TECHNISCHE UNIVERSITÄT DRESDEN

Humanized Mice to study human HSC function in a surrogate host

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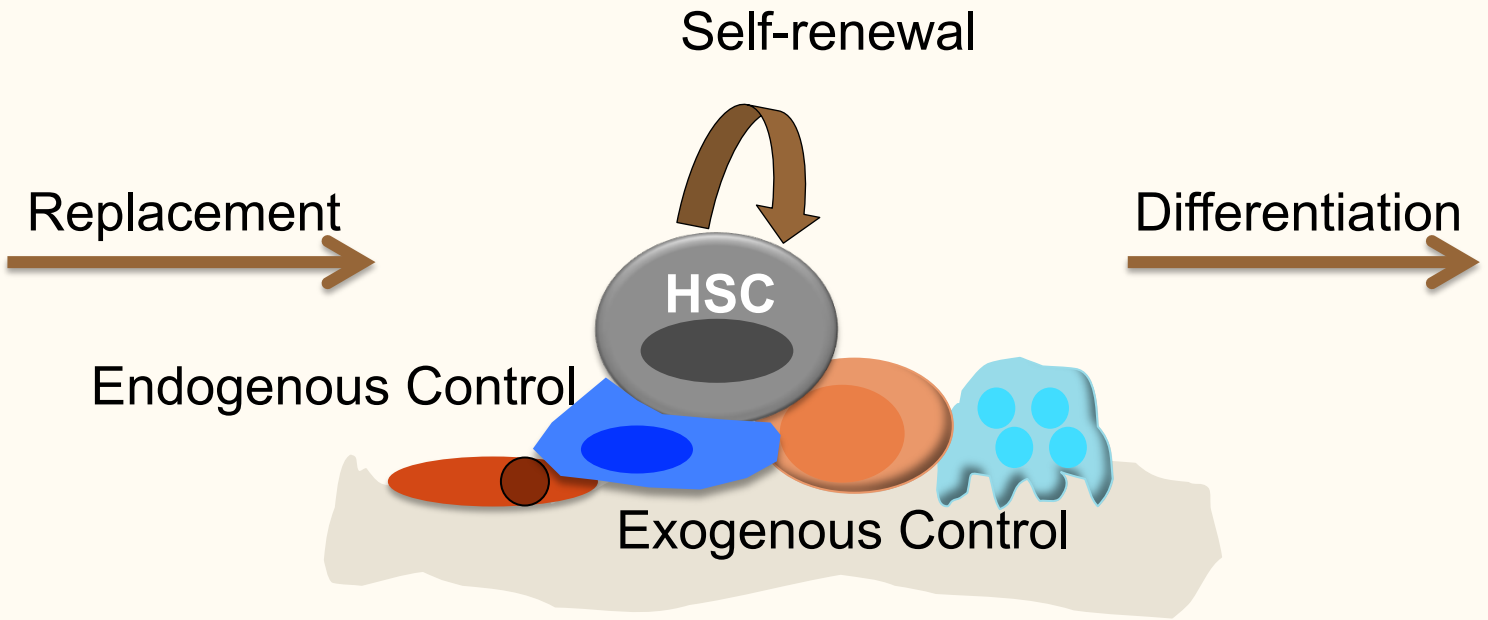
Regeneration in Hematopoiesis, TU Dresden, Germany

Humanized models to study immunity and to accelerate the development of new solutions for human health

Veyrier-du-Lac, April 26-28 2017

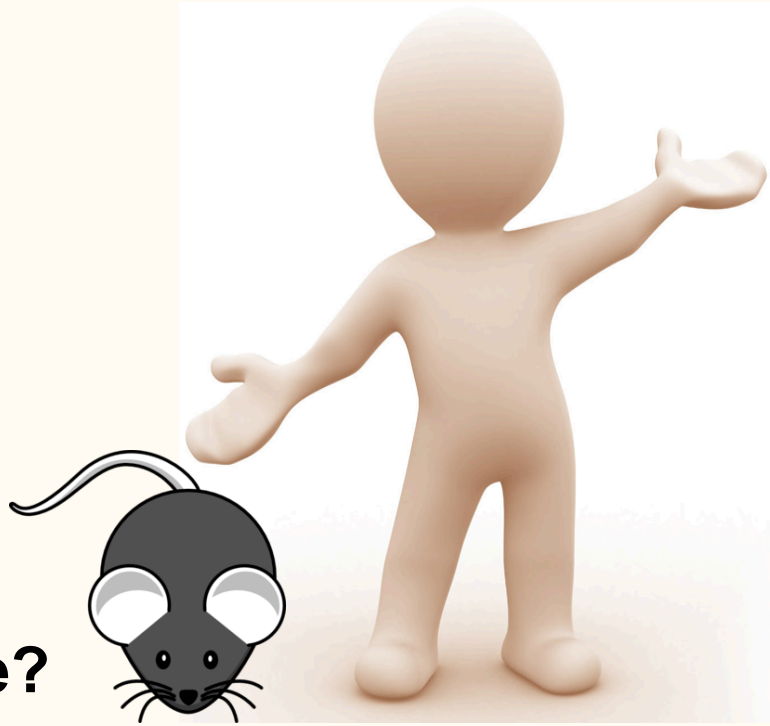
Modulating (human) HSC function in vivo



– Universal recipients across species barriers - improved HSC engraftment
– Inter-species niche compatibility
– Cell-cycle-mediated control of HSC fate decisions

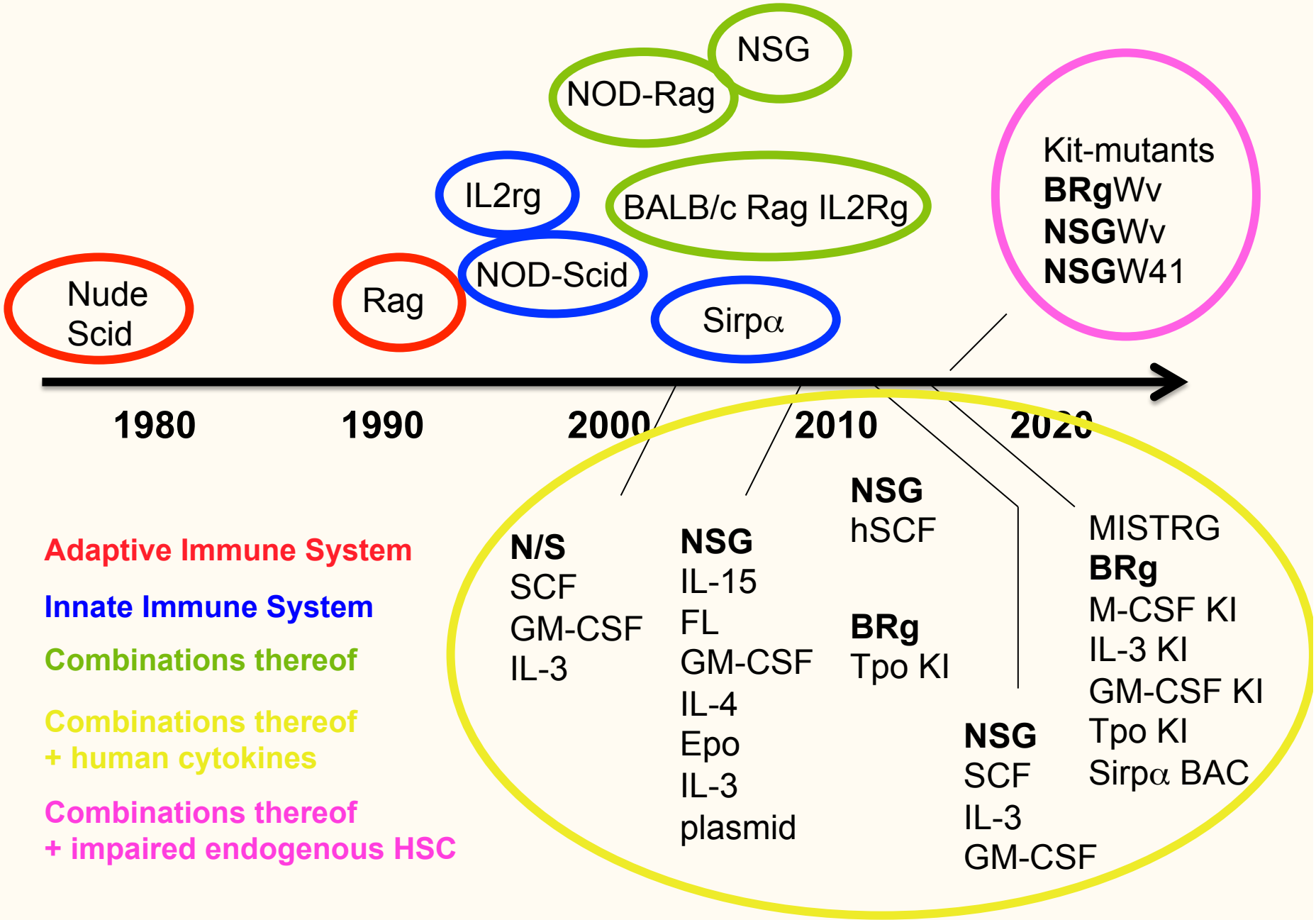
Opening-up the stem cell niches for human HSCs

