CMV hyperimmunglobulin Role In Allo-Immune Response

Konrad Hoetzenecker

Dept of Surgery – Medical University of Vienna

CMV

Incidence of infectious diseases in solid organ transplant recipients (%)

Type of infection	Liver	Kidney	Heart	Lung/Heart-Lung	Pancreas/Kidney-Pancreas
bacterial infections	33-68	47	21-30	54	35
CMV	22-39	8-32	9-35	39-41	50
HSV	3-14	53-1-42	1-42	10-18	6
VZV	5-10	4-12	1-12	8-15	9
Candida spp.	1-26	2	1-5	10-16	32
Mycelial fungi	2-4	1-2	3-6	3-19	3
Pneumocystis carinii	4-11	5-10	1-8	15	NA

CMV = cytomegalovirus; HSV = herpes simplex virus; VZV = varicella zoster virus; NA = not available

Patel et al. Clin Microbiol Rev. 1997 Jan;10(1):86-124.

CMV

- Universal prophylaxis
- Pre-emptive therapy

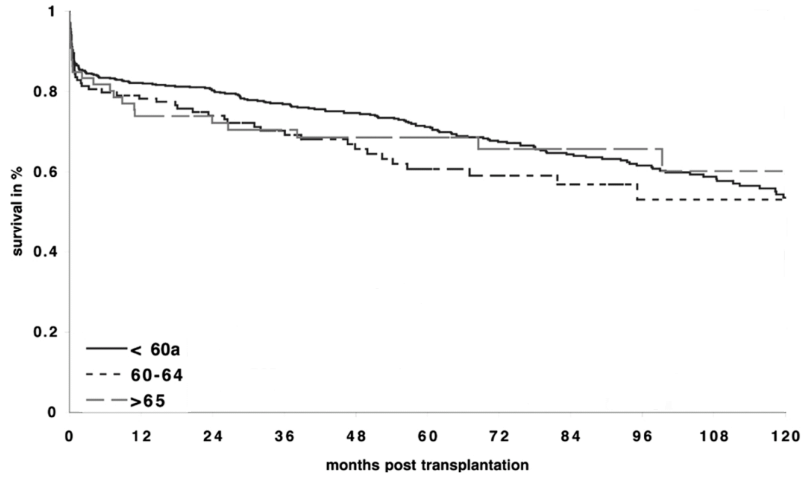
- Anti-viral drugs: (Val)ganciclovir, foscarnet, cidofovir, (aciclovir)
- CMV hyperimmunglobulin (CMVIg)

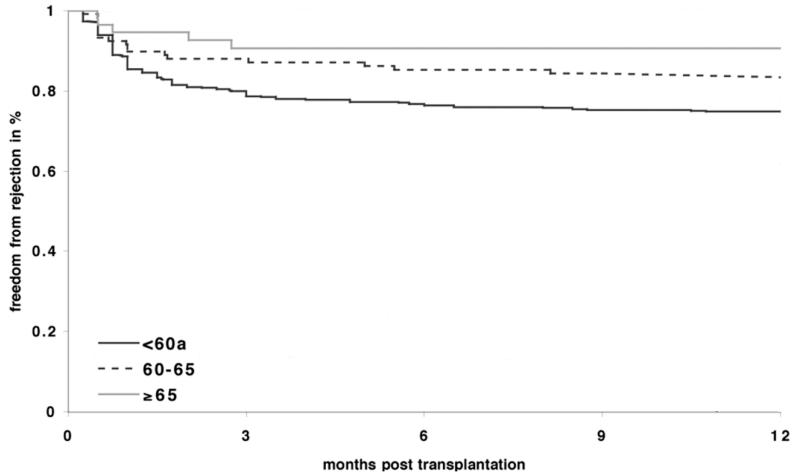
Patient-Management in Vienna

- Triple therapy + induction with rATG
- CMVIg iv day 1, 7, 14, 21, 28 post-operatively (100mg/kg)
- + high-risk patients (D+/R-): ganciclovir

Patient-Management in Vienna

Zuckermann et al. **Long-term survival (>10 years) of patients >60 years with induction therapy after cardiac transplantation.** Eur J Cardiothorac Surg. 2003 Aug;24(2):283-91

