



# MURINE CYTOMEGALOVIRUS INFECTION LEADS TO ELEVATED LEVELS OF TRANSPLANT ARTERIOSCLEROSIS IN A MURINE AORTIC ALLOGRAFT MODEL

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## 1 Introduction

Transplant arteriosclerosis is still the leading cause of late mortality and limits the long-term success of heart transplantation. It is characterized by a diffuse and progressive thickening of the arterial intima that affects minor as well as major coronary arteries of transplanted cardiac allografts. In clinical studies cytomegalovirus infection after heart transplantation is considered as risk factor for developing transplant arteriosclerosis.

Cytomegalovirus infection plays an important role in solid organ and bone marrow transplantations as it can be reactivated during immune suppression. This is quite a considerable problem, as the seroprevalence is between 50% and 80% depending on age, geographic location and socioeconomic group. Primary CMV infection in patients with impaired immune systems can lead to serious disease.

The murine cytomegalovirus is similar to the human virus in course of disease including latency and there are numerous homologies in terms of genomic structure. CMV belongs to the Betaherpesvirinae distinguished by reproducing less quickly than other subfamilies of Herpesviridae. After replication in epithelial cells of mucosa cytomegalovirus can be spread throughout the organism by monocytes, neutrophils and circulating endothelial cells. Infected cells typically grow with nuclear and cytoplasmic inclusions which lead to cytotoxic tissue damage. It was already shown that infection of ApoE<sup>-/-</sup> mice with MCMV leads to arteriosclerotic lesions with elevated expression of arteriosclerotic chemokines such as MCP-1, IP-10 and MIG. All these chemokines are responsible for the attraction of monocytes and T-lymphocytes participating in plaque and neointima formation.

