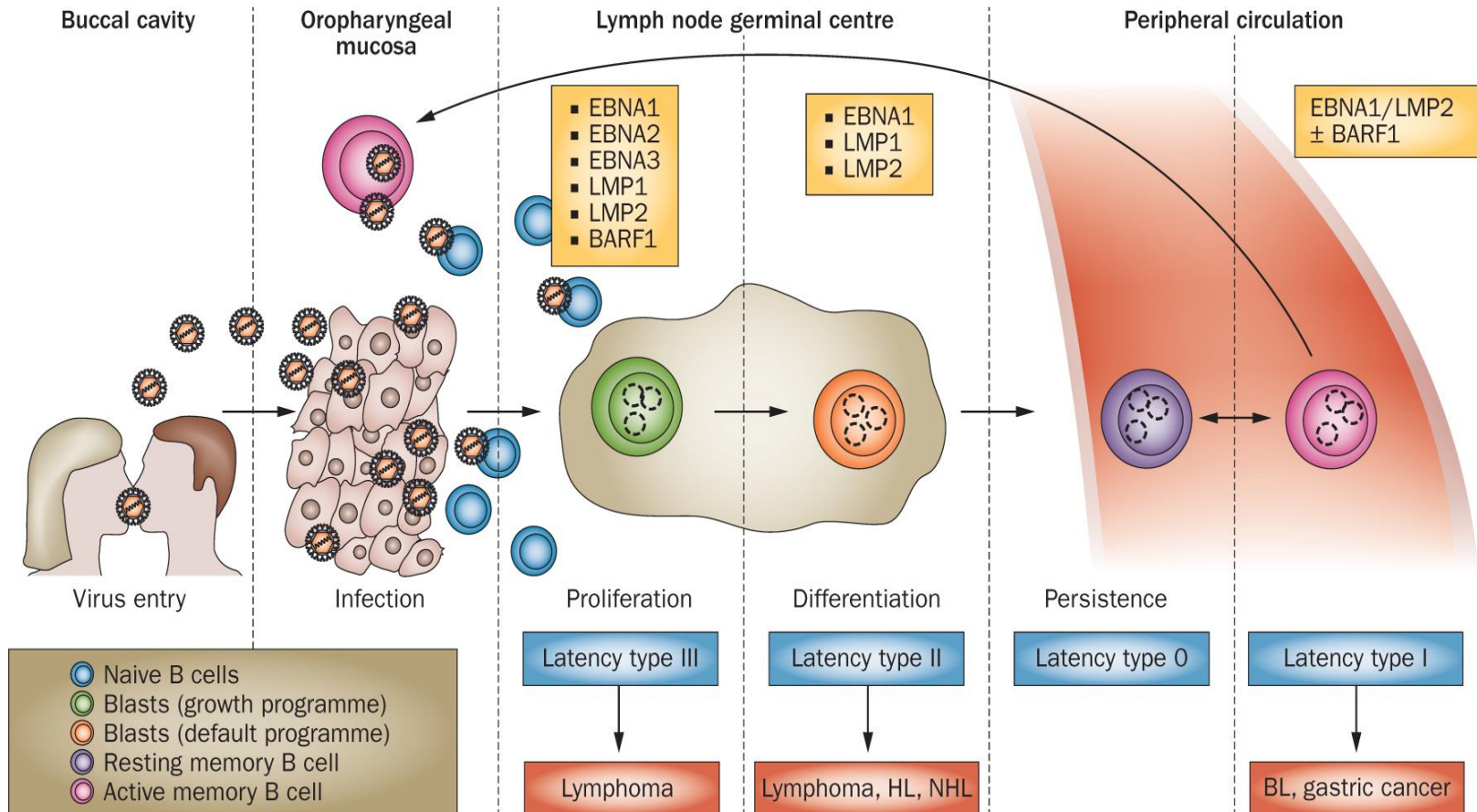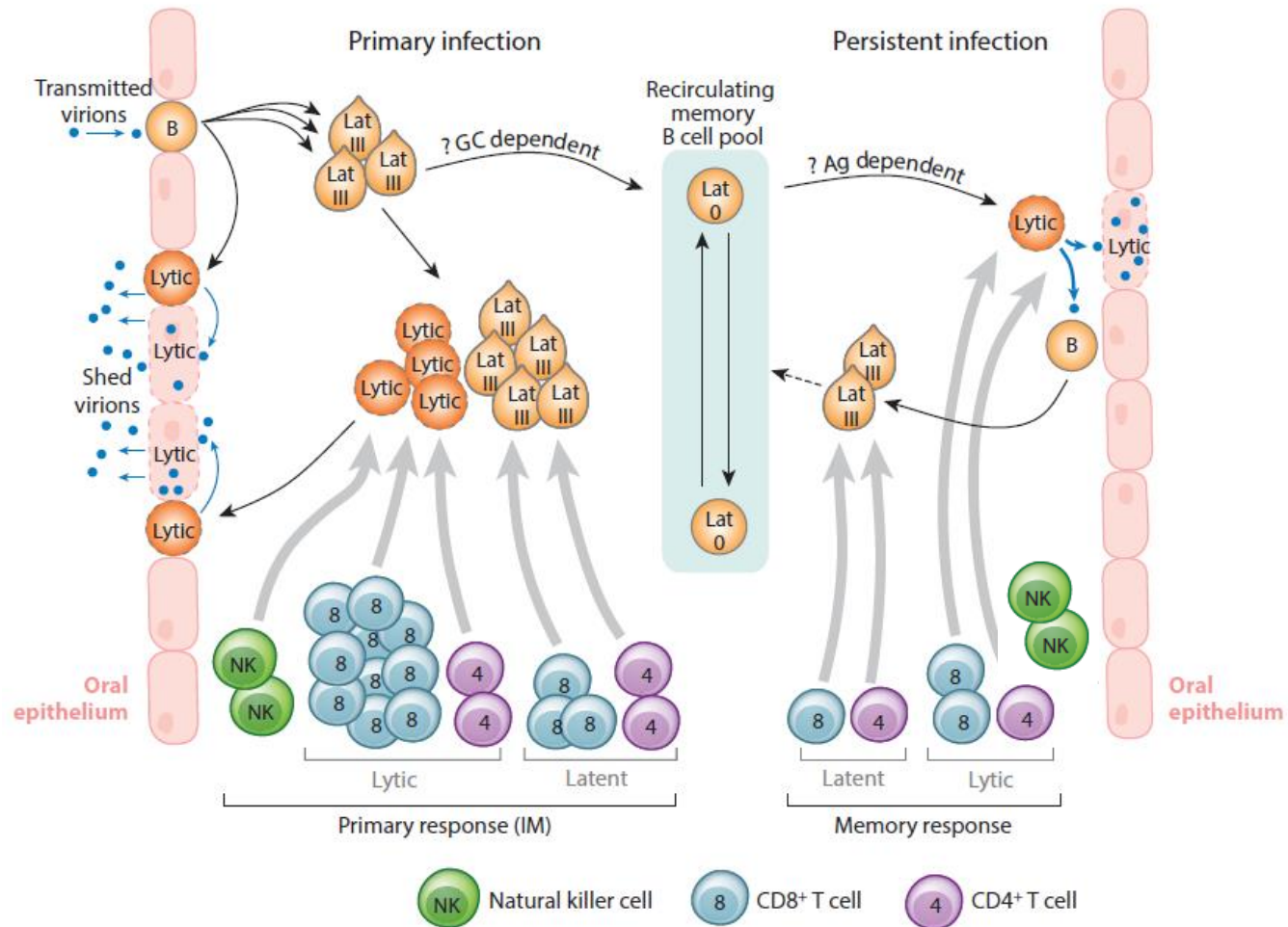# Animal models of human oncogenic gamma-herpesvirus infection