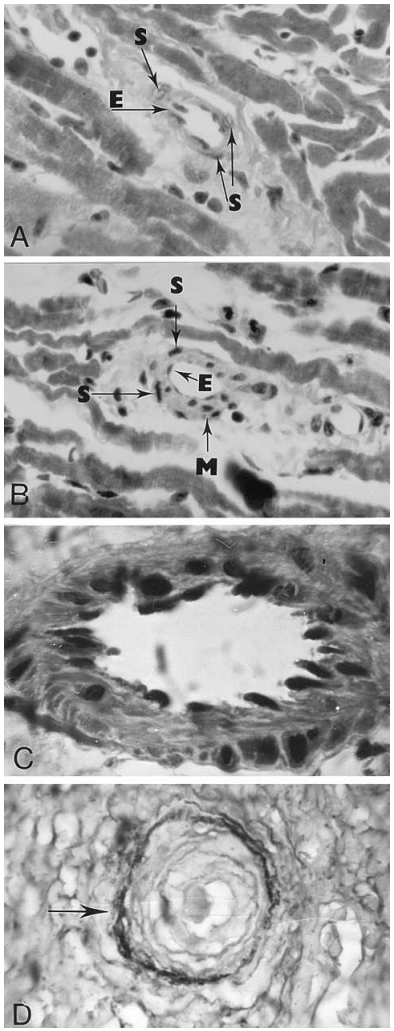




MEDIZINISCHE UNIVERSITÄT WIEN

CMV

- Acute rejection
  - MHC I/II ↑↑↑
  - NfκB
- Chronic graft dysfunction

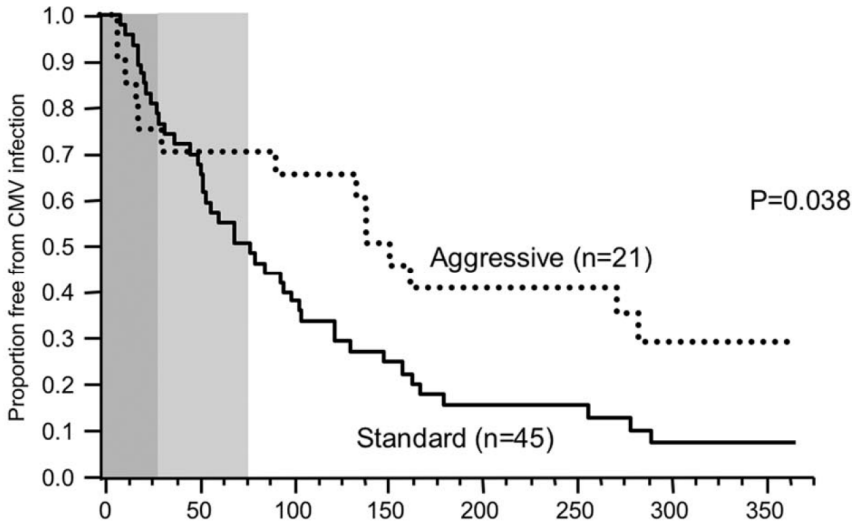


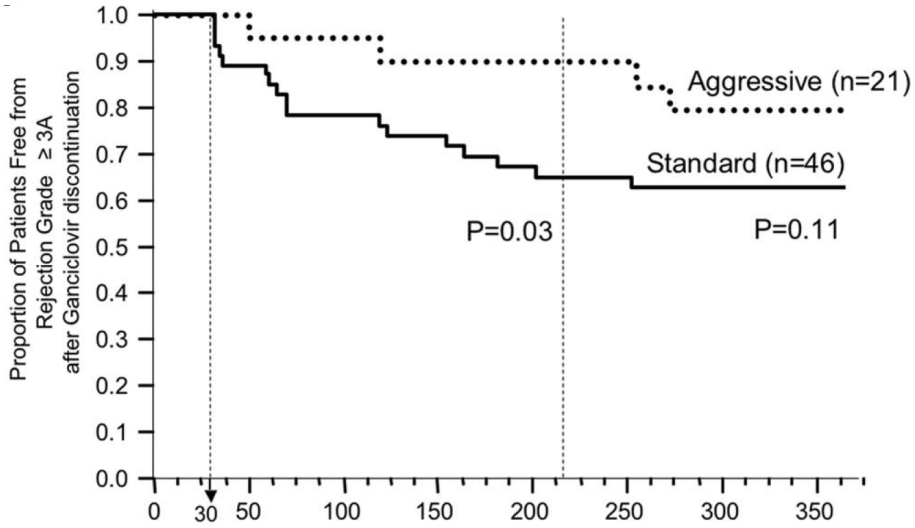
Lemstrom et al. Circulation 1995, 92:2594-2604.

CMVIg

Acute Rejection and Cardiac Allograft Vascular Disease Is Reduced by Suppression of Subclinical Cytomegalovirus Infection

Luciano Potena,[1,2] Cecile T. J. Holweg,[1] Clifford Chin,[1] Helen Luikart,[1] Dana Weisshaar,[3] Balasubramanian Narasimhan,[4] William F. Fearon,[1] David B. Lewis,[5] John P. Cooke,[1] Edward S. Mocarski,[6] and Hannah A. Valantine[1,7]





CMVIg

IMPACT OF CYTOMEGALOVIRUS HYPERIMMUNE GLOBULIN ON OUTCOME AFTER CARDIOTHORACIC TRANSPLANTATION

A Comparative Study of Combined Prophylaxis with CMV Hyperimmune Globulin Plus Ganciclovir Versus Ganciclovir Alone

Hannah A. Valantine,[1,10] Helen Luikart,[2] Ramona Doyle,[3] James Theodore,[4] Sharon Hunt,[5] Philip Oyer,[6] Robert Robbins,[7] Gerald Berry,[8] and Bruce Reitz[9]

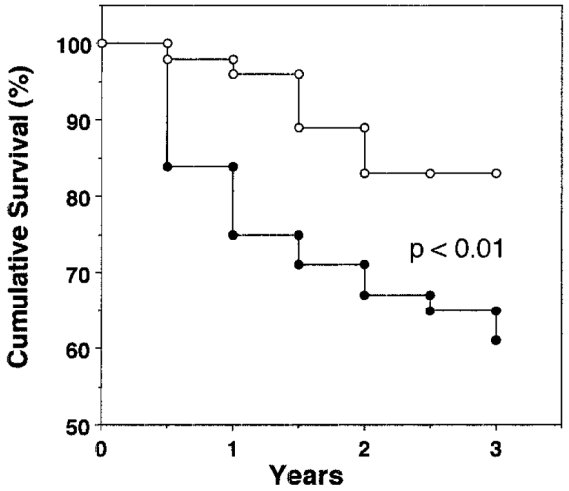


FIGURE 1. Actuarial survival after heart transplantation in patients receiving prophylaxis with CMVIG plus ganciclovir (open circles) compared with patients receiving ganciclovir alone (closed circles).

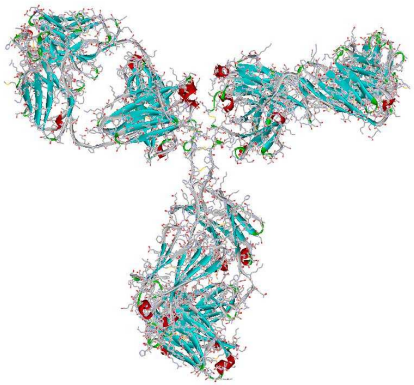
Aggressive treatment: Ganciclovir + CMVIg

CMV eradication

- Acute rejection
  - MHC I/II ↑↑↑
  - NfκB
- Chronic graft dysfunction

CMVIg

- Pooled immmunoglobulins of hundreds CMV-seropositive donors; CMV-titer > 1:7000.
- related to IvIg



Ivlg

- iv administration of immunoglobulins technically possible since 1970
- originally utilized as a substitution therapy in congential immune deficiency disorders
- since 80s increasing indications in autoimmune diseases and inflammatory disorders

IvIg

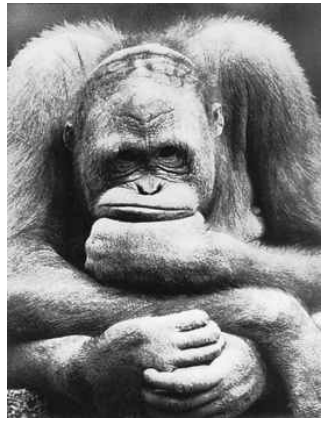
Proved beneficial effects of IvIg therapy (adapted from Emmi et al)
Acquired immune thrombocytopenias
Autoimmune neutropenias
Autoimmune hemoltic anemia
Autoimmune erythroblastopenia
Autoimmune myocarditis
Von Willebrand's disease
Hemophilia A and B associated with antibodies to factors VIII and IX
Dermatomyositis
SLE
Lambert-Eaton syndrome
RA
ANCA positive systemic vasculitis
Goodpasture's syndrome
Antiphospholipid syndrome
Chronic fatique syndrome
MS
Intractable childhood epilepsy (Lennox Gastaut and West's syndrome)
Rasmussen encephalitis
Stiff-man snydrome
Thyroid-related eye disease
therapy-refractory kidney and bone marrow graft rejections
GvH disease
Steroid dependent asthma
IBD

Abbr.: SLE - systemic lupus erythematosis, RA - rheumatoid arthritis, ANCA - anti neutrophil cytoplasmatic antibodies, MS - mulitple sclerosis GvH - graft versus host, IBS - inflammatory bowel diseases

Emmi et al. Neurol Sci. 2002 Apr;23 Suppl 1:S1-8.