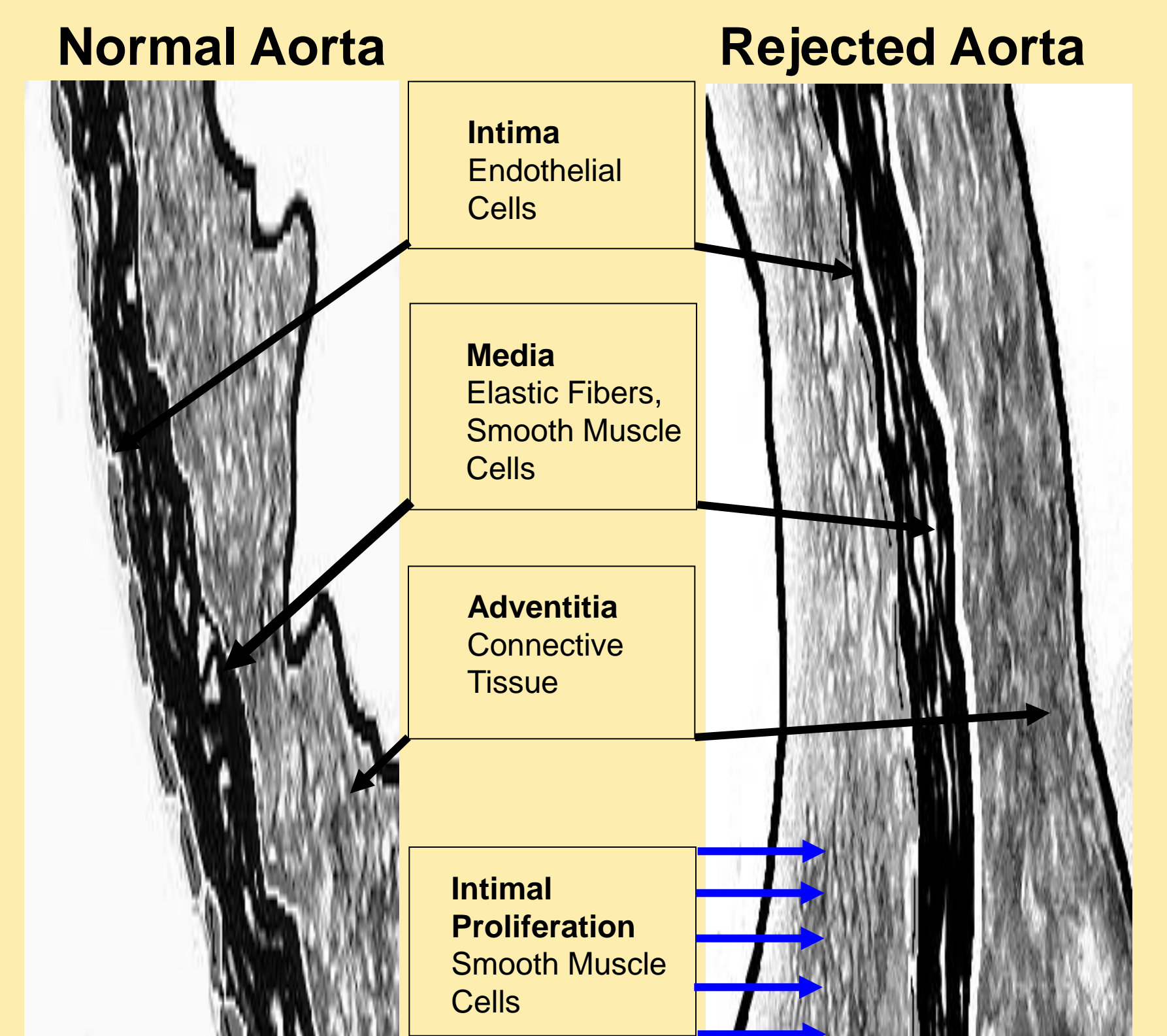
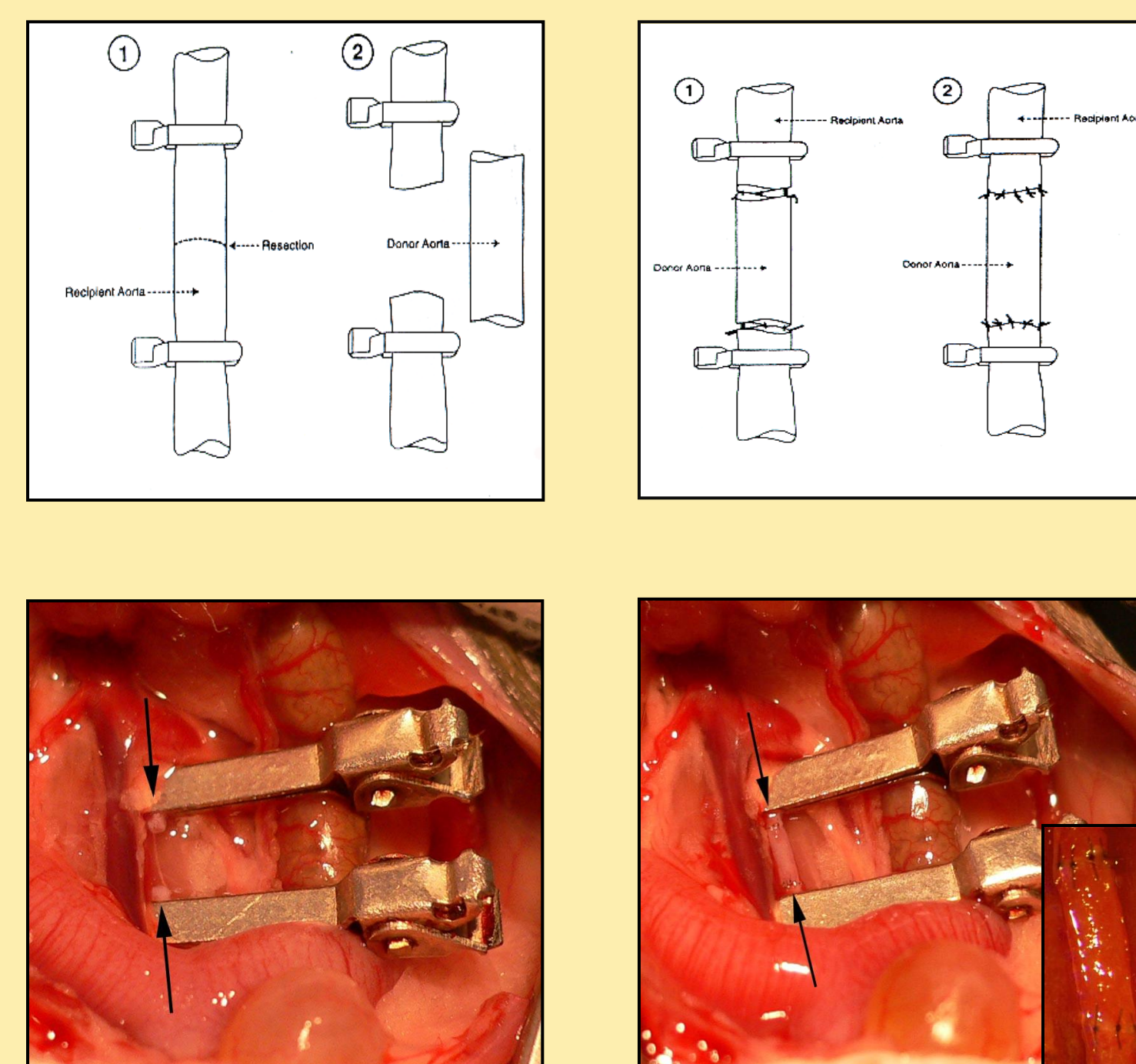
**The aim of this study** was to investigate the effect of murine cytomegalovirus infection on the development of transplant arteriosclerosis in an experimental aortic allograft model in the presence and absence of immune suppression.