Christian Münz
Viral Immunobiology
Institute of Experimental Immunology
University of Zürich

# Lytic and latent EBV infection

Cell-mediated immune control of EBV

1. Role of NK cell responses during EBV infection

- Does NK cell depletion alter EBV infection?

- Which program of EBV infection is influenced by NK cell responses?

- Does loss of NK cell mediated immune control predispose for infectious mononucleosis (IM), an immunopathology of massive CD8^{+} T cell expansion during primary EBV infection?

EBV infection of mice with reconstituted human immune system components

Irradiate new born immunodeficient NOD-*scid* $\gamma_c^{-/-}$ mice with 100cGy
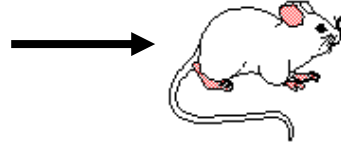
Transplant $1\text{-}3\times10^5$ human CD34$^+$ cells via intrahepatic or intravenous injection

12 weeks

Determine composition of reconstituted human immune system in peripheral blood

intraperitoneal infection with 10^5 RIU EBV for 6 weeks +/- NK cell depletion with αNKp46 antibody
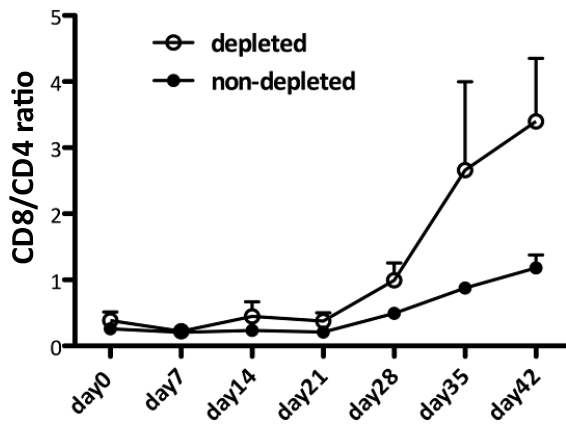
Analyse viral loads, tumor formation and immune compartments longitudinally in peripheral blood and after 6 weeks in the spleen, blood, bone marrow, mesenteric lymph node and tumor microenvironment
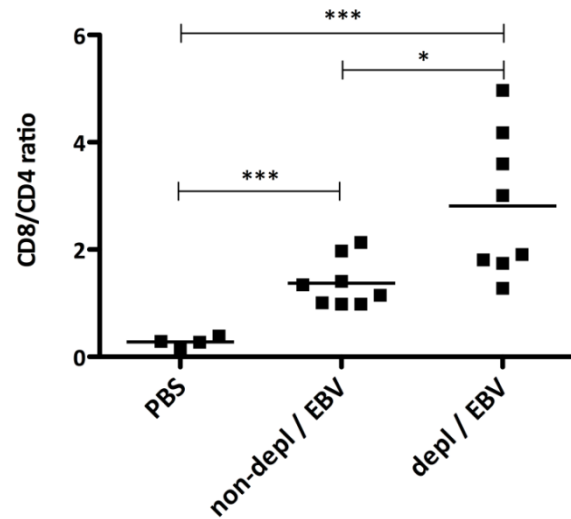