Ivlg

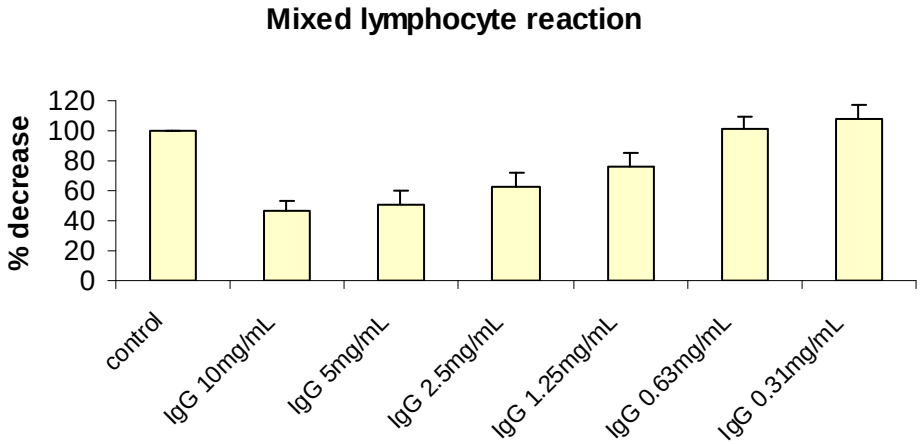
- Mode(s) of action still unclear → many theories



- Natural antibodies
- Anti-idiotype antibodies
- Modulation of complement
- Auto-antibodies
- Triggering of Fc-receptors
- Acceleration of auto-antibody catabolism by binding to FcRn

→ immunomodulatory effects

IvIg data of our group



Pooled IgG (Sigma) – MLR

IvIg suppress clonal proliferation

Aim of the Study

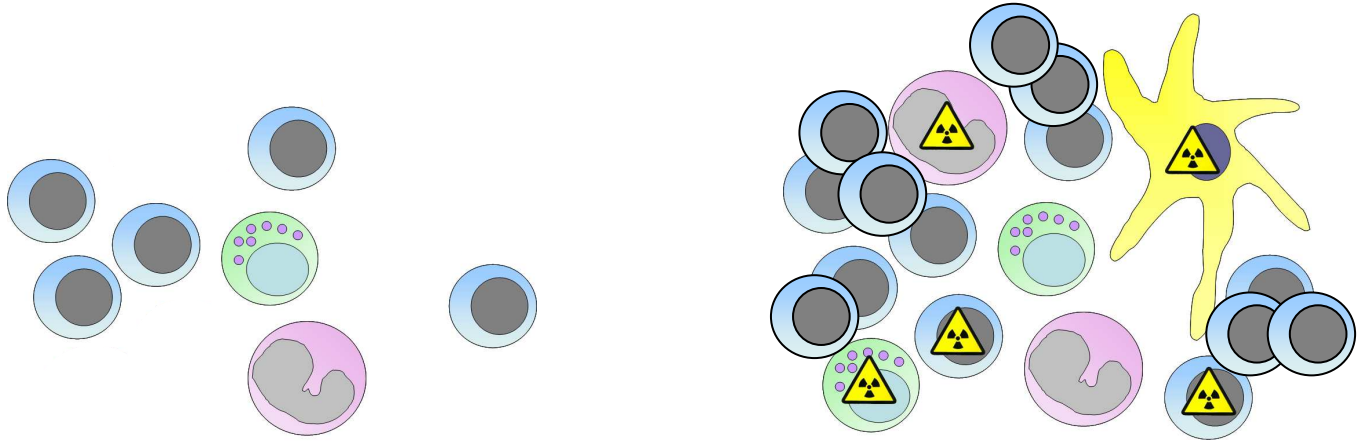
- **Describing effects of CMVIg on transplant-relevant immune functions**
- **Effector cells (T cells, NK cells)**

  (1) inhibition of proliferation?
  (2) cell viability?
  (3) NK cell function?

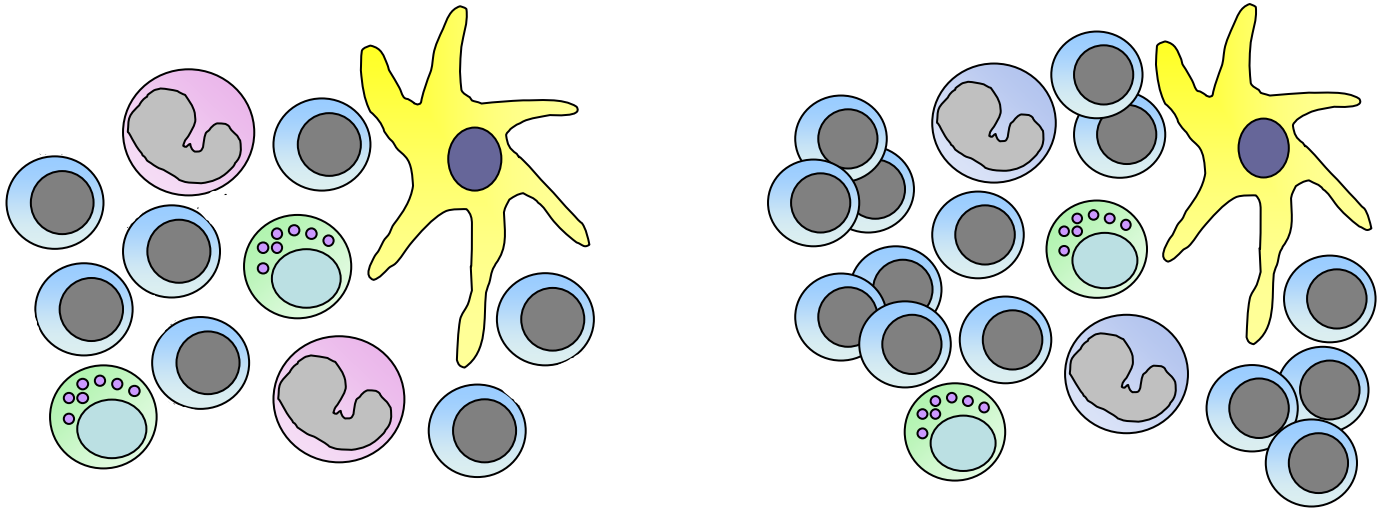
- PBMCs (Peripheral blood mononuclear cells) of 10 healthy volunteers
- Cytotect® - Biotest, Cytoglobin® - Bayer; in therapeutical concentrations (2.5 mg/mL)

(1) inhibition of proliferation?