- In vivo study of human HSC function and hematopoiesis
- Human immune responses in mice
- Mechanisms of blood cell-based diseases

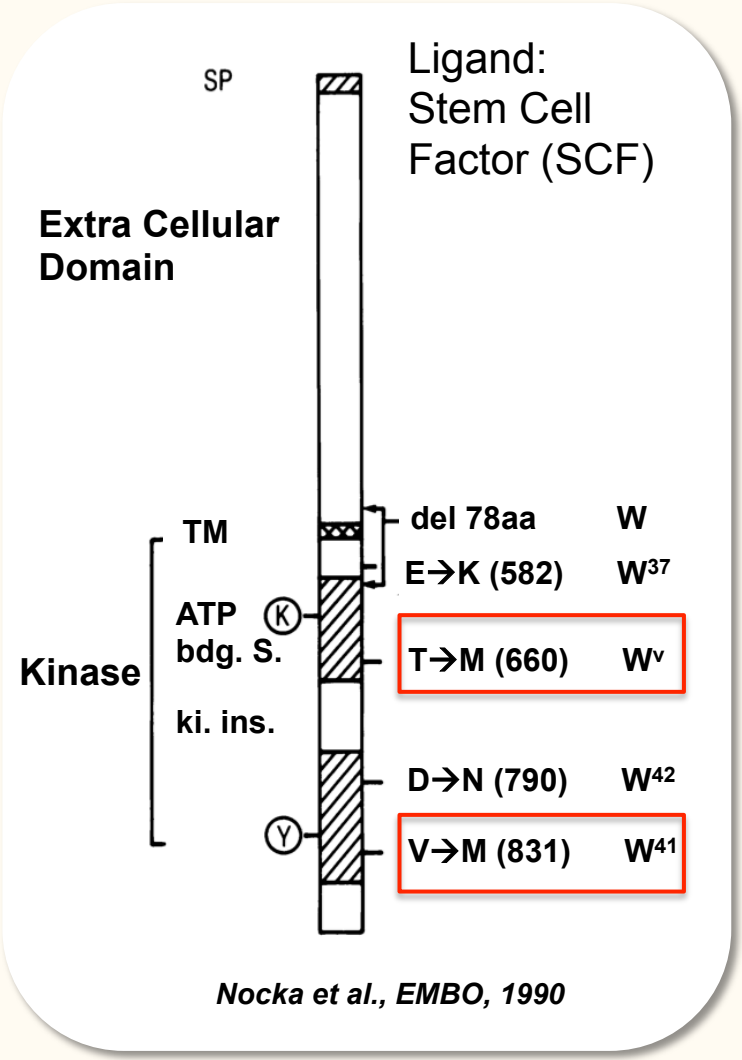


Regeneration of human HSCs in Mice?

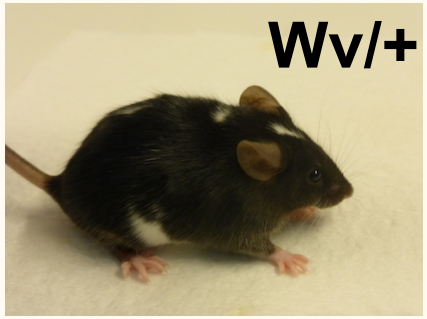
Approaches for the making of ‚humanized mice'