### Literature:

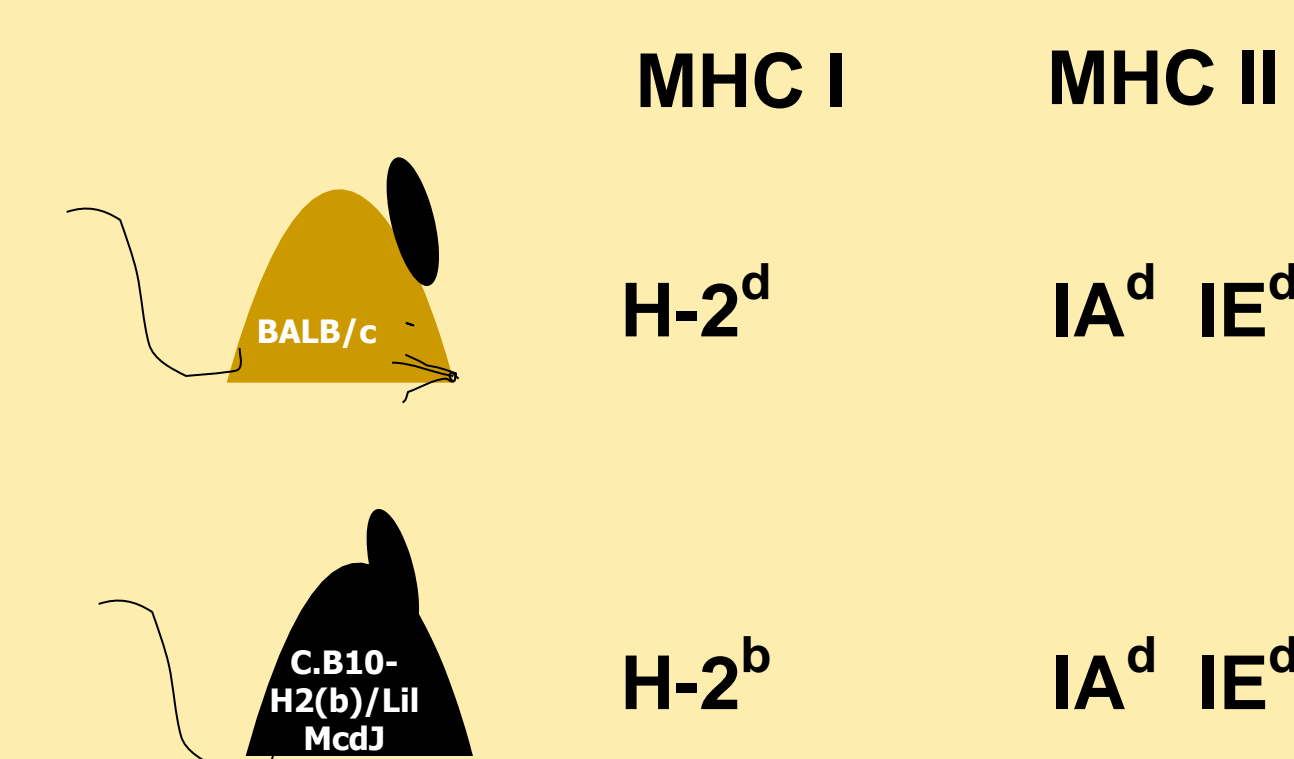
Koulack et al., *Microsurgery* 1995  
 Thomas Stamminger, *Deutsches Ärzteblatt* 1997  
 Ensminger et al., *Journal of Heart and Lung Transplantation* 2000  
 Ensminger et al., *Transplantation* 2002  
 Krmpotic et al., *Microbes and Infection* 2003  
 Burnett et al., *Circulation* 2004