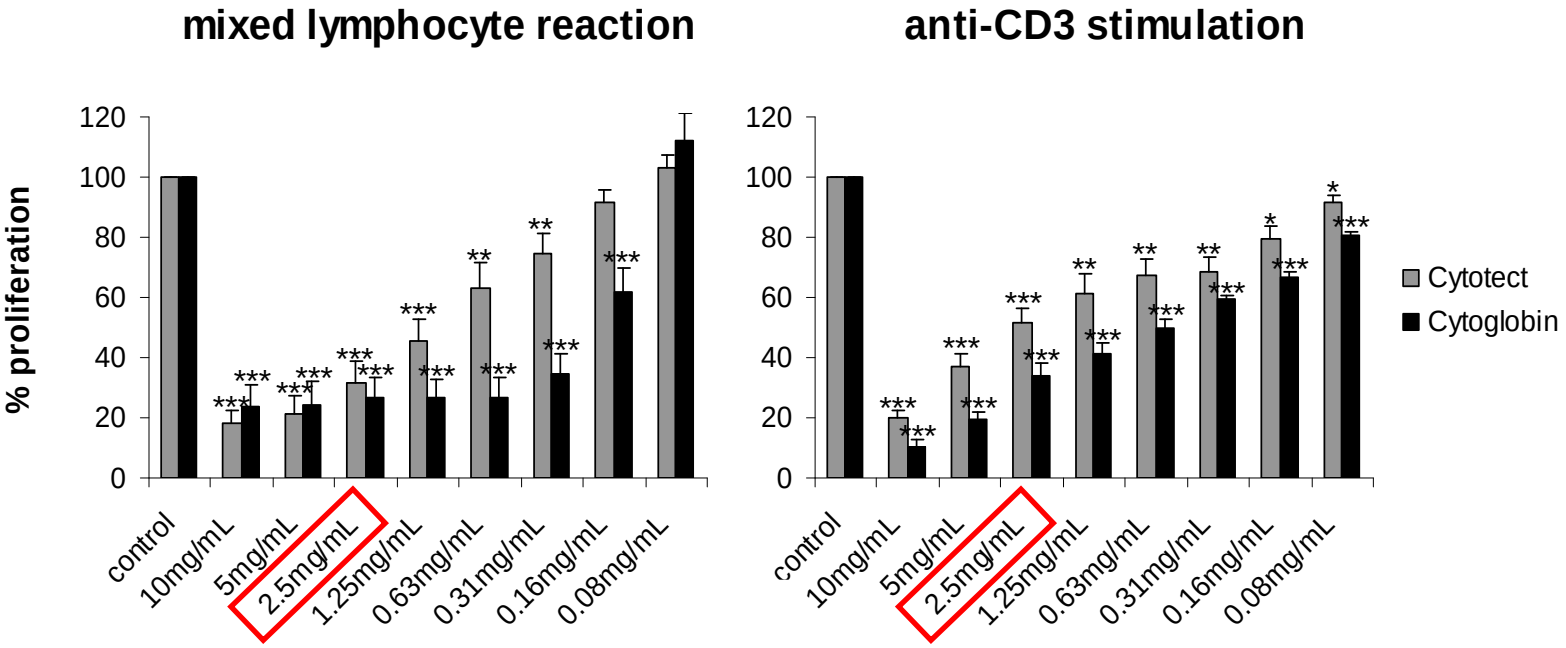
Mixed lymphocyte reaction (MLR)



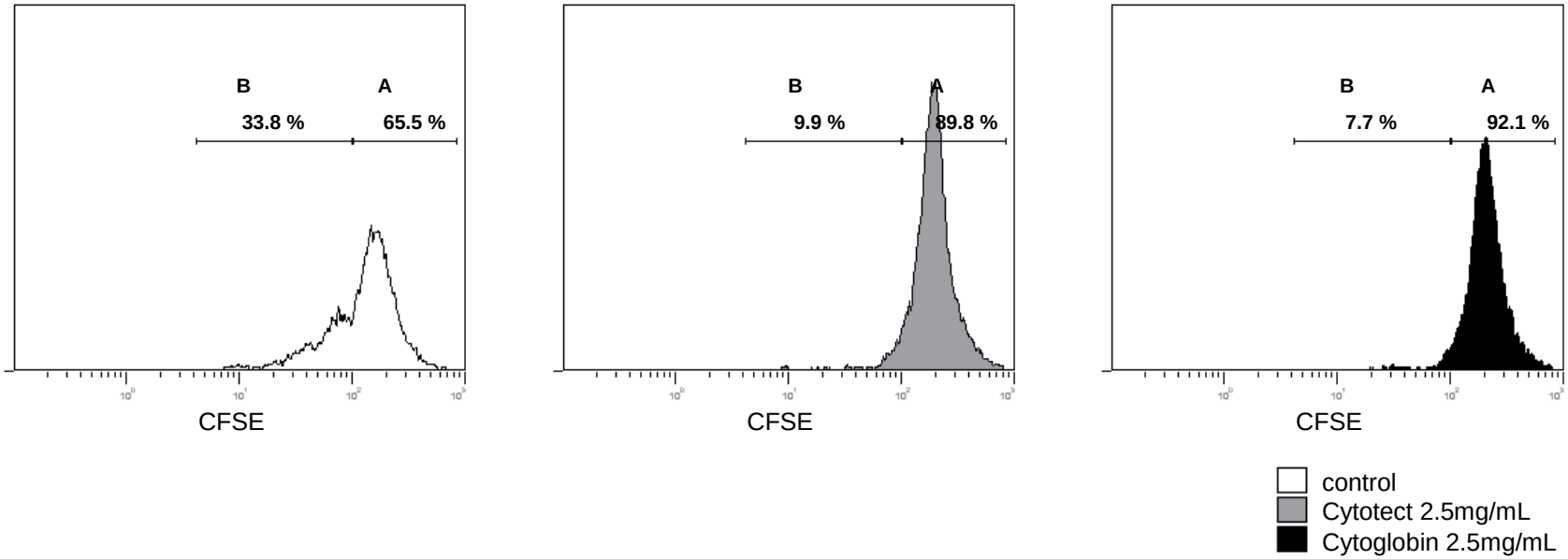
anti-CD3 blastogenesis assay



(1) inhibition of proliferation?

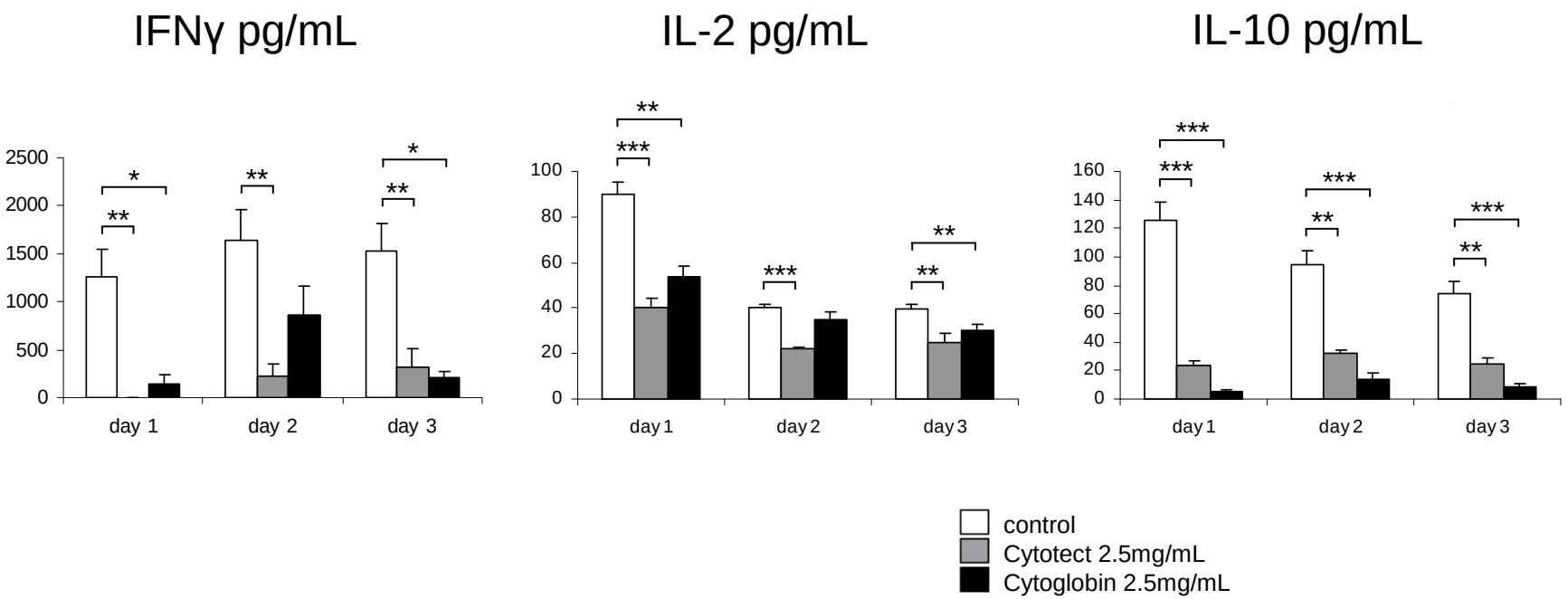


(1) inhibition of proliferation?