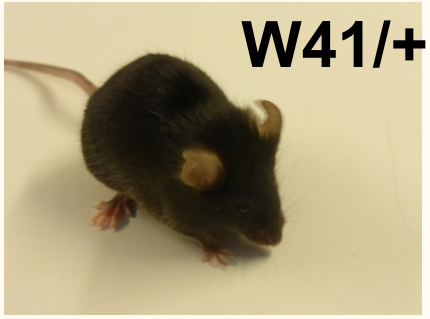


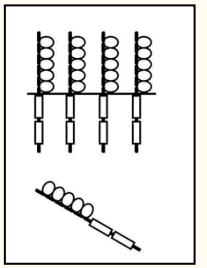
Kit is a hot-spot for mutations

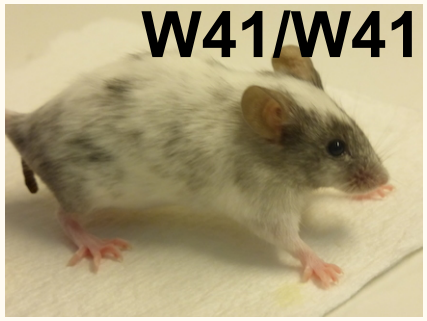


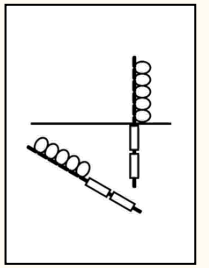
Nocka et al., EMBO, 1990





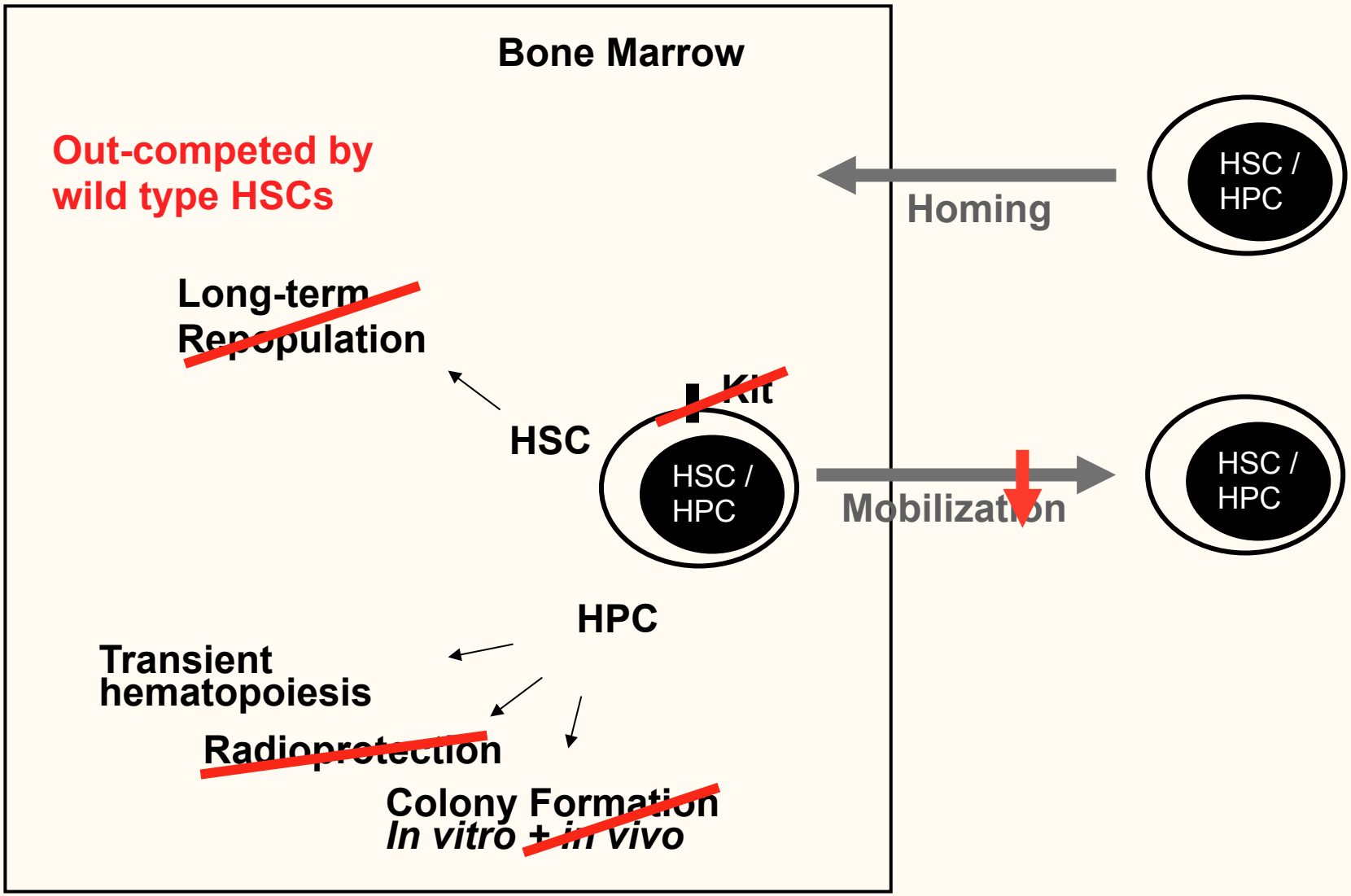




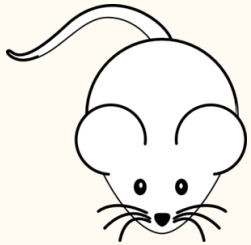


Wv/Wv	W41/W41
Severe anemia	Mild anemia
sterile	**fertile**

HSC/HPC function in Kit-mutant mice



Opening up the stem cell niche:
Combining immunodeficiency with non-competitive HSCs