NK cell depletion alters lytic EBV infection
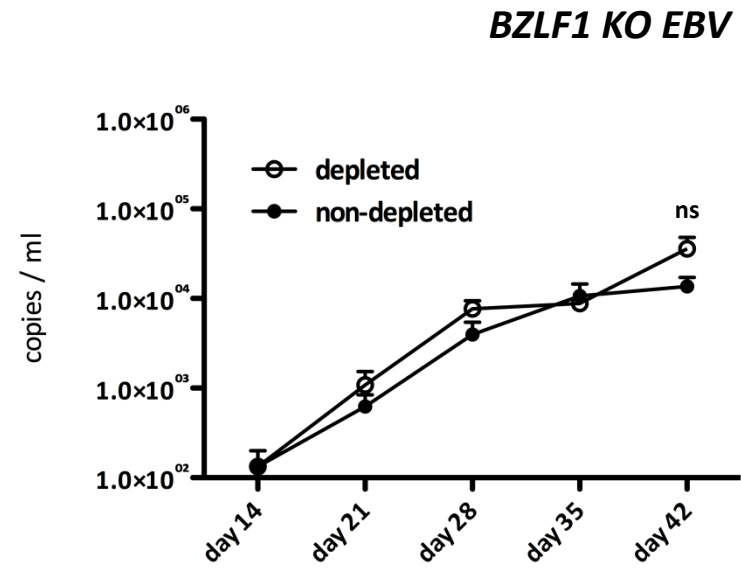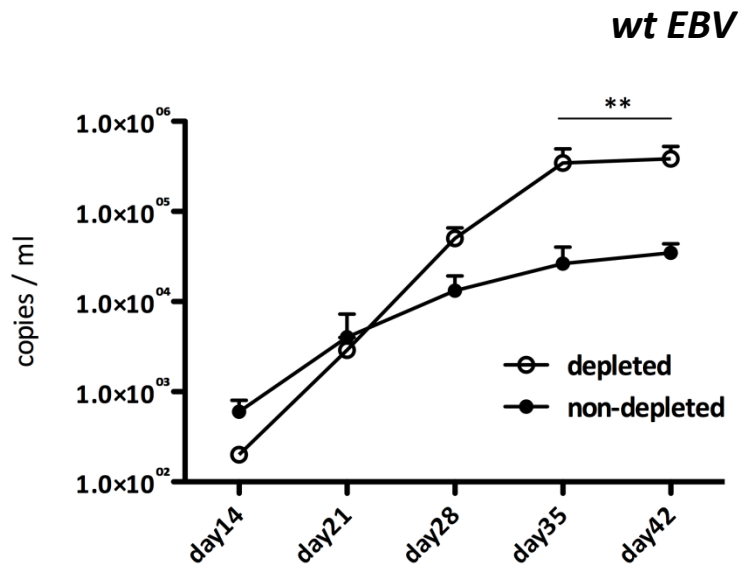
NK cell depletion leads to IM-like increased CD8$^+$ T cell expansion during primary EBV infection
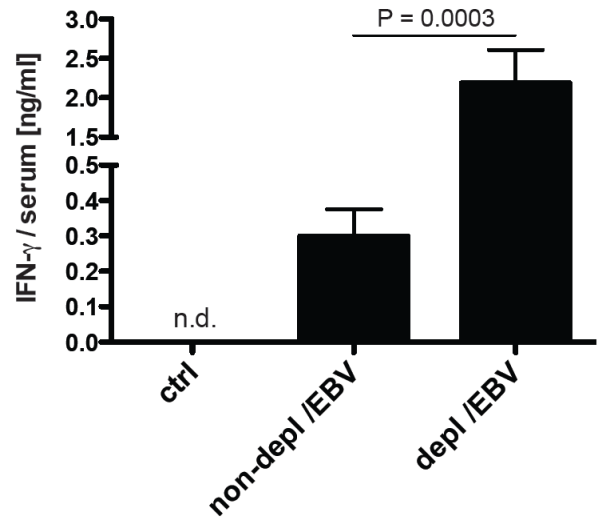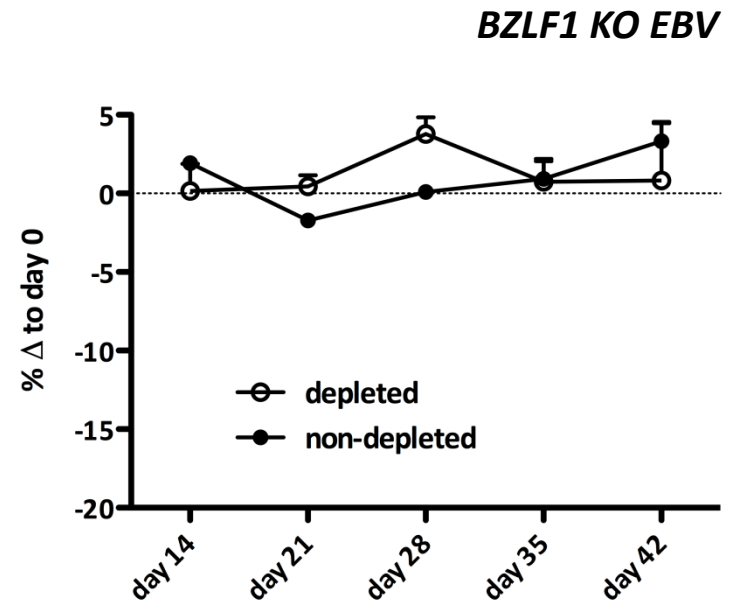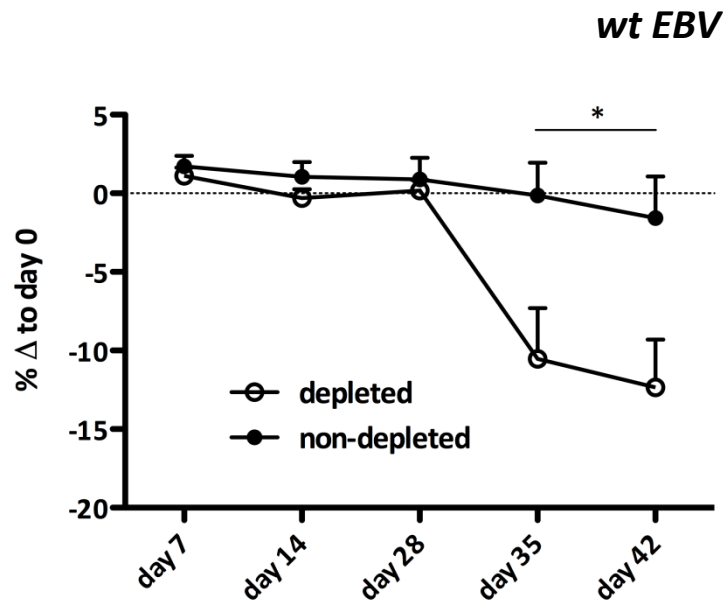
Uncontrolled lytic replication leads to weight loss in EBV infected huNSG mice
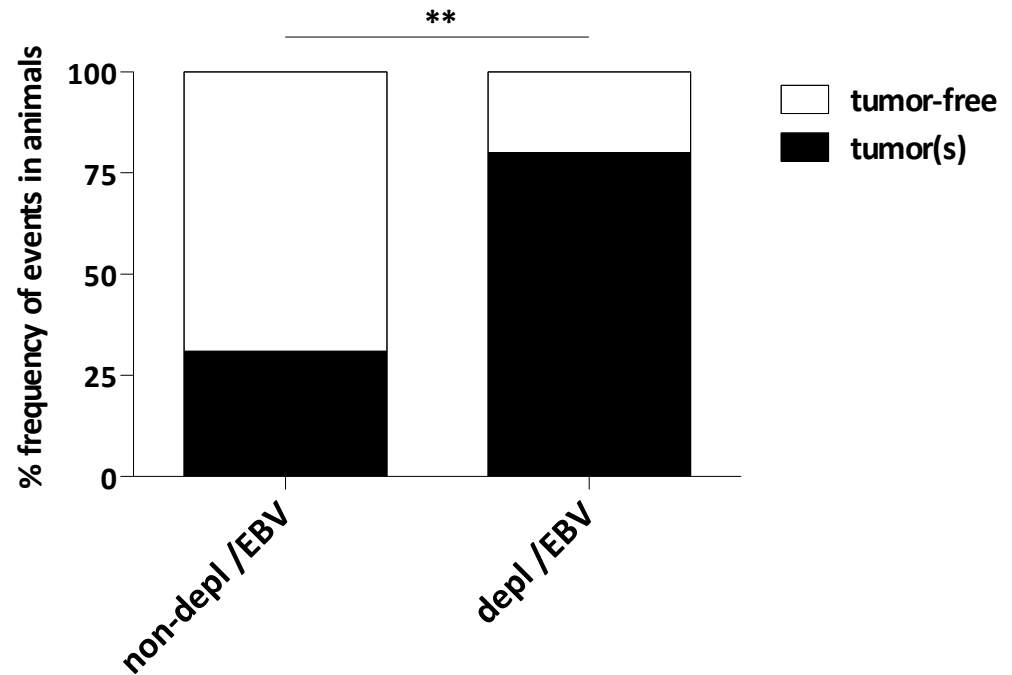
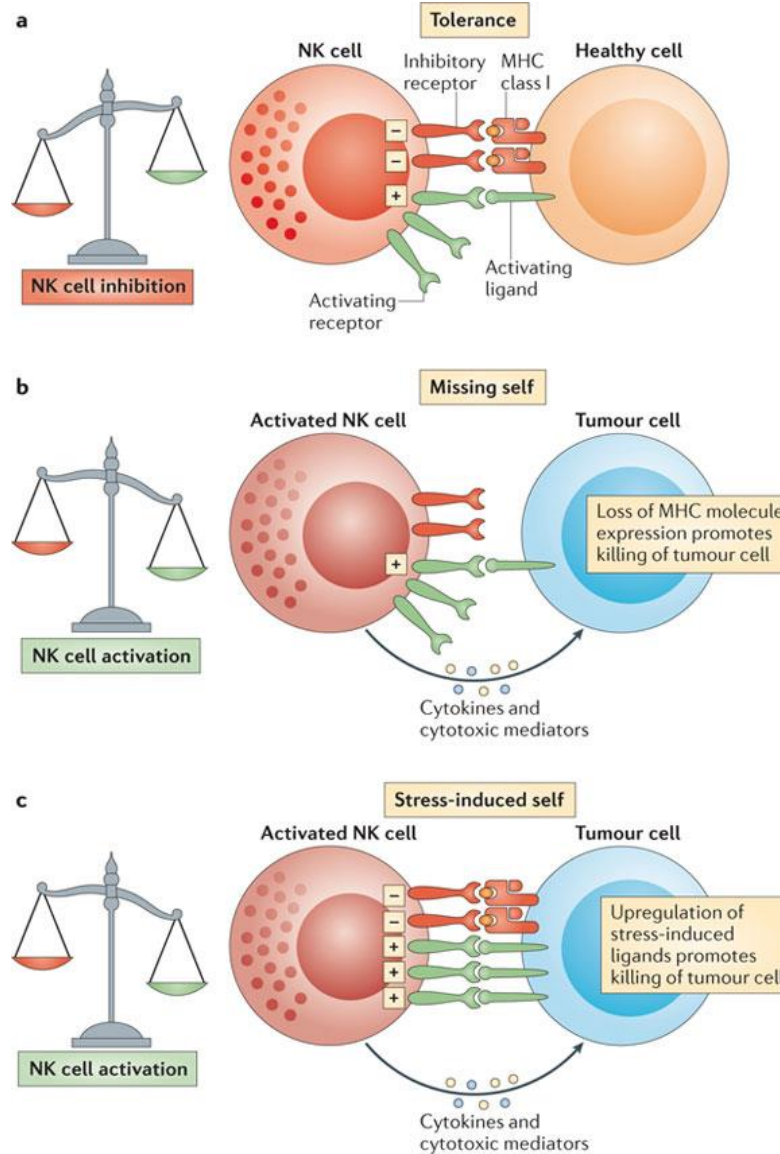# NK cell depleted mice develop more tumors during EBV infection
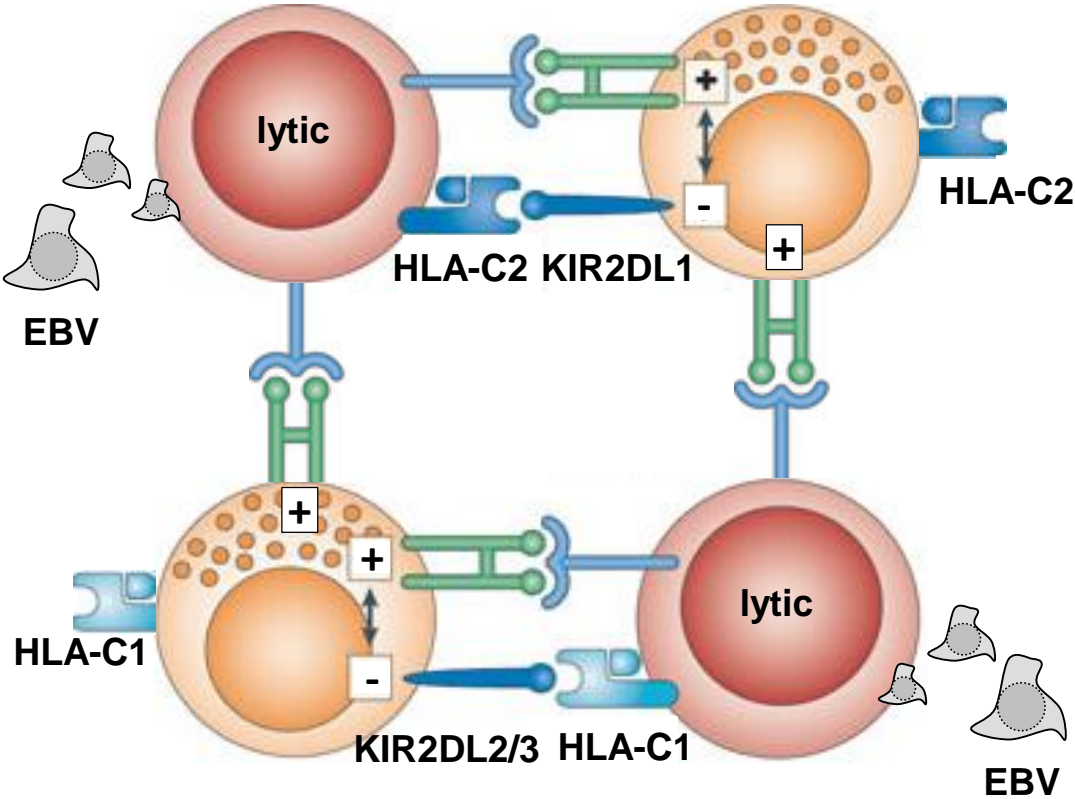
NK cell depleted liver