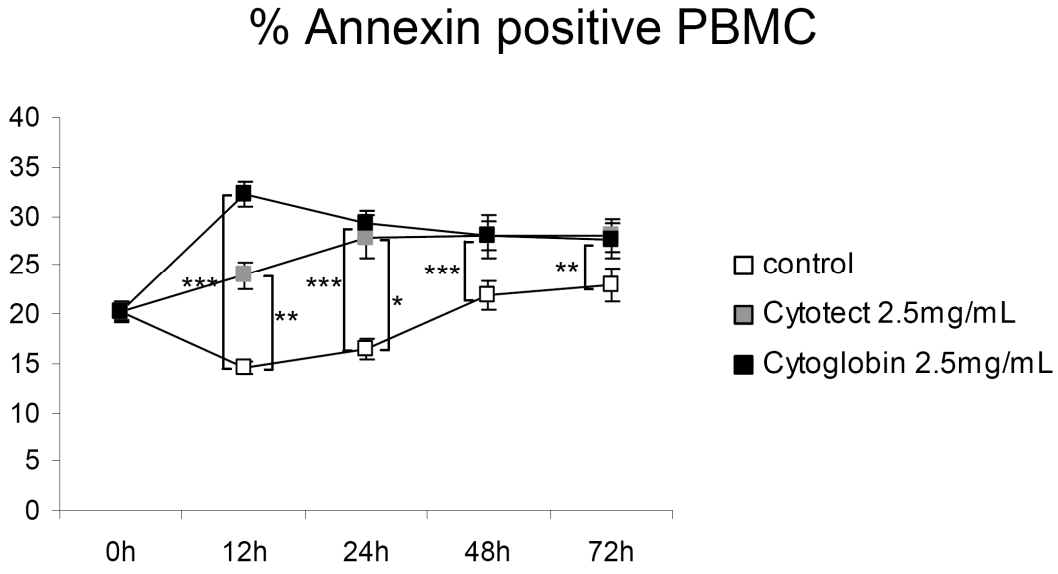


	% G0-G1	% S	% G2-M
control	85,3 ± 2,9	11,7 ± 2,3†‡	3,0 ± 0,7†‡
Cytotect 2.5mg/mL	98,8 ± 0,3	1,1 ± 0,3†	0,1 ± 0,1†
Cytoglobin 2.5mg/mL	95,9 ± 1,4	3,7 ± 1,1‡	0,4 ± 0,4‡

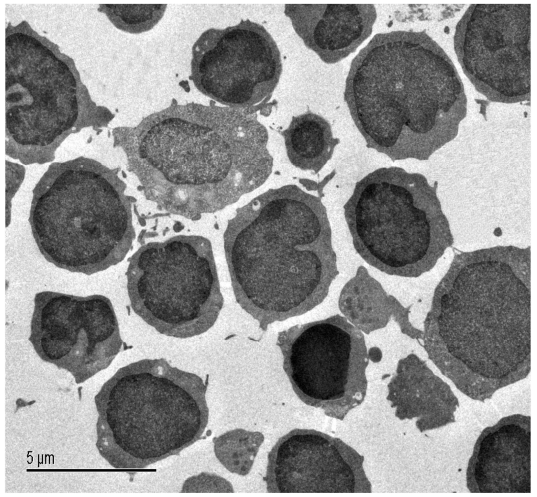
cells reduce their cytokine-talk



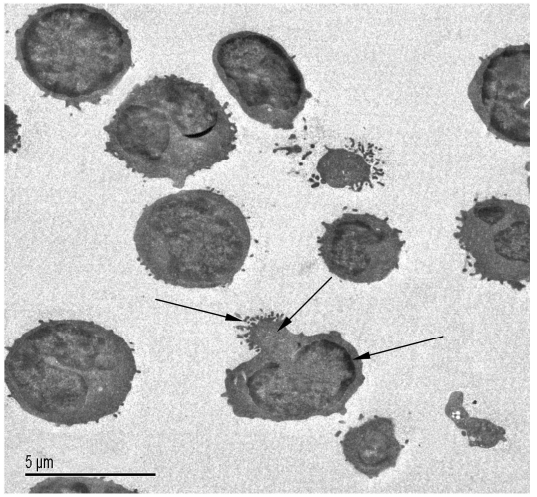
(2) cell viability?



control

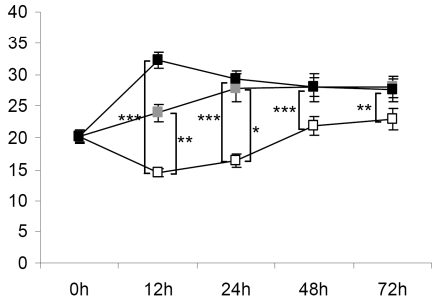


CMVIg-incubated

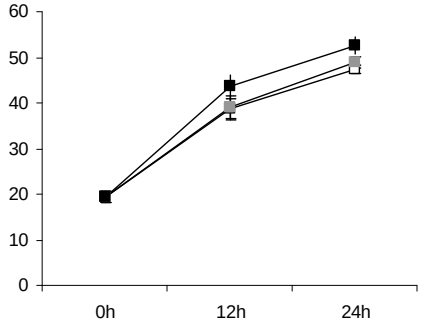


(2) cell viability?