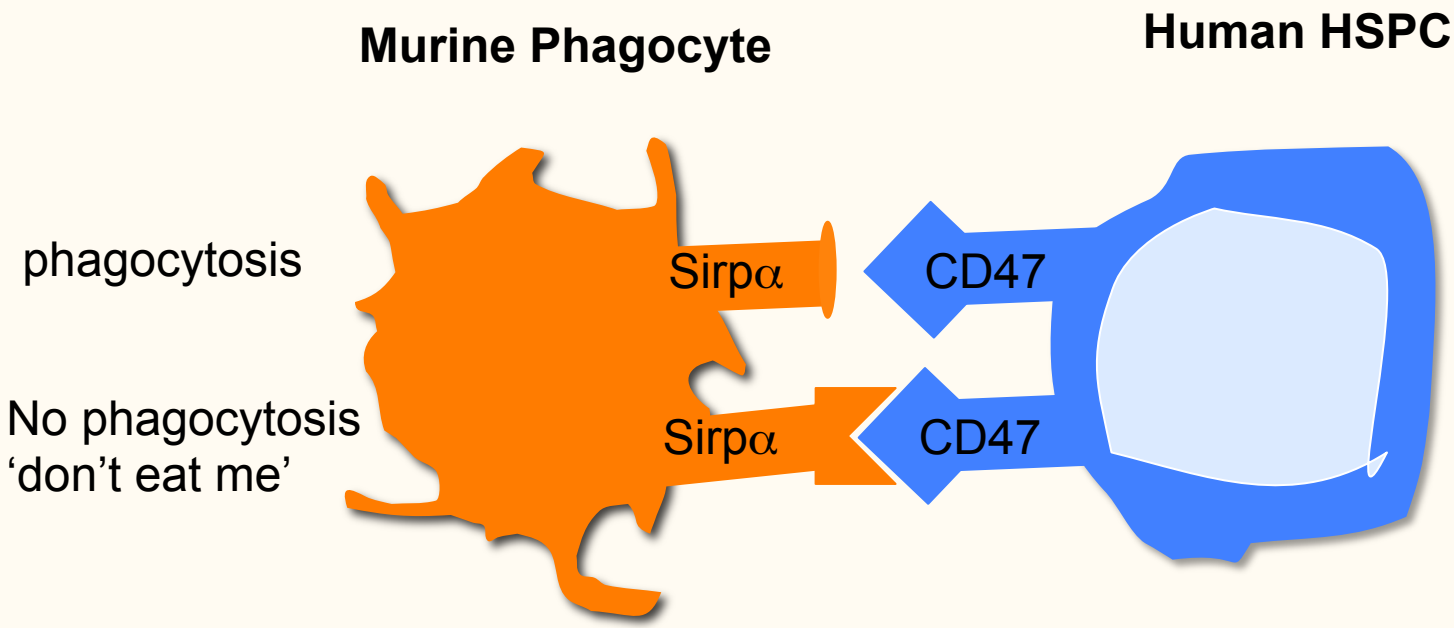
Allogeneic

Transplantation

Rag2^{-} Il2rg^{-} Kit$^{W/Wv}$

Nat Methods, 2009

Allelic variants of Sirpα modulate human HSPC engraftment

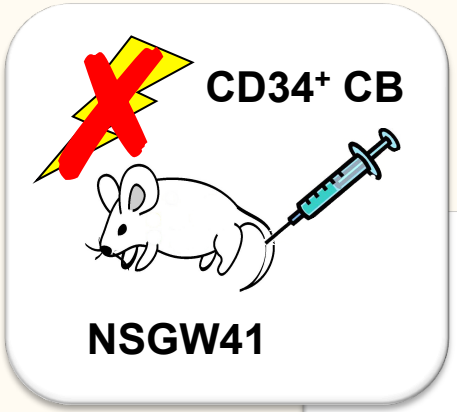


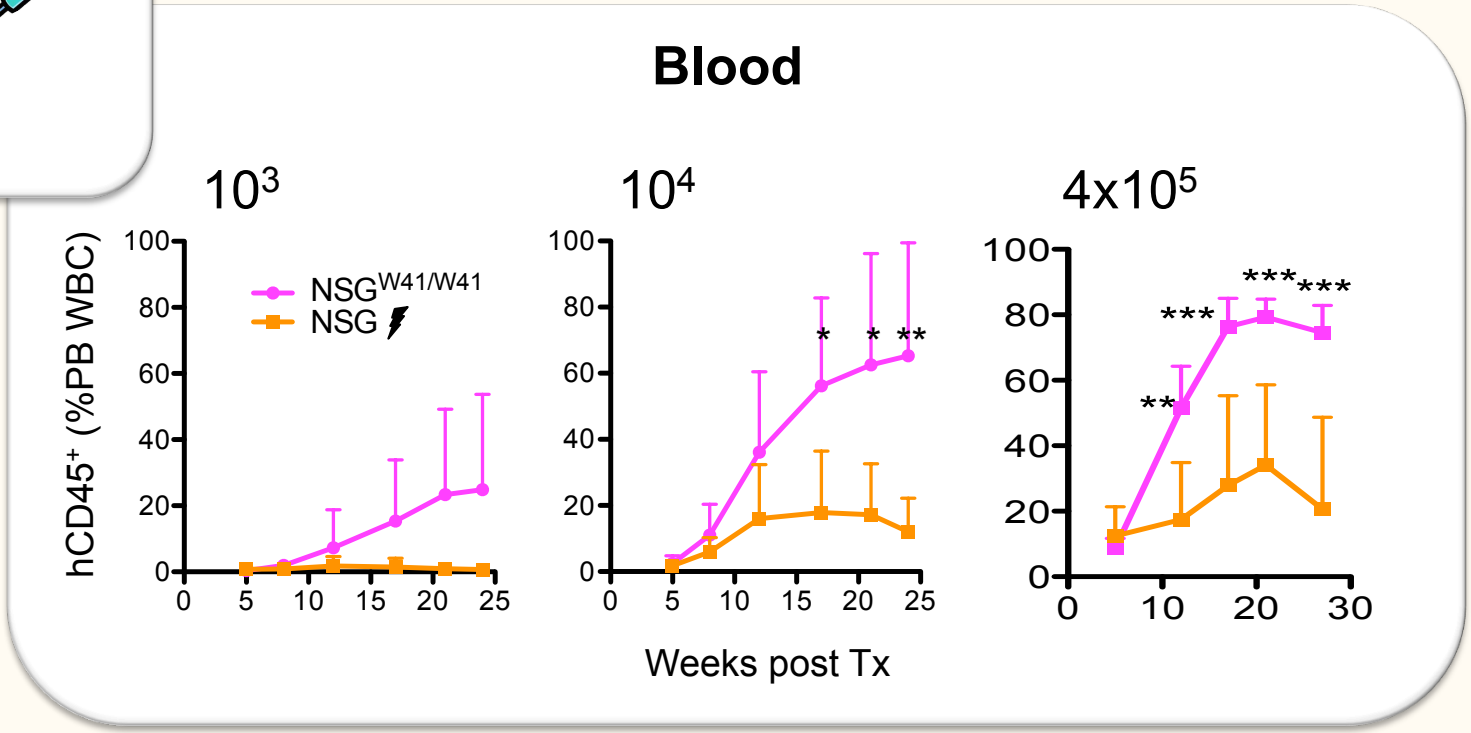
Polymorphism in *Sirpa* modulates engraftment of human hematopoietic stem cells

Katsuto Takenaka[1,6], Tatiana K Prasolava[2,6], Jean C Y Wang[1,3], Steven M Mortin-Toth[2], Sam Khalouei[2], Olga I Gan[1], John E Dick[1,4] & Jayne S Danska[2,5]

NATURE IMMUNOLOGY VOLUME 8 NUMBER 12 DECEMBER 2007

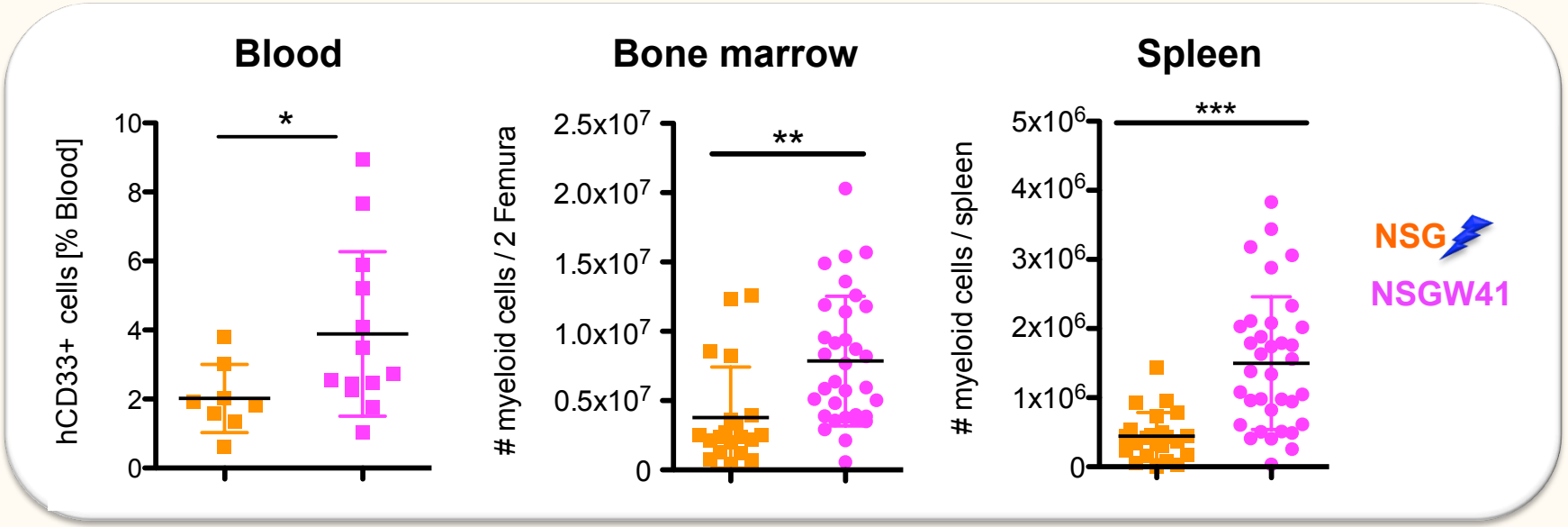
Great sensitivity for human HSC engraftment in NSGW41