## 2 Material and Methods

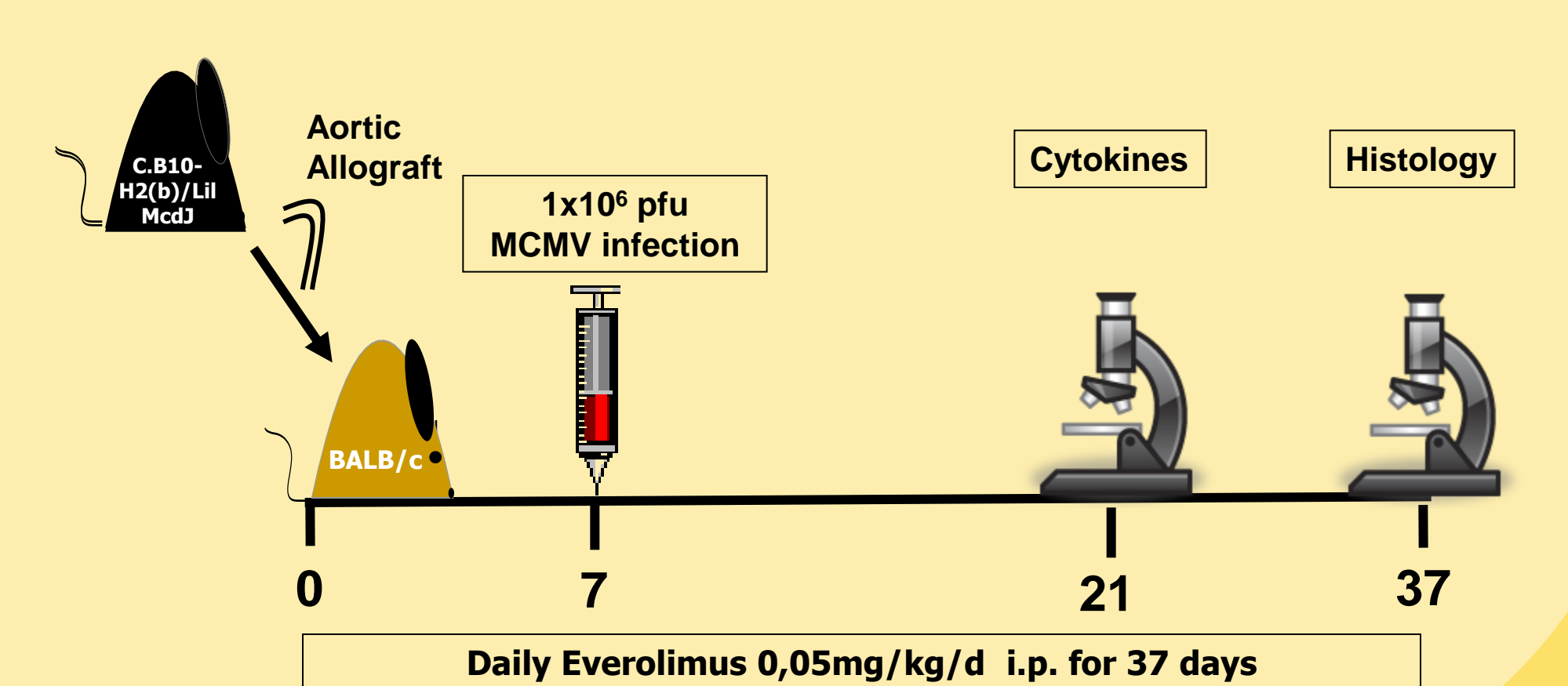
### 1. Abdominal Aortic Transplantation



### 2. Mouse Strains

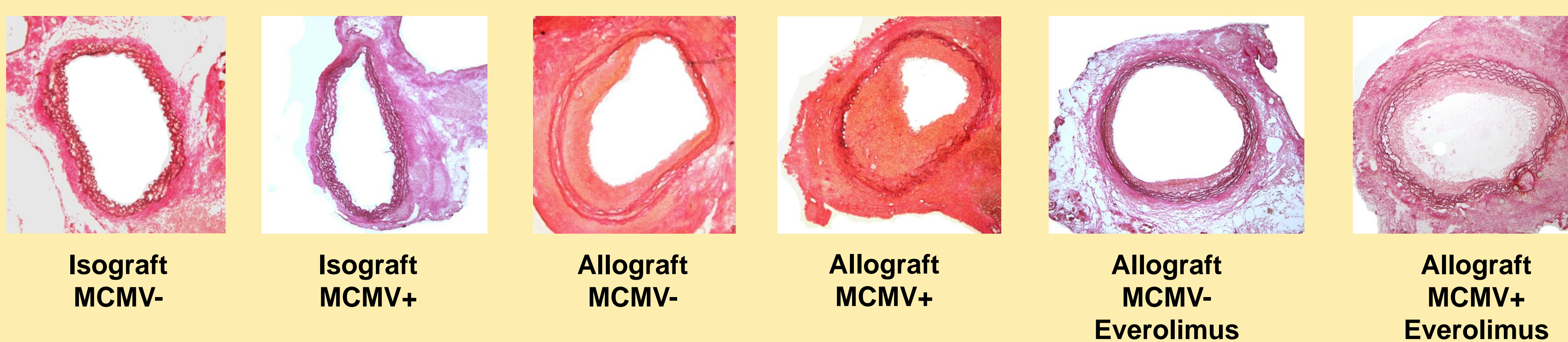


### 3. Experimental Protocol

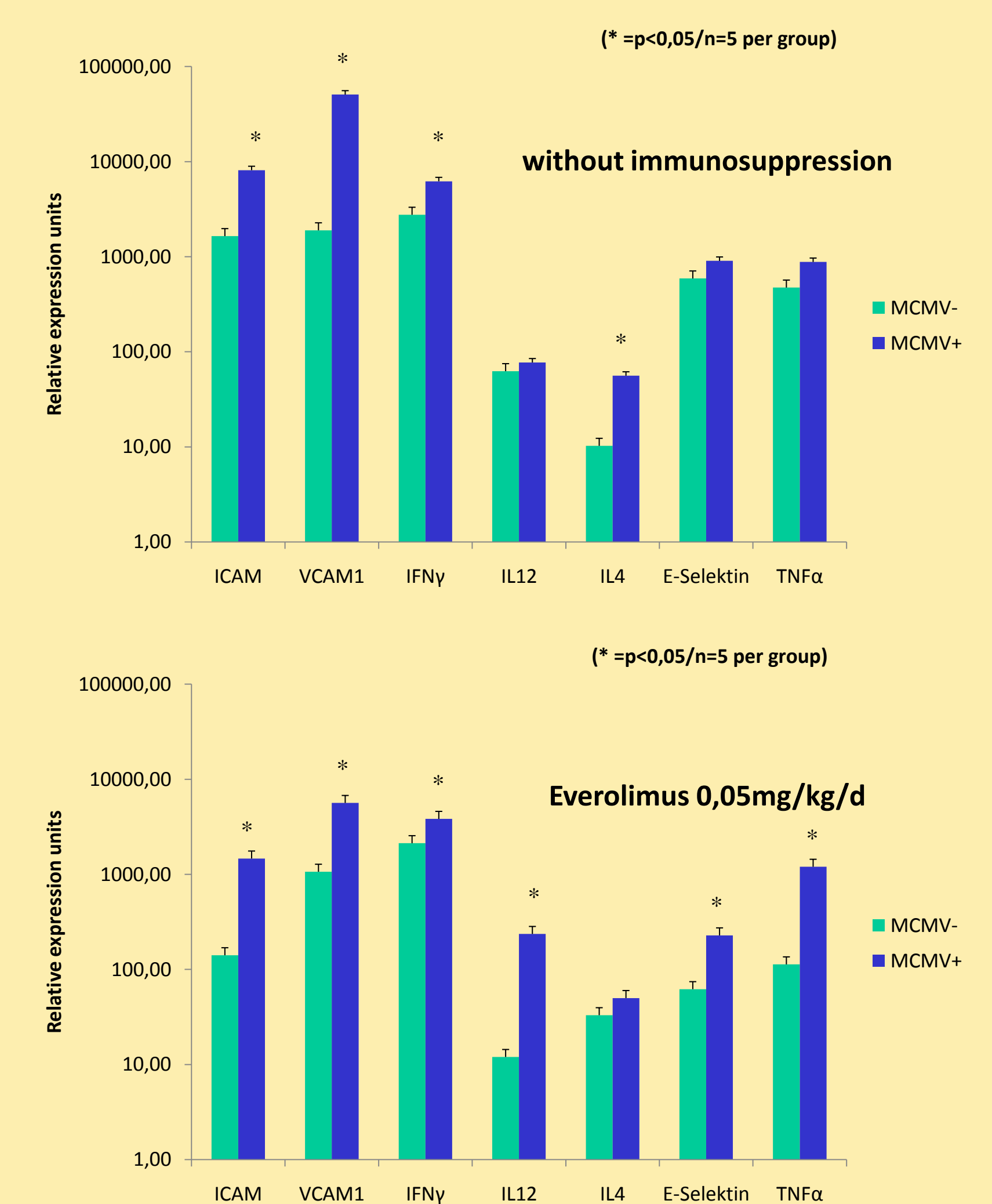


## 3 Results

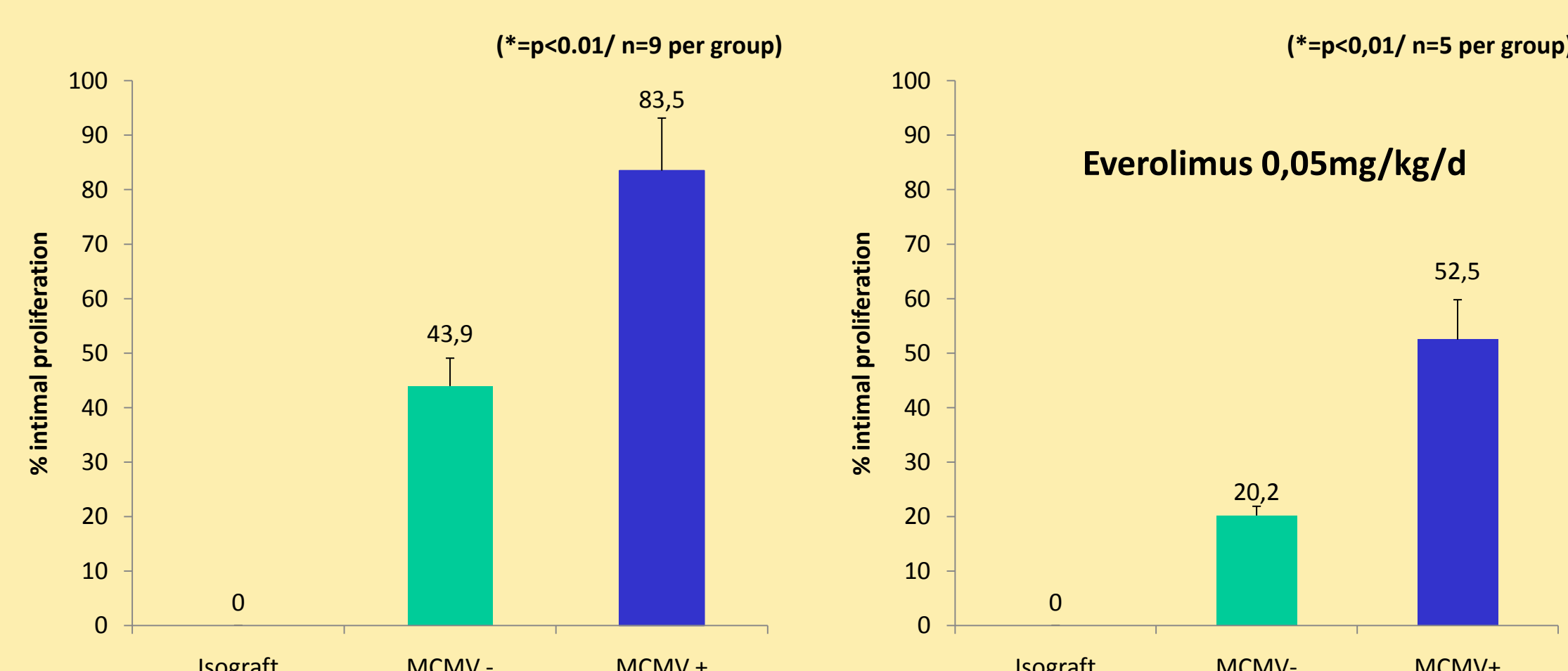
### 1. Intimal Proliferation on Day 37



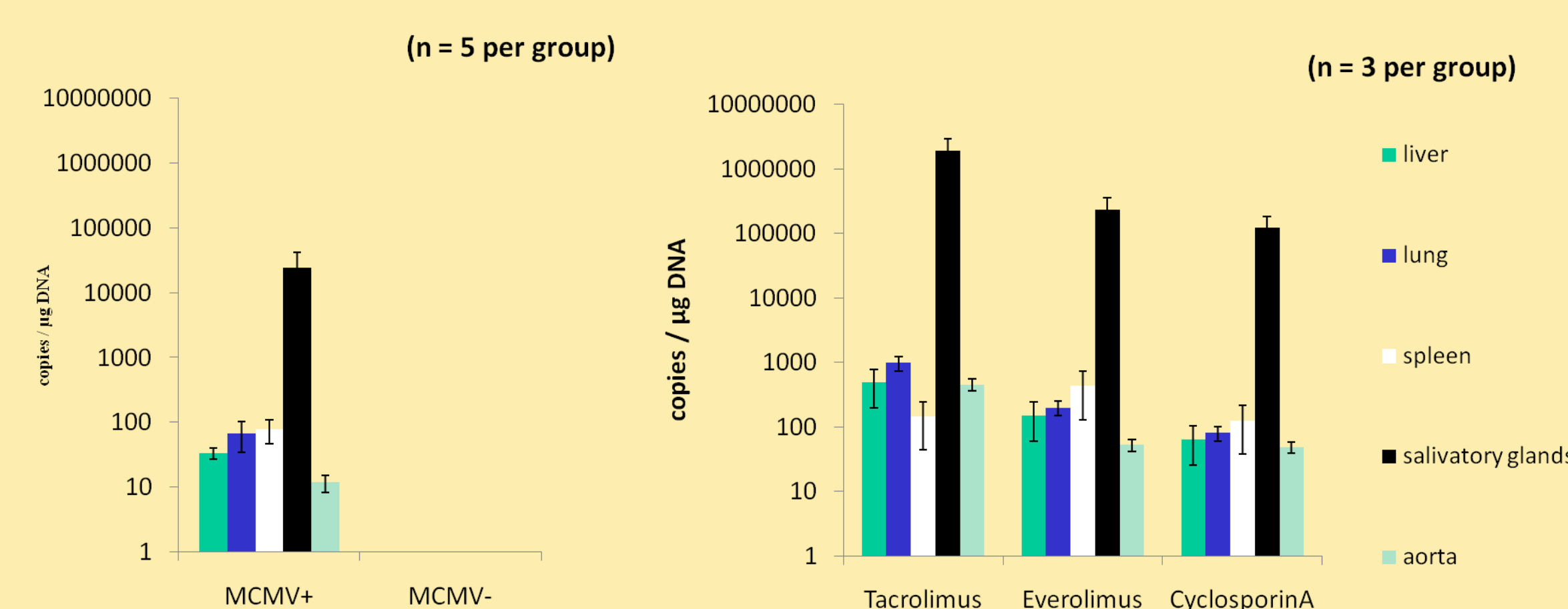
### 4. Intra-graft mRNA Expression on Day 21



### 2. Quantitation of Intimal Proliferation (day 37)



### 3. In vivo infection of recipient mice with MCMV (day 37)



## 4 Conclusion

1. Significant amounts of transplant arteriosclerosis were present in all experimental allograft groups with and without immune suppression.
2. After infection with MCMV there was significantly more intimal proliferation as compared to uninfected controls [intimal proliferation in absence 78,3±9% (MCMV+) vs. 44,4±9,7% (MCMV-) and presence of immunosuppression 52,5±7% (MCMV+) vs. 20,2±1,3% (MCMV-)]
3. In addition we could also confirm the presence of MCMV for the duration of the experimental protocol by PCR within the liver, lung, spleen, salivary glands, and the aortic transplant itself, augmented with immune suppression.
4. Following infection with the murine cytomegalovirus significant more expression of ICAM-1, VCAM-1, IFN-γ, IL4 and TNF-α was detected in the aortic transplant. We could show similar effects after treatment with immune suppression.
5. These data suggest that murine cytomegalovirus infection plays an important role in the development of transplant arteriosclerosis.

## 5 Correspondence

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