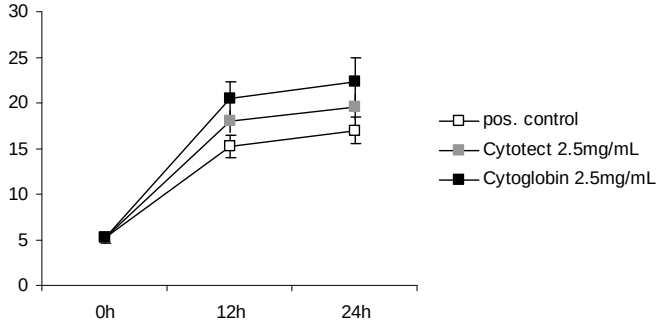
% Annexin positive PBMC



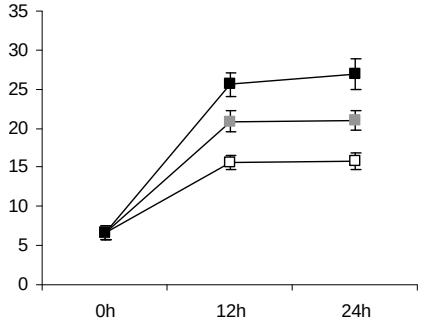
CD19+ cells



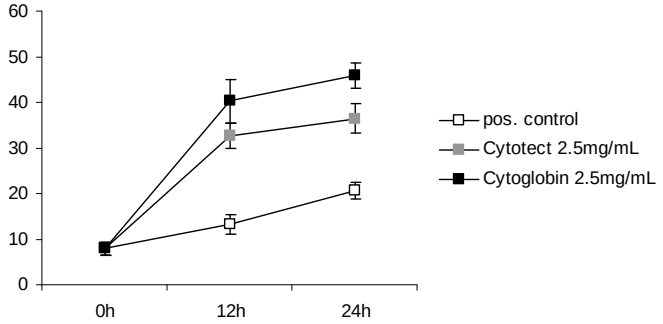
CD4+ cells



CD8+ cells

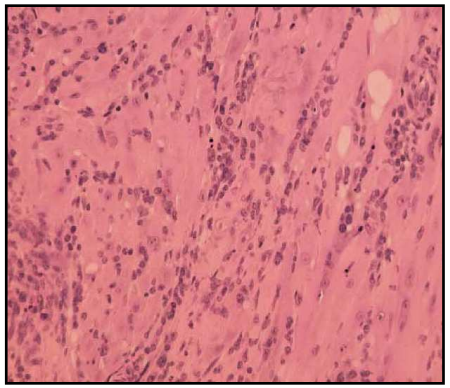


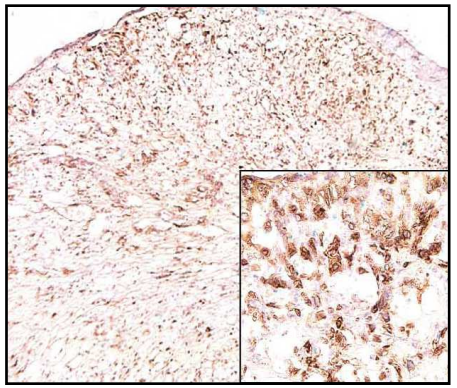
CD56+ cells



(2) cell viability?

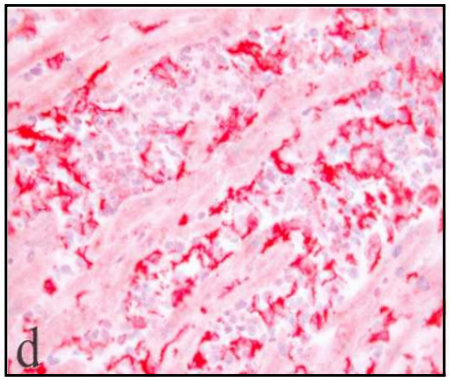
cytotoxic CD8+ T cells

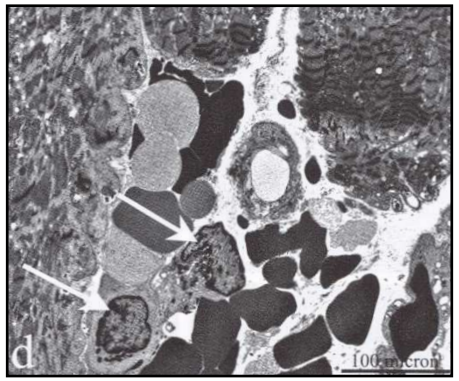




Kreisel et al. Nat Med. 2002 Mar;8(3):233-9.

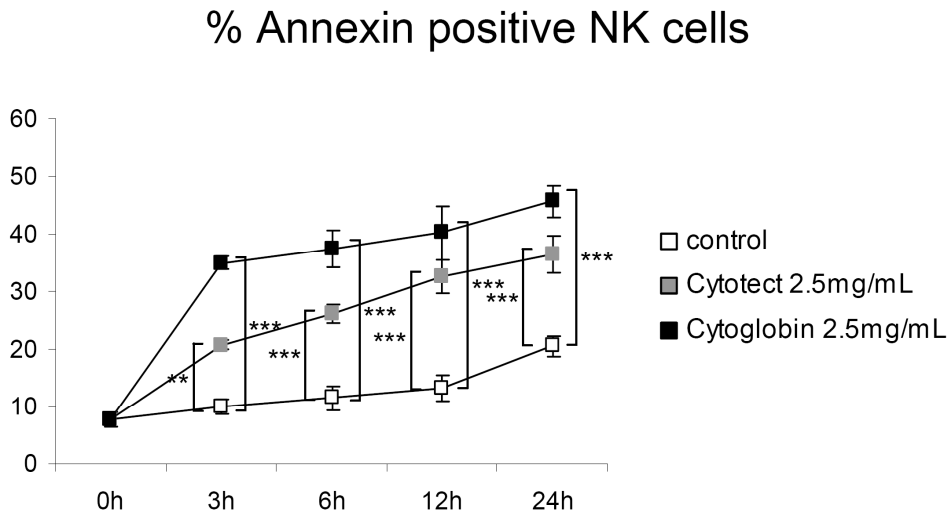
NK cells



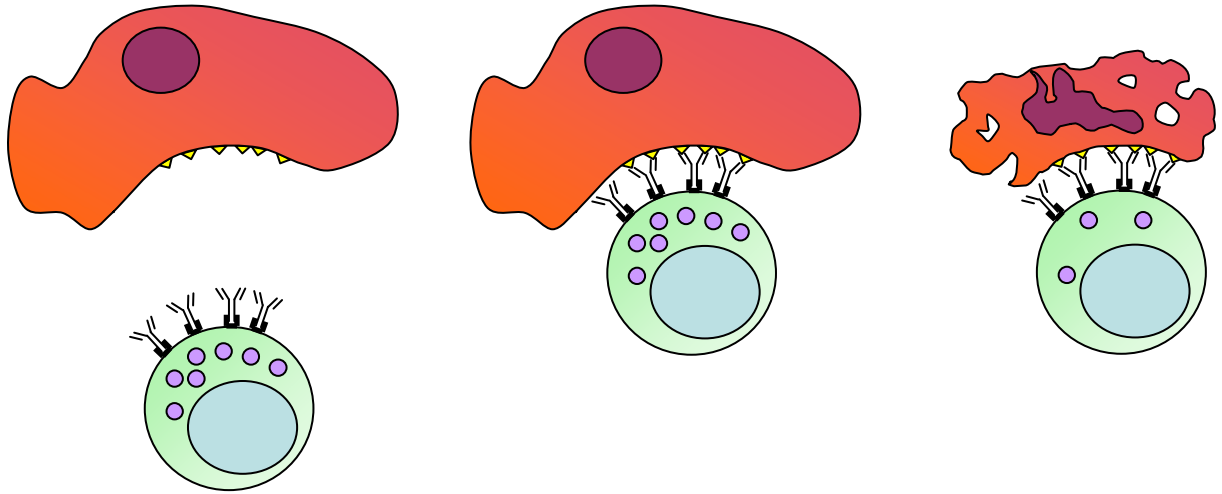


Sorrentino et al. J Pathol. 2006 Jul;209(3):400-10.

(2) cell viability?