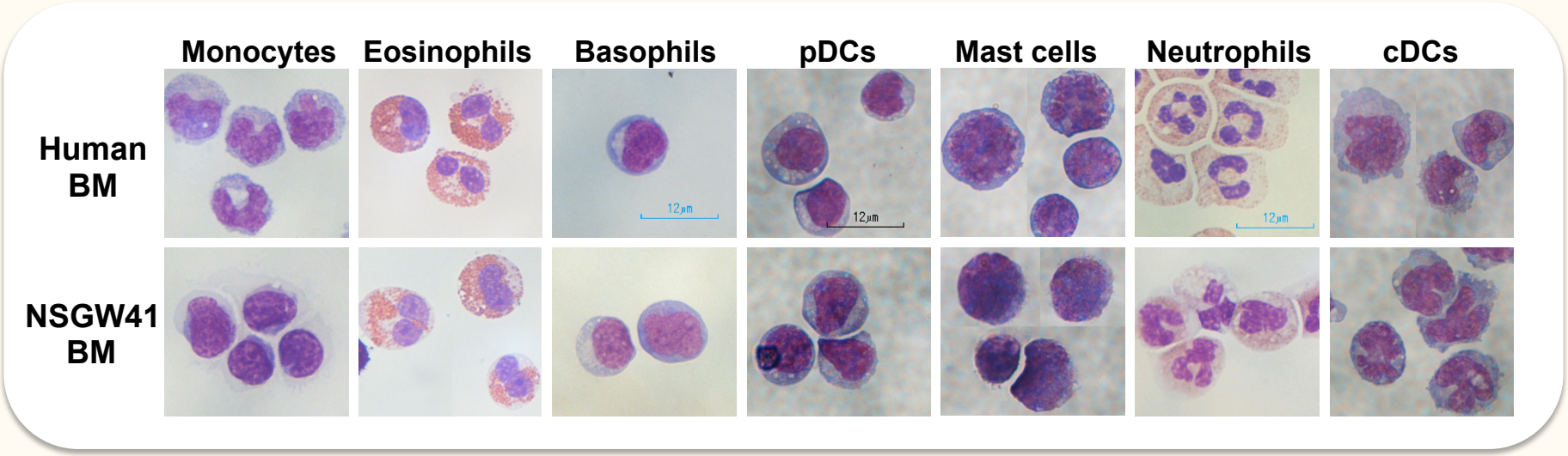




Cell Stem Cell, 2014 | HMR, 2015 | J Exp Med, 2015 | Stem Cell Rep, 2016

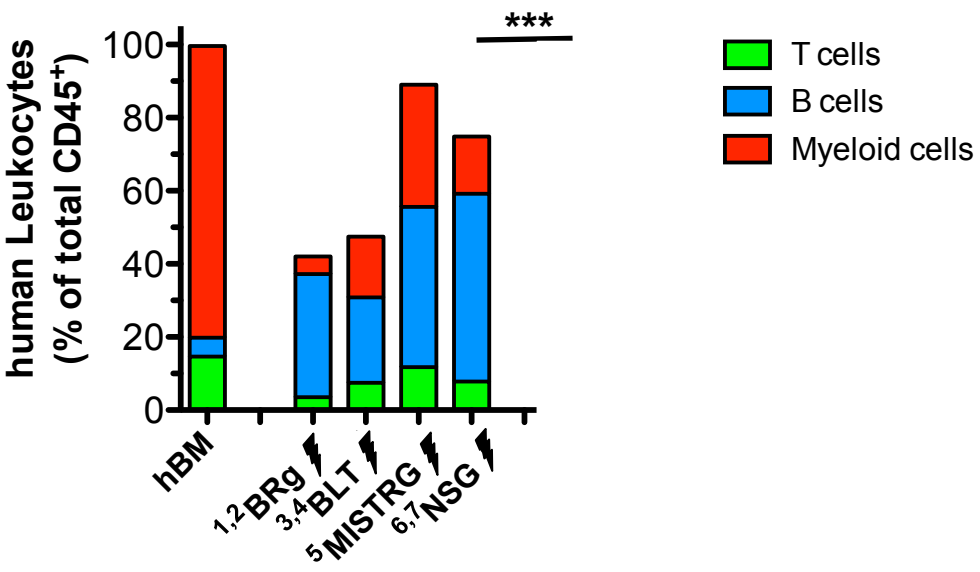
Improved myeloid reconstitution in NSGW41 mice





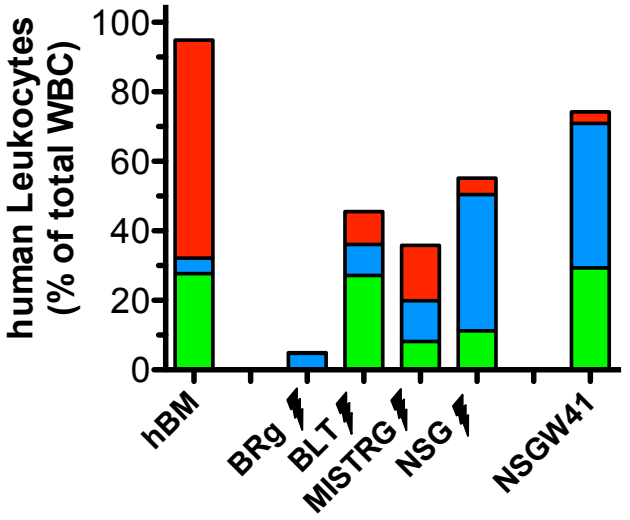
Multilineage engraftment

Bone Marrow

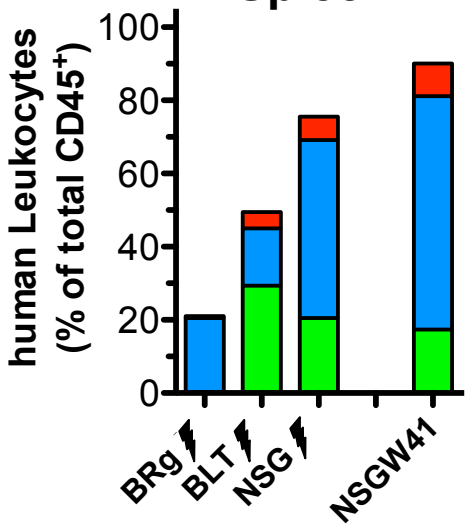


[1]Cosgun, Rahmig et al., *Cell Stem Cell*; 2014, [2]Traggiai et al.,*Science*, 2004; [3]Melkus et al., *Nat Med*, 2006; [4]Lan et al., *Blood*, 2006; [5]Rongvaux et al., *Nat Biotechnol*, 2014; [6]Ishikawa et al., *Blood*, 2005; [7]Ito et al., *Blood*, 2002

