Project 13: Fcγ-Receptor mediated immune control of cytomegalovirus infection *in vivo*

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Summary:
Cytomegaloviruses (CMV) belong to the β-subgroup of herpesviruses, with a large double-stranded DNA genome encoding approx. 200 genes which are transcribed in a cascade fashion of immediate early (IE), early (E) and late (L) genes. The completion of the protracted CMV replication cycle takes 72 to 96 hours. Like all herpesviruses CMVs persist in the infected host for life with alternating episodes of latent infection and recurrent replication. While being clinically symptomless in immunocompetent individuals, CMV can cause severe disease in immunocompromised individuals, like transplant and AIDS patients, reflecting the delicate balance between the immune system responding to the infection and the evasion of the virus from immune control.
IgG responses are crucial in antiviral defence and instrumental for the serodiagnosis of infections. Receptors for the Fc domain of immunoglobulin (Ig) G (FcγR) comprise a family of surface molecules connecting humoral and cellular immune responses. FcγRs I, II and III on immune cells recognizing the Fc-part of IgG differ regarding IgG binding affinity, IgG subclass specificity, cellular expression profiles and pathogen elimination mechanisms elicited after activation. Upon IgG binding, FcγRs trigger a multitude of effector mechanisms such as Ab dependent cellular cytotoxicity (ADCC), phagocytosis, endocytosis of immune complexes, cytokine production, Ab production and facilitation of antigen presentation, linking both branches of immunity.

Our long term goal is to establish an optimized IgG based immunotherapy of CMV infection. The following important steps towards this goal will be taken:

- Elucidation of the role of distinct FcγRs in CMV infection by using various FcγR-deficient mice infected with mouse CMV.
- In parallel, already available MCMV-specific IgG monoclonal antibodies will be defined for their antigen specificity and compared for their FcγR activation capacities *in vitro* and their protective capacity *in vivo*.
- Finally cloning of the antibody encoding genes will allow for exchange of the heavy chain subclass and subsequent in vivo testing for optimal therapeutic effects.