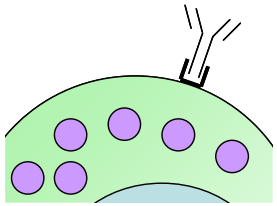


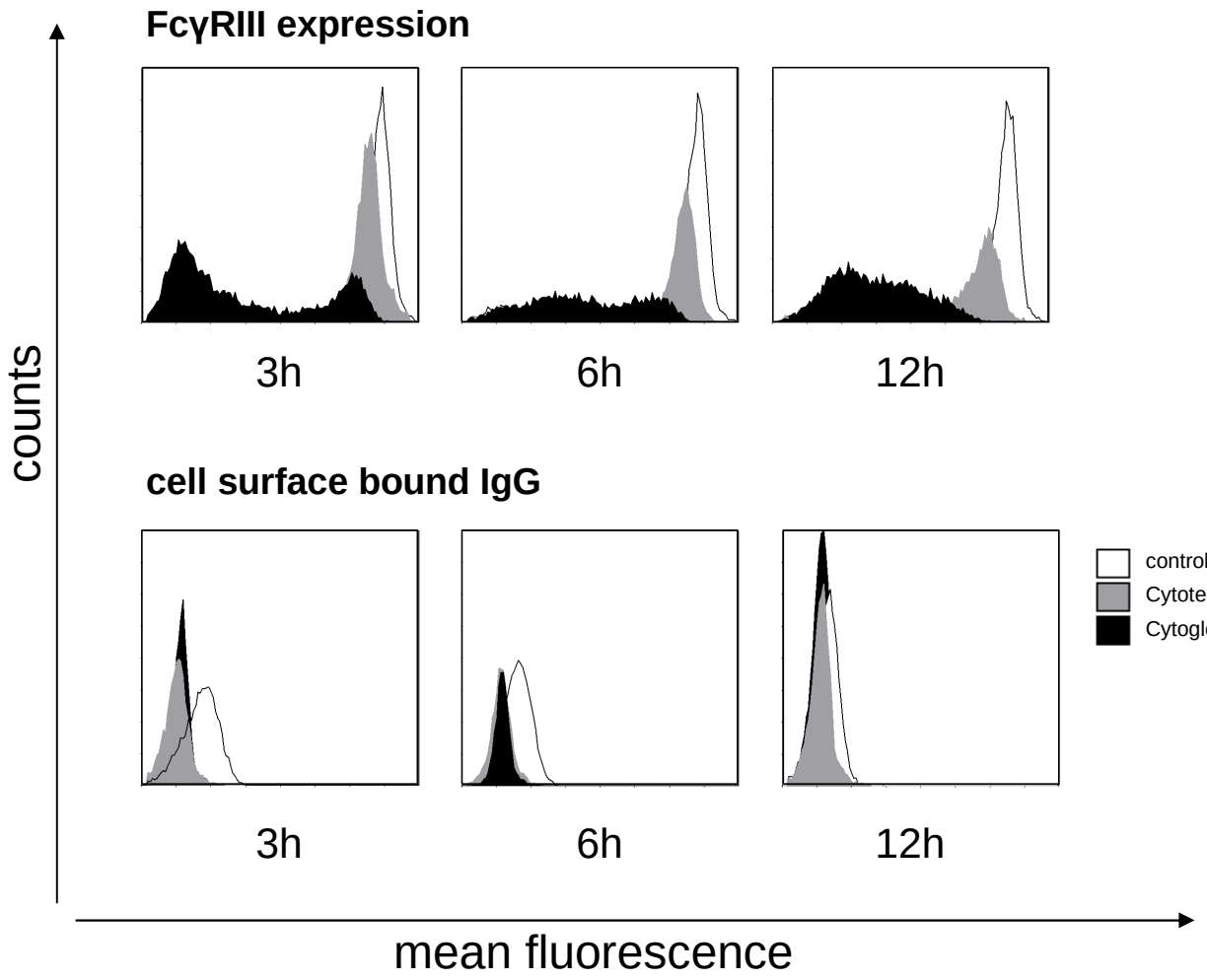
ADCC



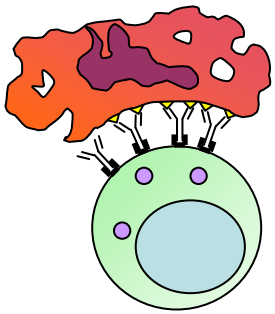
1. vital NK cell
2. FcγRIII
3. cell membrane bound IgG
4. matching antigen

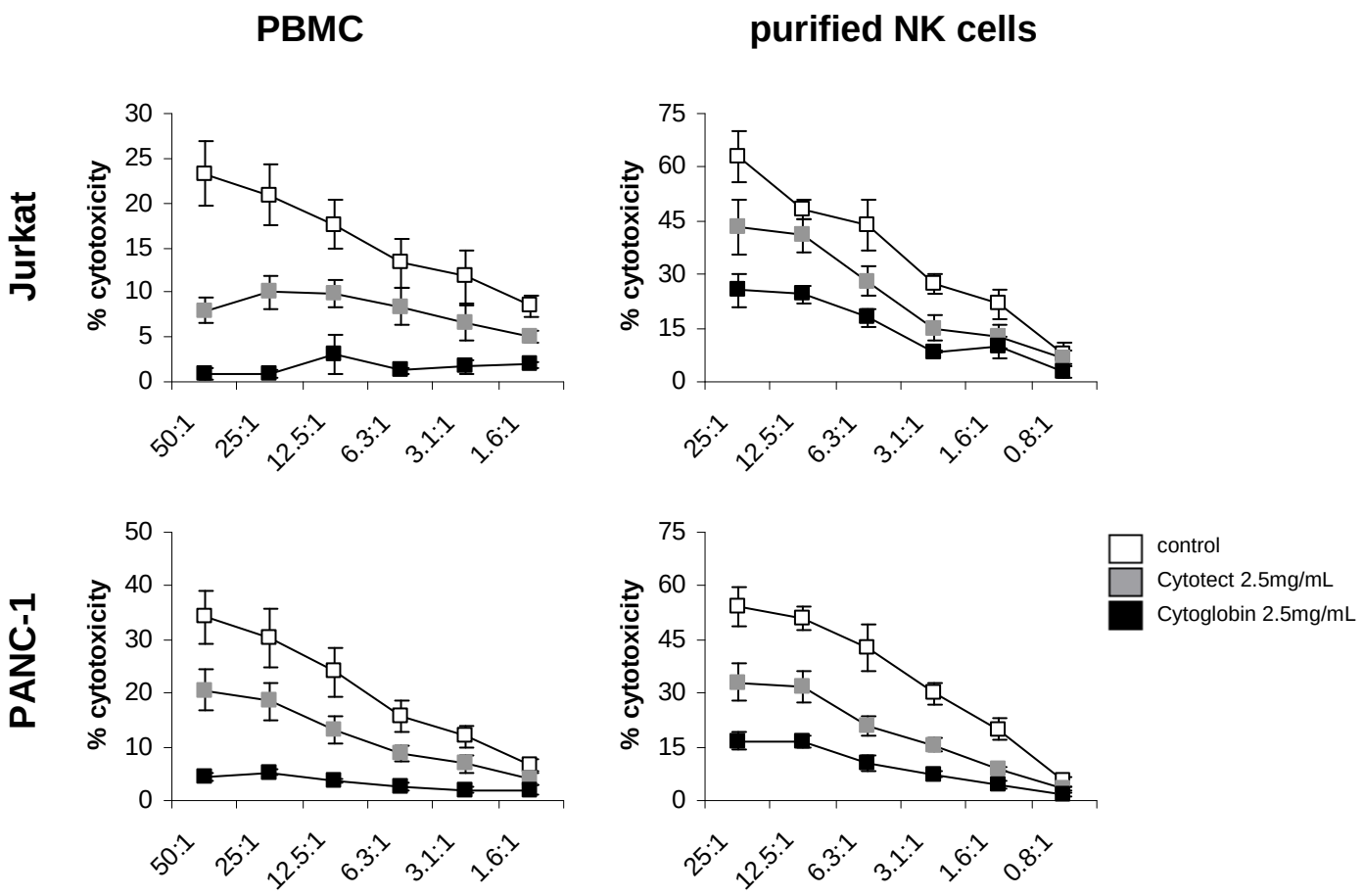
ADCC




FcγRIII expression
3h
6h
12h
counts
cell surface bound IgG
3h
6h
12h
control
Cytotect 2.5mg/mL
Cytoglobin 2.5mg/mL
mean fluorescence