tumor incidence

NK cell recognition

Vivier et al., Nat Rev Immunol 2012
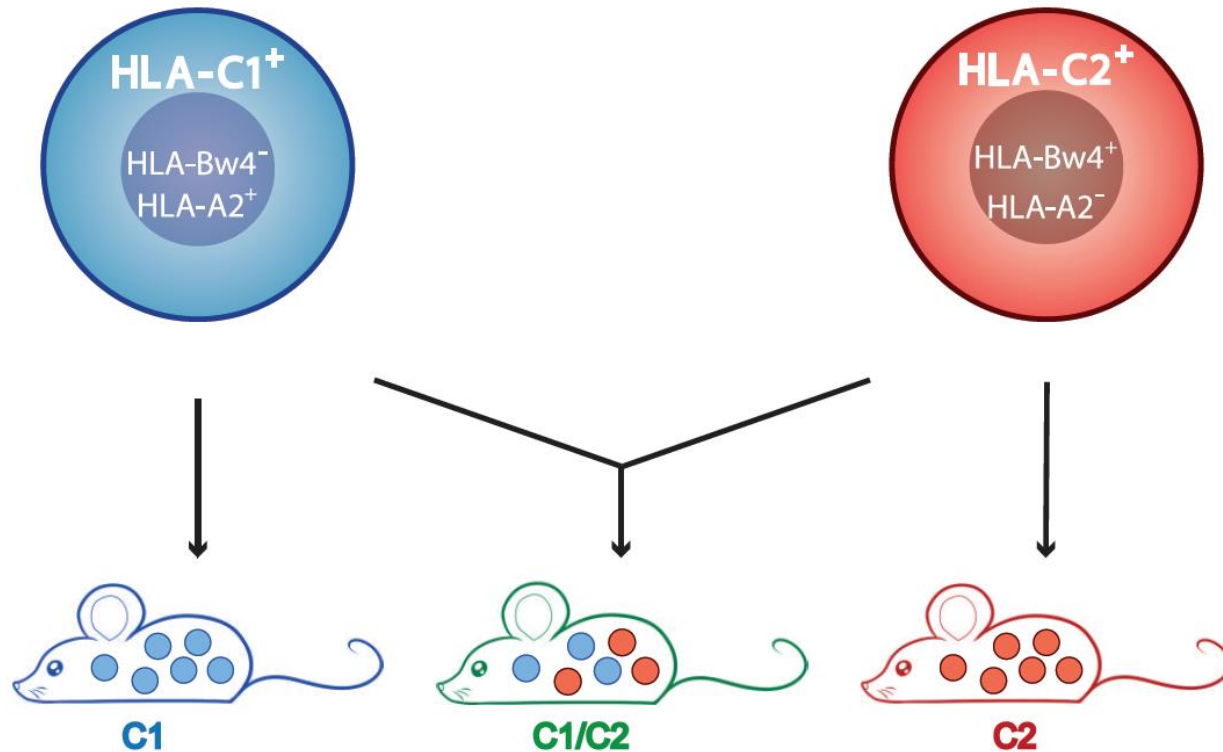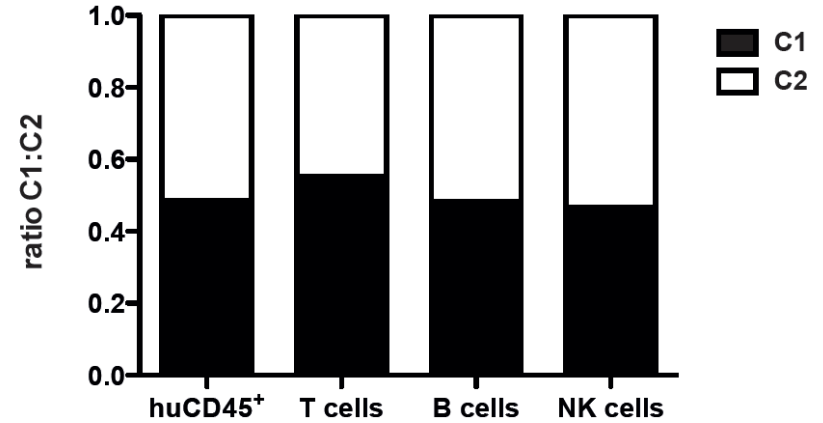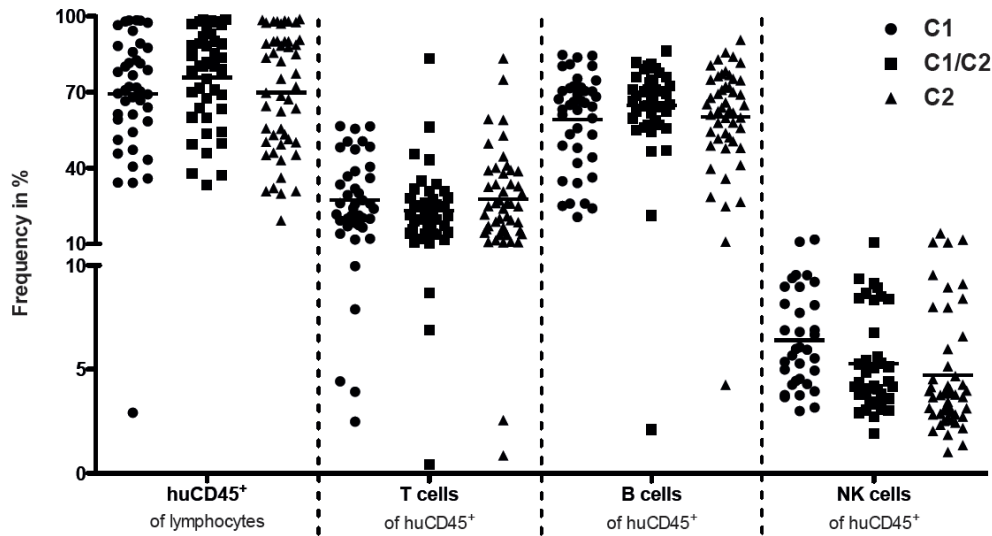
Increasing EBV specific immune control by KIR ligand mismatching