Peripheral Blood



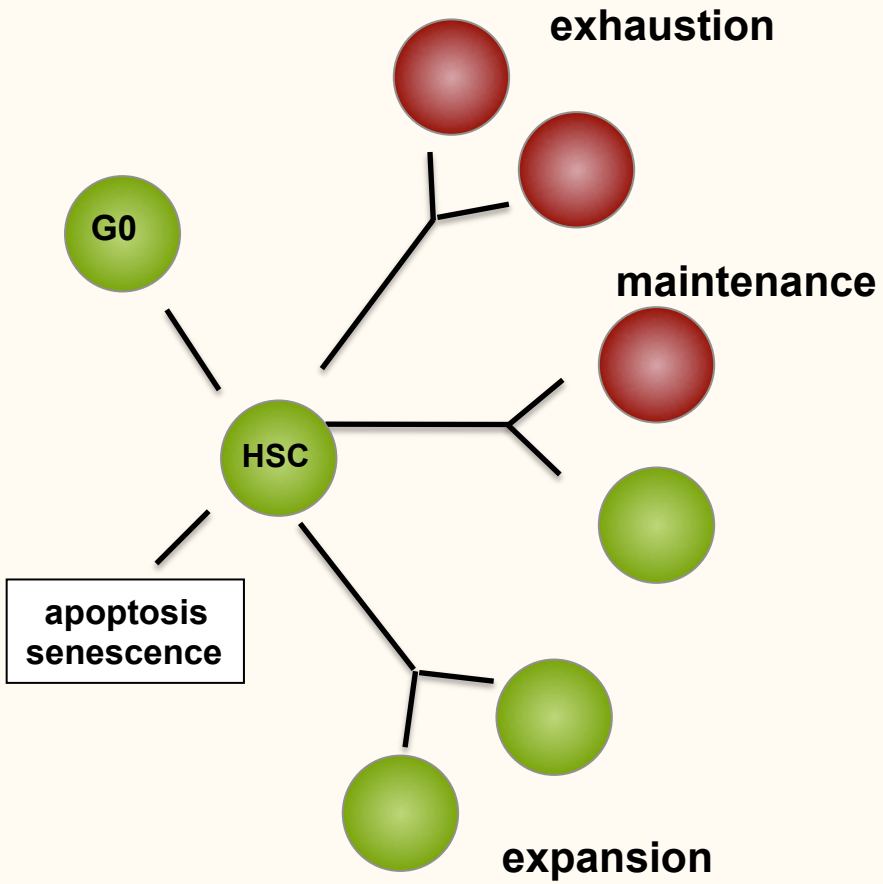
Spleen



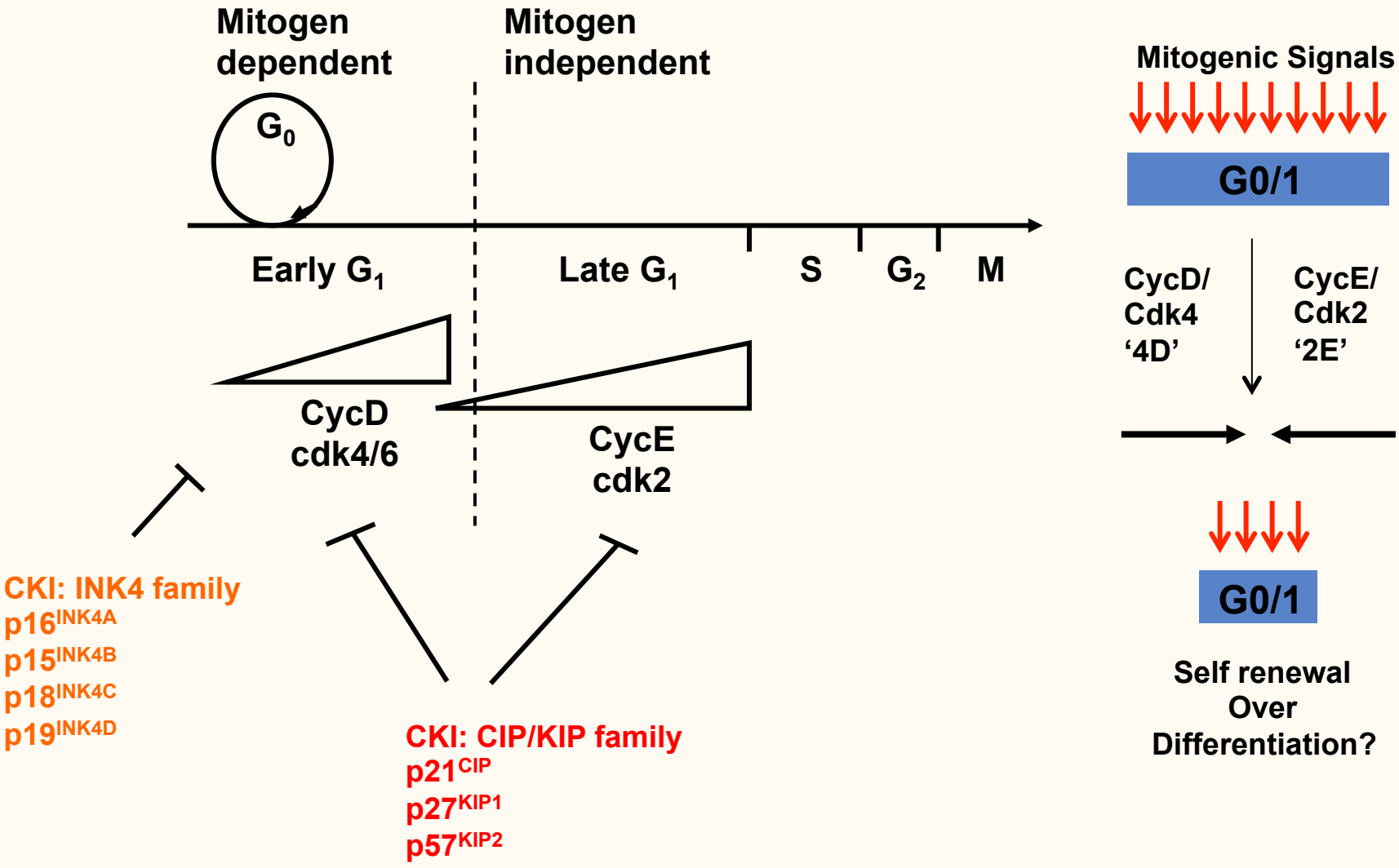
NSGW41 makes possible:

- **Transplant w/o irradiation conditioning**
- **Peripheralization of mature cells**
- **Continuous high myeloid output**

– Universal recipients across species barriers - improved HSC engraftment
– Inter-species niche compatibility
– Cell-cycle-mediated control of HSC fate decisions



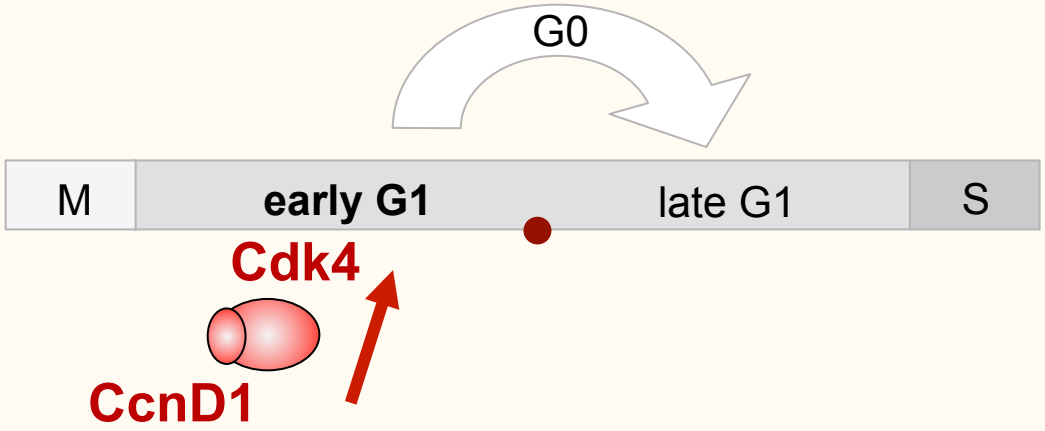
Cell cycle progression a key regulator of stem cell fate?

