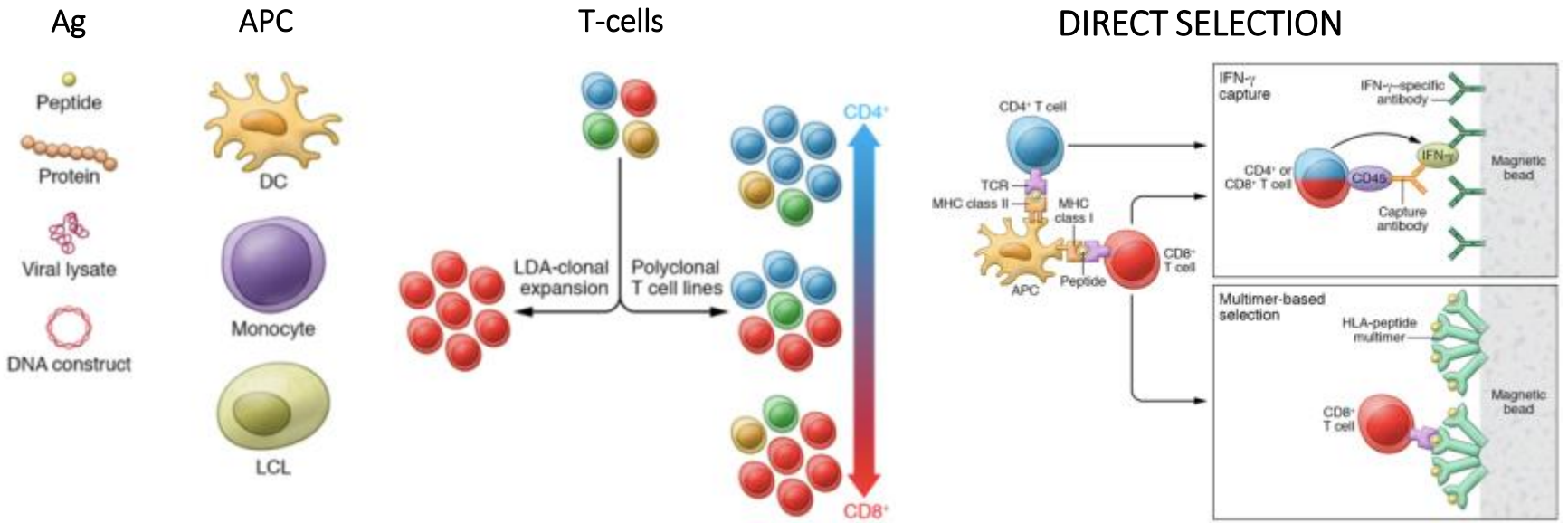
Prospect

Many of these issues have been addressed:

- availability of multi-target T-cell products in an "off the shelf " approach,
- reports of *in vivo* antiviral activity and clinical responses, under certain conditions.

"The feasibility to manufacture multi-target cellular therapies has been demonstrated; the time is now to systematically assess their value in infectious disease."

Ex vivo manufacturing of virus-specific T-cells (VST)



Virus-derived peptides, proteins, viral lysate

APC from autologous or CMV-positive donor or genetically-engineered APC

Ag-specific T-cell induction and expansion

Roddies C & Peggs KS. J Clin Invest 2017

The Journal of Infectious Diseases MAJOR ARTICLE

CMV-specific T-cell transfer for refractory CMV infection after haplo-identical stem cell transplantation: the quantitative and qualitative immune recovery for CMV

Pei et al., J Infect Dis 2017

Design:
Single-center, n=32 infused
PBMCs from healthy CMV-positive donors, 7d expansion
Flow cytometry = count of IFN-γ-producing $CD4^+$ and $CD8^+$ specificity = 51.2%

Primary end-point = safety (infused-related toxicities)

Safety:
Adverse events: nausea, fatigue

Efficacy:
Improvement in proliferative capacity of the CMV-specific CD8+ T cells
Decreased expression of PD-1 on CMV-spcfq T cells
CMV clearance: 27/32

Clinical Infectious Diseases MAJOR ARTICLE

Autologous adoptive T-cell therapy for recurrent or drug-resistant CMV complications in solid organ transplant recipients: a single-arm open-label phase I clinical trial

Smith et al., Clin Infect Dis 2018

Design:
Single-center, n=13 infused
Autologous PBMCs – 14d expansion
Median Ag IFN-γ-producing $CD8^+$ specificity = 51.2%

Primary end-point = safety

Safety:
Adverse events: nausea, fatigue
No change in graft status

Efficacy:
Clinical response 11/13
Anti-CMV response (median) : $3.2x10^4$ to $1.2x10^3$ copies/mL (> 1 log)
ATV discontinuation: 5/13

Future directions and challenges of anti-CMV immunotherapy

1. Standardization of manufacturing
2. Storage and quality control : assessment of poly-functional T-cell repertoire
3. T-cell stocks: “off the shelf samples” ready for infusion
4. Open randomized controlled trials of non-inferiority *vs.* ATV prophylaxis or preemptive strategy
5. Long-term evaluation on immune reconstitution and graft tolerance

Conclusions

Cell-mediated immune assays = characterizing **CMV-specific signature**
composite immune biomarkers associated with control

Antiviral drug pipeline : MBV and LTV

Harmonization of definitions: refractory/resistant/intolerant CMV infections

2018: 3^{d} international consensus guidelines on the management of CMV in solid organ transplantation

T-cell adoptive transfer

CMV vaccine

Alternatives : « repurposing »

Inhibiteurs de mTOR: EVEROLIMUS, Sirolimus
Kidney transplantation
Cross-effect BK virus nephropathy

Pacual J et al. Transpl Infect Dis. 2016 Dec;18(6):819-831
Hocker B et al. Am J transplant 2016

ARTESUNATE (accès palustre)
Inhibition des l'expression des protéines très précoces du CMV

Efferth and Kaina, Critical Reviews in Toxicology, 2010, 1–17
Shapira et al., CID 2008:46
Wolf et al.,Antiviral research 2011

LEFLUNOMIDE (polyarthrite rhumatoïde)
Inhibe les étapes tardives du cycle viral (tégumentation du virion)

Chacko and John, Transplant infectious disease 2012;14: 111–120

Leflunomide

- Immunosuppressant agent (indication arthritis)
- Activity against CMV *in vitro*: inhibits apoptosis
- Case reports and small series for refractory CMV infection and disease
- May work in combination
- Monitoring for toxicity required:
  Hematologic
  Hepato-pancreatic
- Systematic evaluation needed