Mixed human CD34$^+$ hematopoietic progenitor cell chimeras
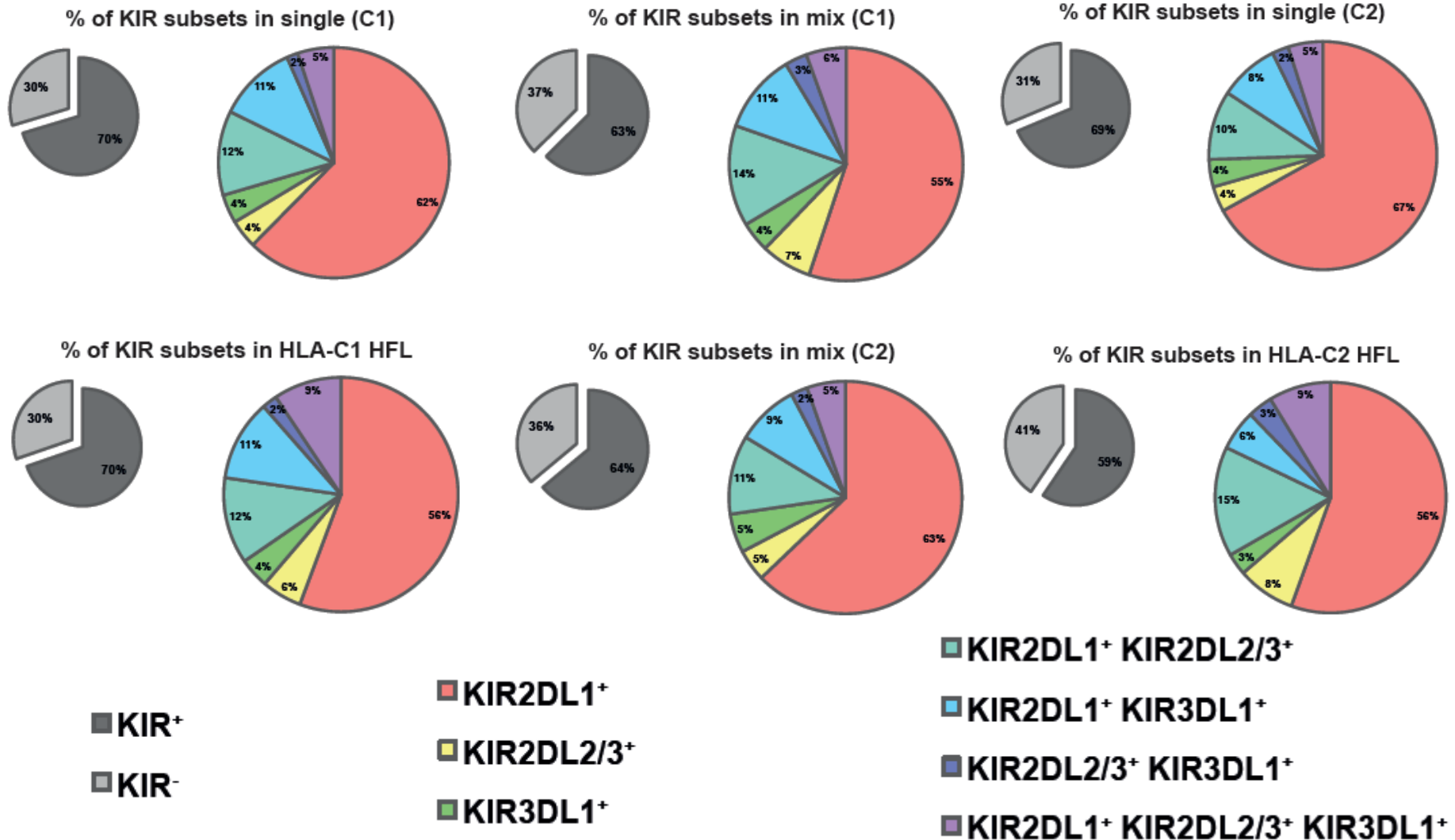
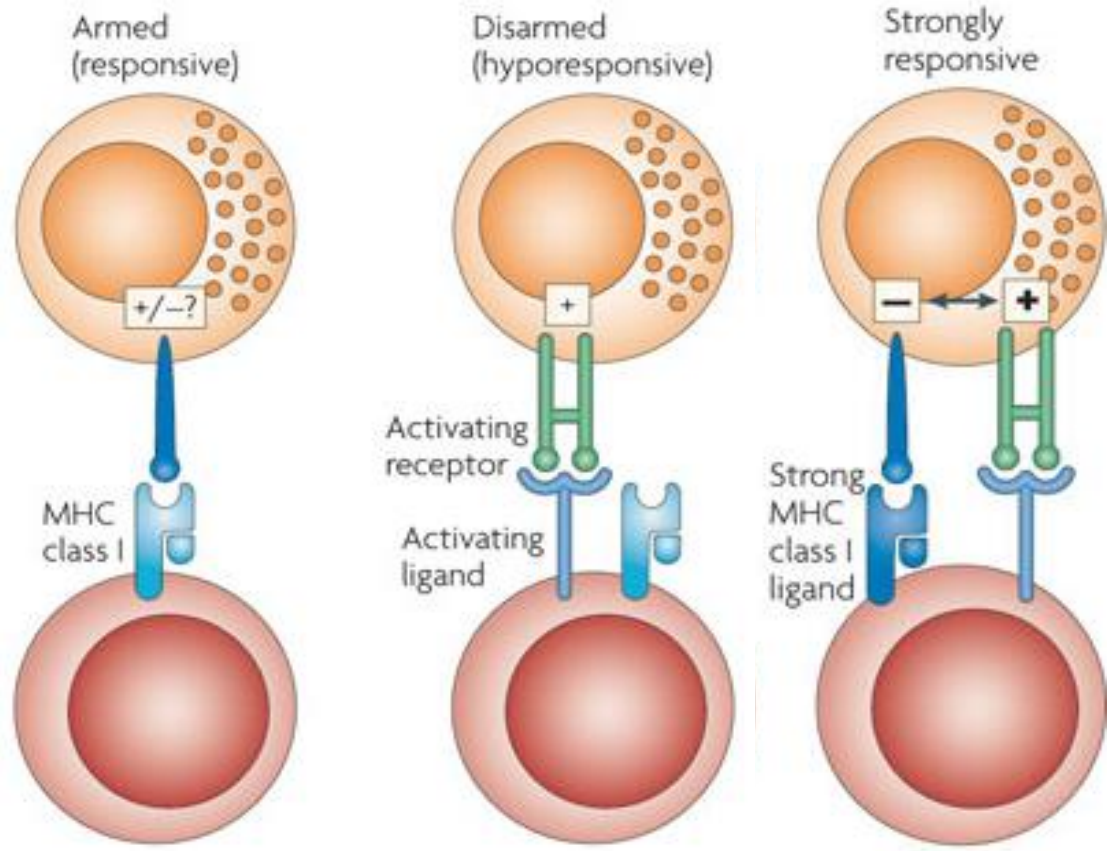# Two donors reconstitute side-by-side in huNSG mice

The NK cell repertoire is not influenced by mismatched HLA in trans
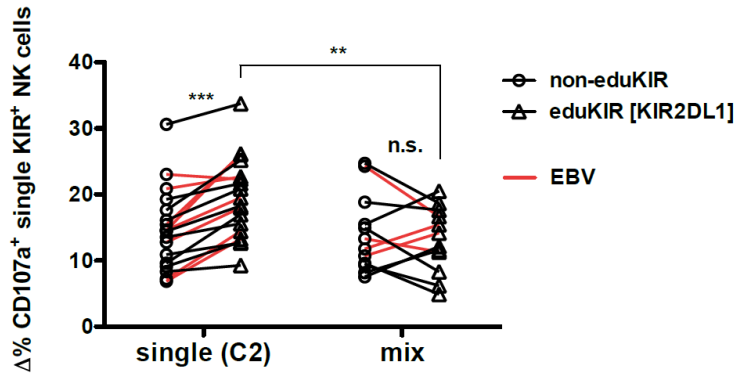