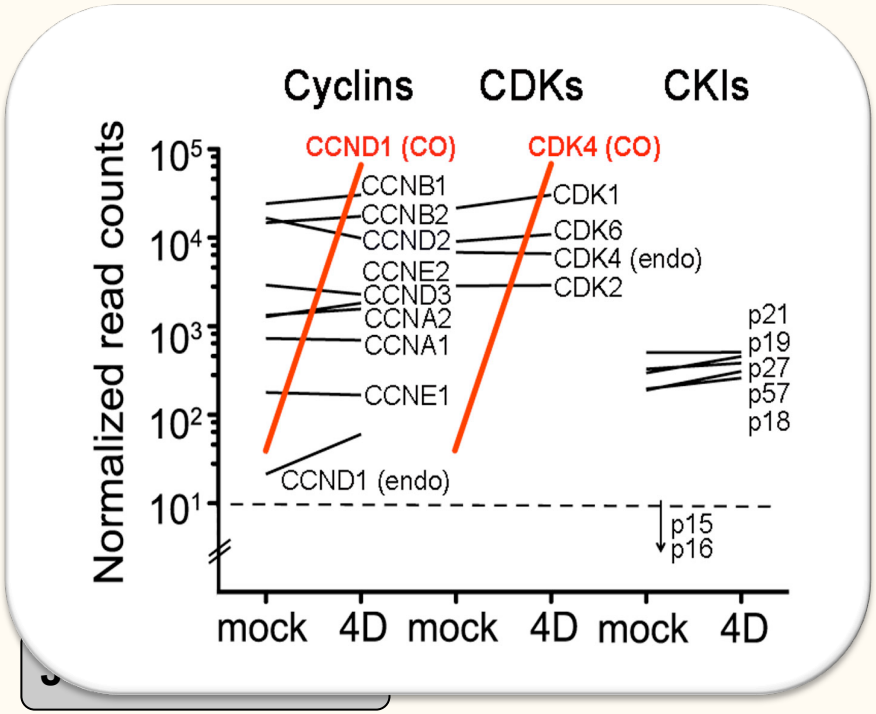


J Exp Med, 2015

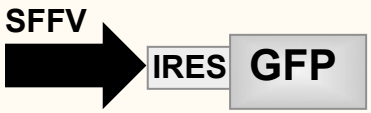
Overexpression of 4D

CD34⁺ human HSPCs

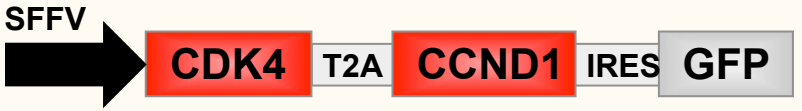




mock



4D



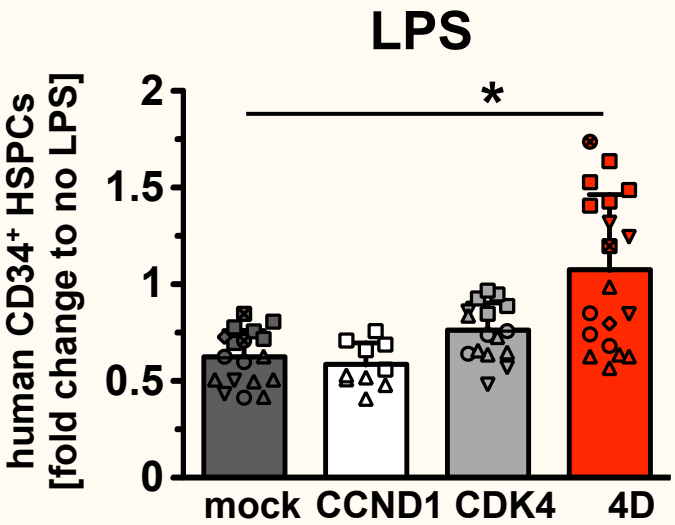
4D protects HSPCs from differentiation

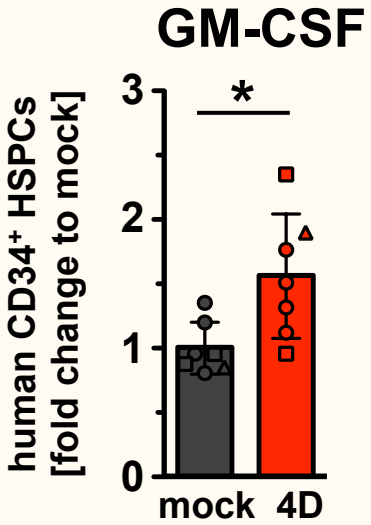
differentiation induction *in vitro*:

4d after transduction

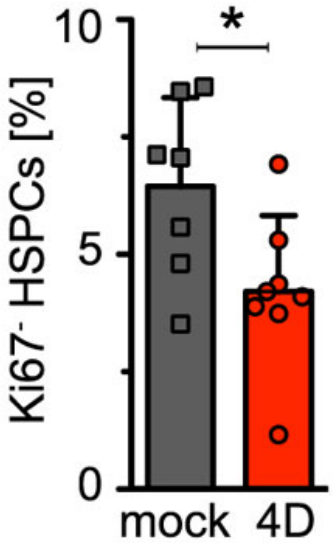
6-8 days with LPS / GM-CSF →

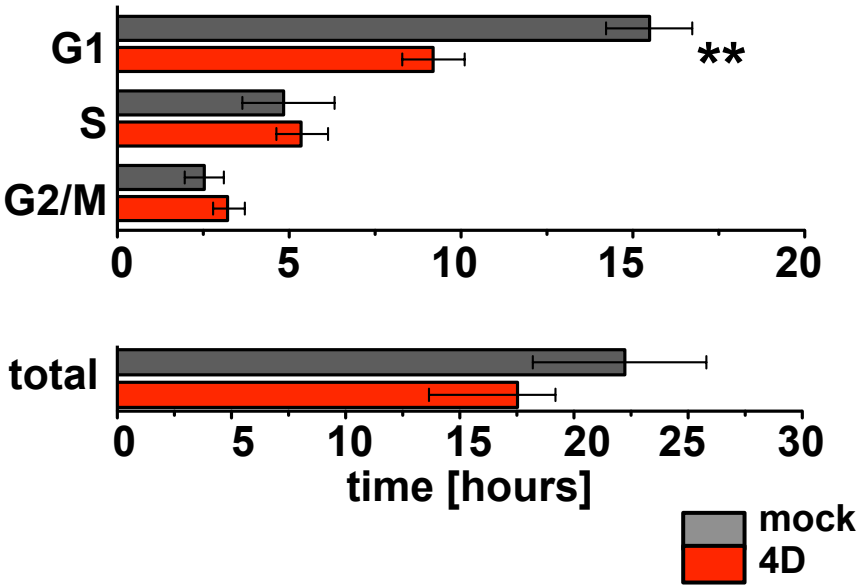
HSPC maintenance?





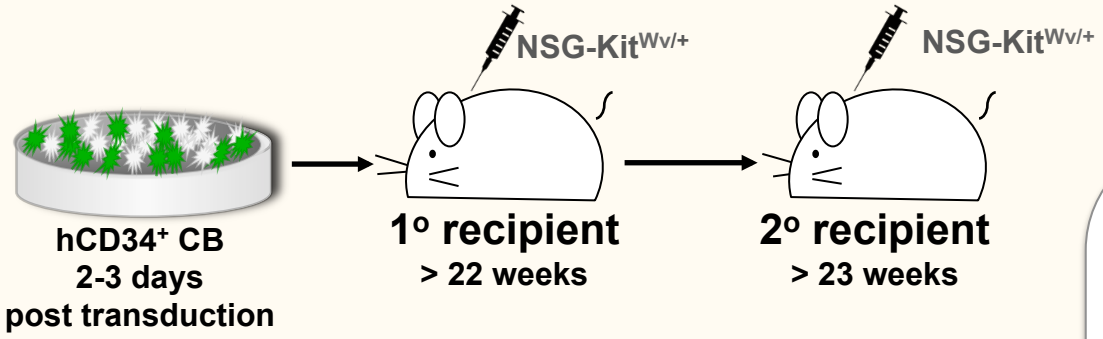
Overexpression of 4D results in G0-to-G1 transition and accelerated transit through G1