ADCC



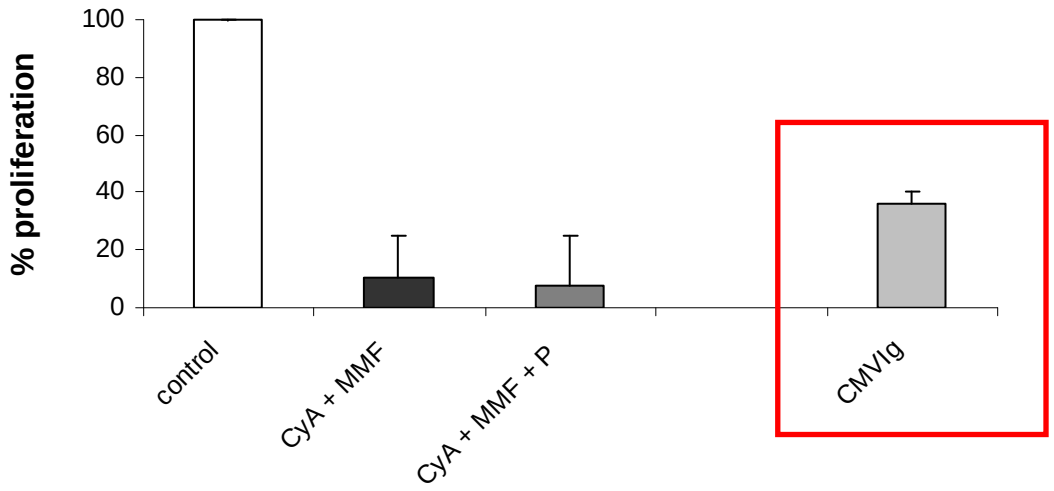

PBMC
purified NK cells
Jurkat
PANC-1
% cytotoxicity
50:1
25:1
12.5:1
6.3:1
3.1:1
1.6:1
0.8:1
control
Cytotect 2.5mg/mL
Cytoglobin 2.5mg/mL

Conclusion

- CMVIg:
  - Inhibition of proliferation
  - T cell und NK cell depletion
  - ADCC

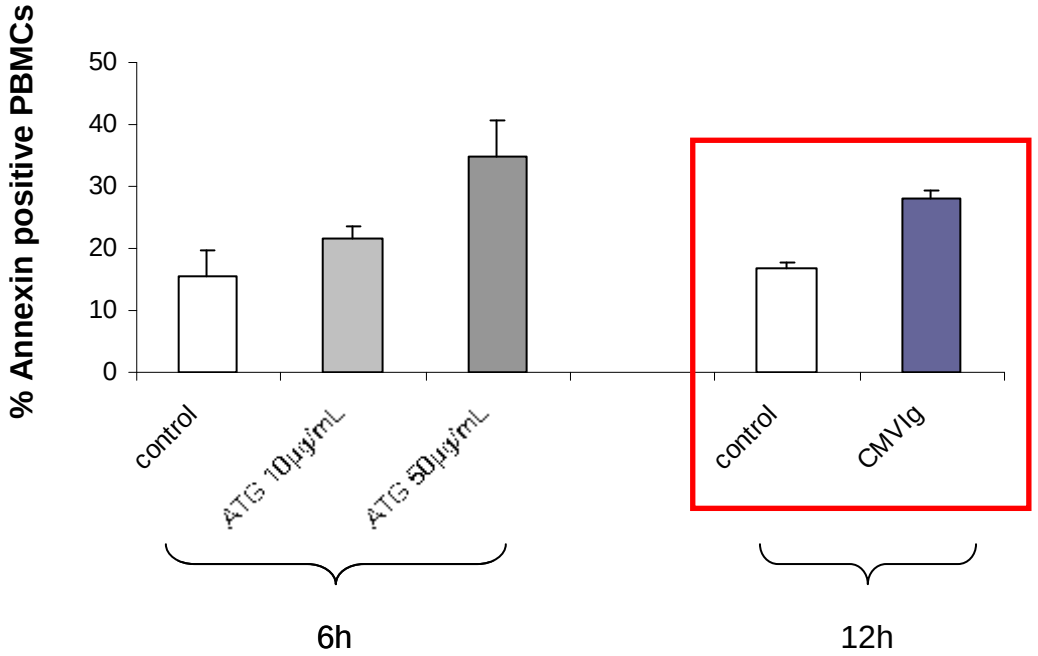
→ reduction of rejection rates and formation of TACAD

Conclusion – anti-proliferation



Hutchinson et al. Transpl Immunol. 2004 Jun-Jul;13(1):55-61.

Conclusion – cell viability



Dubey et al. Ann Hematol. 2003 Aug;82(8):496-9.

CMVIg

IMPACT OF CYTOMEGALOVIRUS HYPERIMMUNE GLOBULIN ON OUTCOME AFTER CARDIOTHORACIC TRANSPLANTATION

A Comparative Study of Combined Prophylaxis with CMV Hyperimmune Globulin Plus Ganciclovir Versus Ganciclovir Alone

Hannah A. Valantine,[1,10] Helen Luikart,[2] Ramona Doyle,[3] James Theodore,[4] Sharon Hunt,[5] Philip Oyer,[6] Robert Robbins,[7] Gerald Berry,[8] and Bruce Reitz[9]

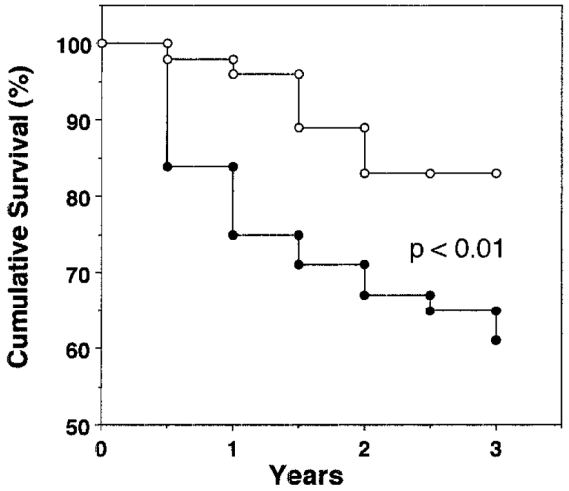


Figure 1. Actuarial survival after heart transplantation in patients receiving prophylaxis with CMVIG plus ganciclovir (open circles) compared with patients receiving ganciclovir alone (closed circles).

Aggressive treatment: Ganciclovir + CMVIg

CMV eradication

+

allo-immune response ↓↓↓

Vielen Dank für die Aufmerksamkeit