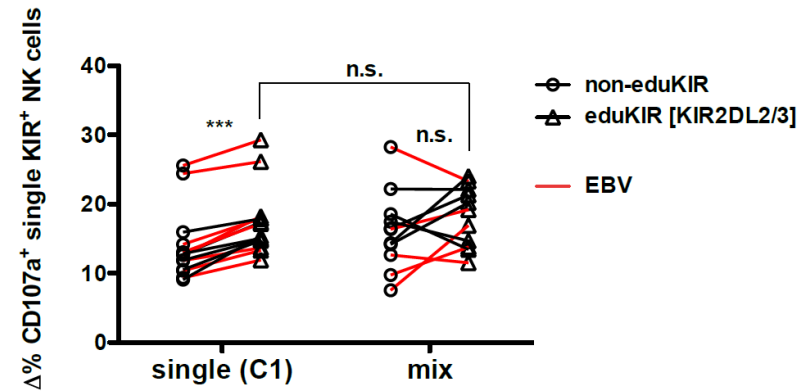Landtwing et al., J Clin Invest 2016

NK cell education

NK cell education is disarmed by non-cognate HLA in trans
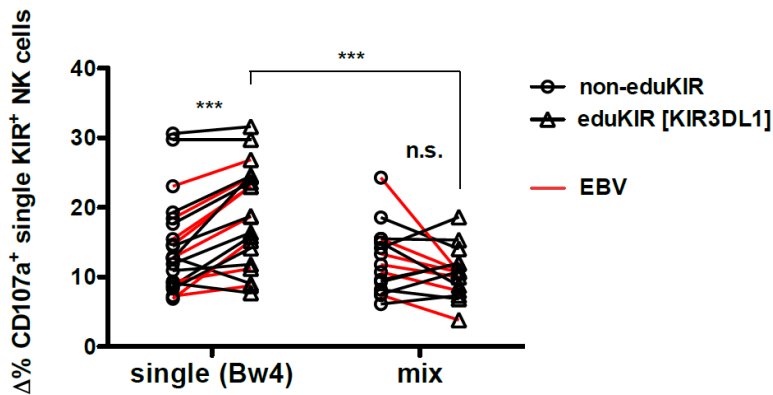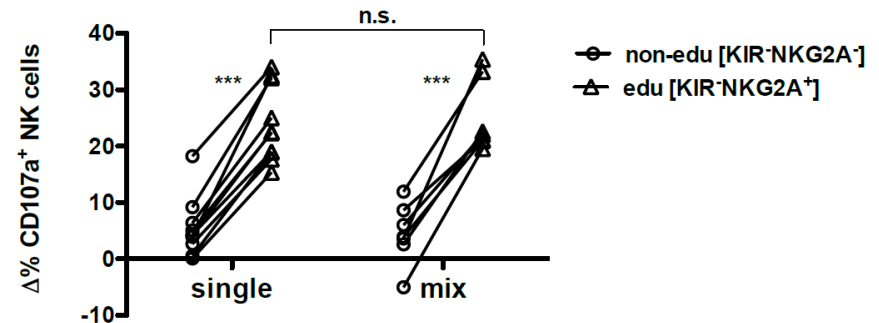
Mixed HLA-mismatched chimeras control EBV infection better
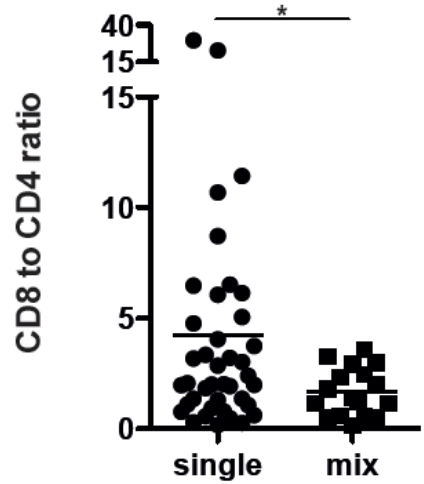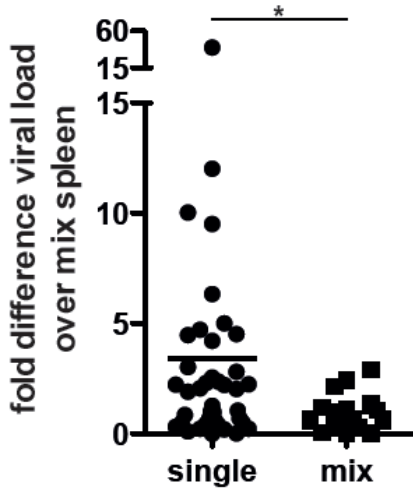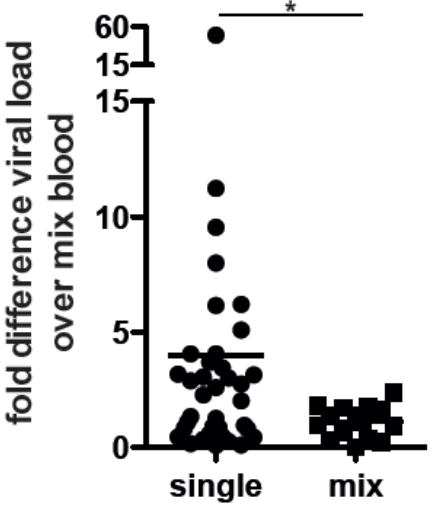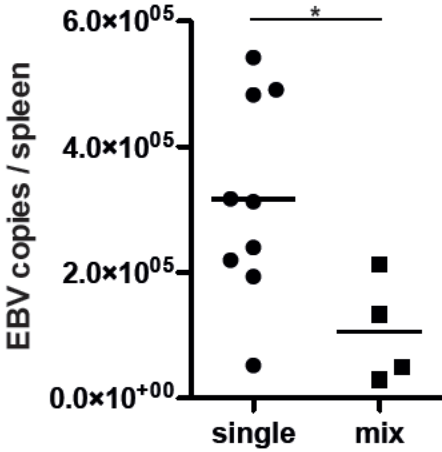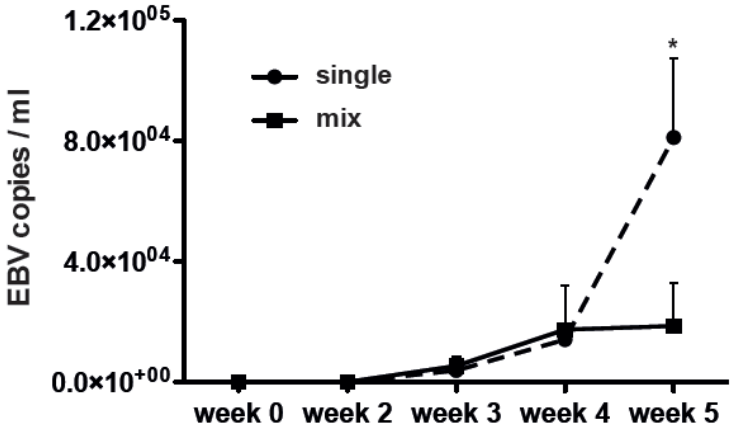
NK cells are responsible for this improved immune control
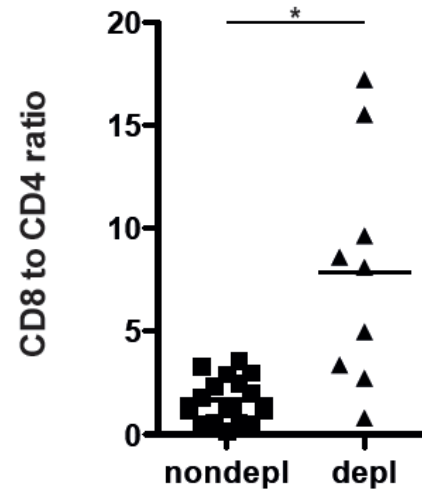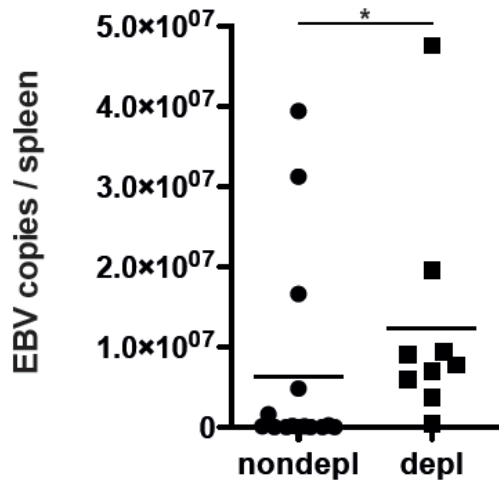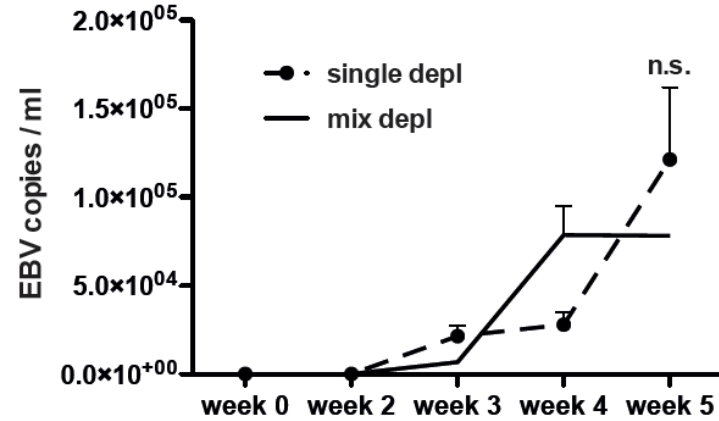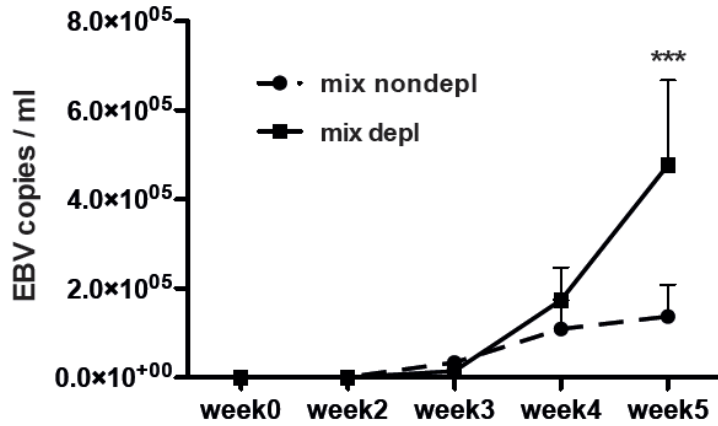
Summary 1:

1. NK cells with an early differentiated NK cell repertoire and HLA mediated education reconstitute in NSG mice and restrict EBV infection in vivo.

2. Plasma virus titers and lytically replicating EBV infected B cells are elevated in NK cell depleted and EBV infected huNSG mice.

3. Loss of NK cell mediated immune control of EBV leads to increased CD8^{+} T cell expansion during EBV infection, similar to the immunopathology during IM.

4. Lytic replication that is no longer controlled by NK cells leads to weight loss and tumorigenesis in EBV infected huNSG mice.

5. Mixed HLA mismatched NK cell reconstitution allows inefficient KIR engagement and better EBV specific immune control.

In vivo model of EBV infection and immune control

- EBV establishes persistent infection in mice with reconstituted human immune system components. This infection is controlled by **T cells** with contributions of CD4$^+$ and 2B4$^+$ CD8$^+$ T cells.
Strowig et al., J Exp Med 2009; Antsiferova et al., PLoS Pathogens 2014; Chijioke et al., J Infect Dis 2015

- DC targeted vaccination can elicit low level T cell responses and the reconstituted **human DC compartment** can be investigated for its reactivity towards adjuvant candidates in this in vivo model.
Gurer et al., Blood 2008; MeixIsperger, Leung et al., Blood 2013

- Innate leucocyte compartments are established and functional. **NK cells** can target MHC class I negative tumor cells in these mice. These NK cell responses restrict lytic EBV infection and infectious mononucleosis symptoms in vivo.
Strowig, Chijioke et al., Blood 2010; Chijioke et al., Cell Reports 2013; Landtwing et al., J Clin Invest 2016

- **Mutant EBV** and novel strain infections phenocopy clinical manifestations in patients, including tumorigenesis. The in vivo model allows to characterize polymorphisms in the viral genome with respect to infection and immune control in vivo.
White, Rämer et al., J Clin Invest 2012; Tsai et al., Cell Reports 2013

Acknowledgments

Vanessa Landtwing

Ana Raykova

Donal McHugh

Monica Loi

Maria Pena

Anita Murer

Julia Rühl

Nicole Caduff

Hana Zdimerova

Christine Engelmann

Yun Deng

Katarina Schmidt

Bithi Chatterjee

Obinna Chijioke

Laure-Anne Ligeon

Cornelia Gujer

Petra Paul

Charlotte Montespan

Danusia Vanoaica

Anne Müller

Viral Immunobiology (Münz Laboratory)
Institute of Experimental Immunology
University of Zürich

Vivien Beziat
Imagine Institute, Paris, France

Kalle Malmberg
University of Oslo, Norway

Alessandro Moretta
University of Genua, Italy

Guido Ferlazzo
University of Messina, Italy

Tarik Azzi

David Nadal
Children's hospital, University of Zürich

Alexandra Papoudou-Bai
University of Ioannina, Greece

Gerald Niedobitek
Pathology, Sana Hospitals, Berlin

Ethel Cesarman
Weill Cornell Medical School, New York, USA

David Blackbourn
University of Surrey, UK

Thomas Schulz
Hannover Medical School, Germany

Andrea Zbinden

Riccarda Capaul
Medical Virology, University of Zürich

Henri-Jacques Delecluse
German Cancer Research Institute, Heidelberg

Adam Grundhoff
Heinrich Pette Institute, Hamburg, Germany