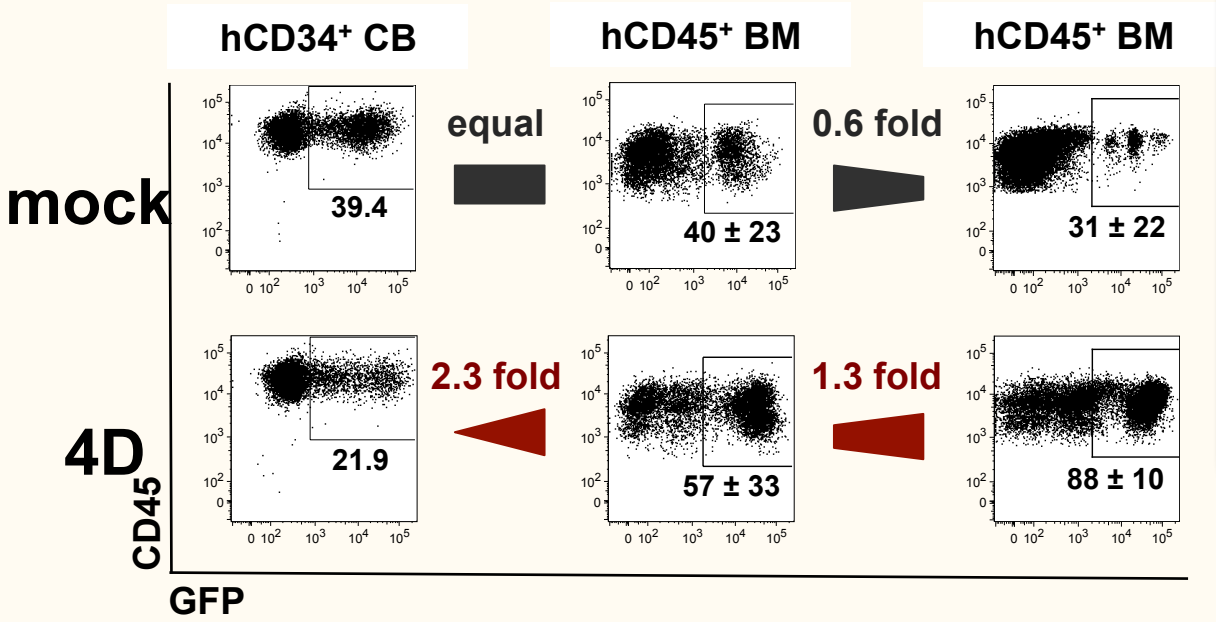


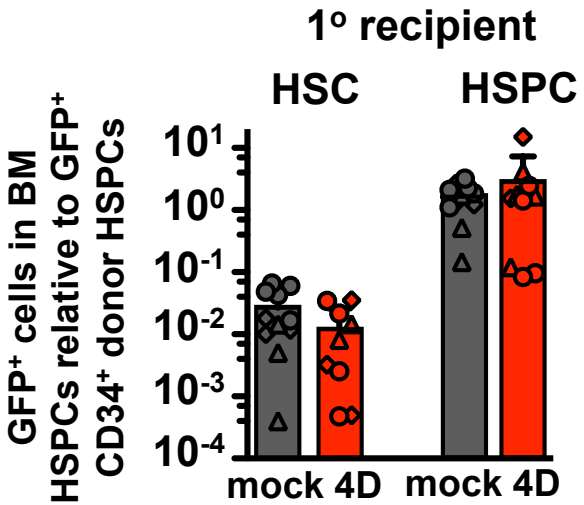


Thomas Höfer, Erika Kuchen
Theoretical Systems Biology
DKFZ, Heidelberg

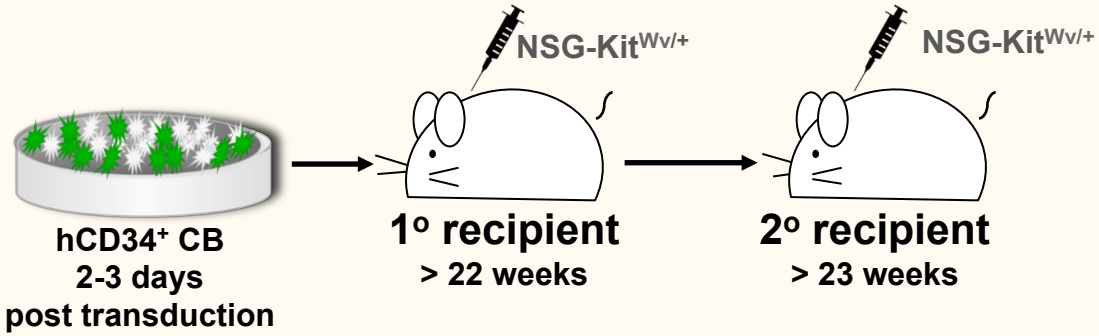
4D increases human leukocyte engraftment in vivo

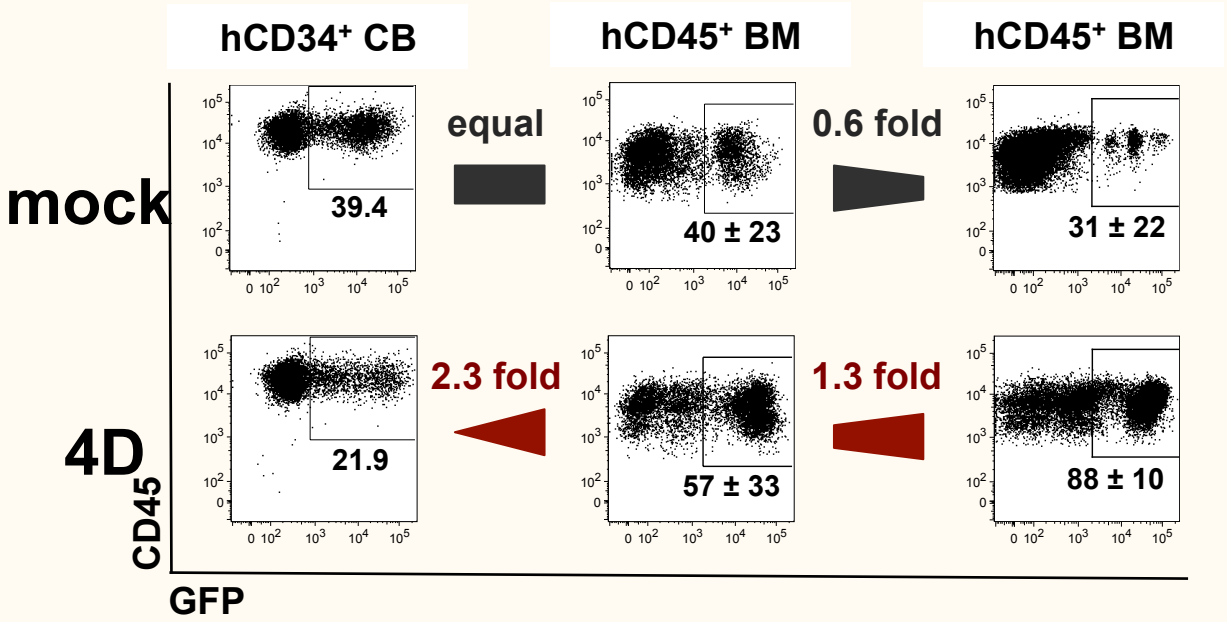


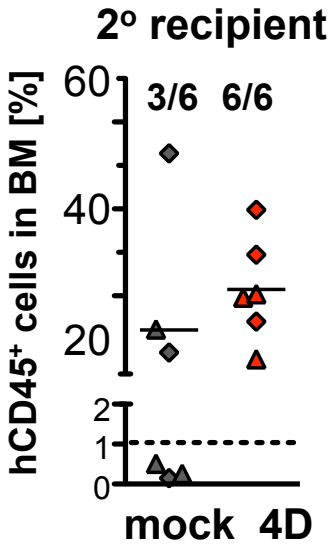




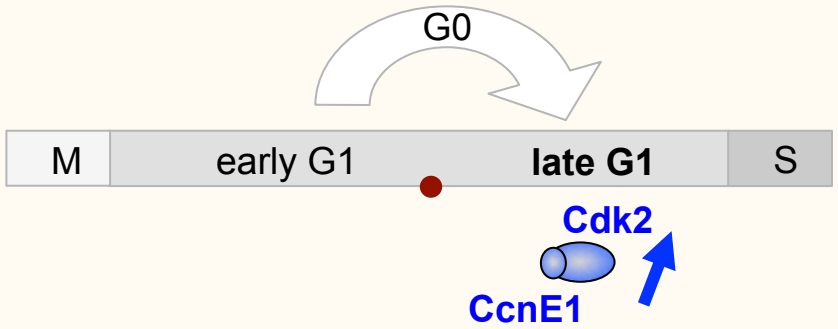
4D increases human leukocyte engraftment in vivo

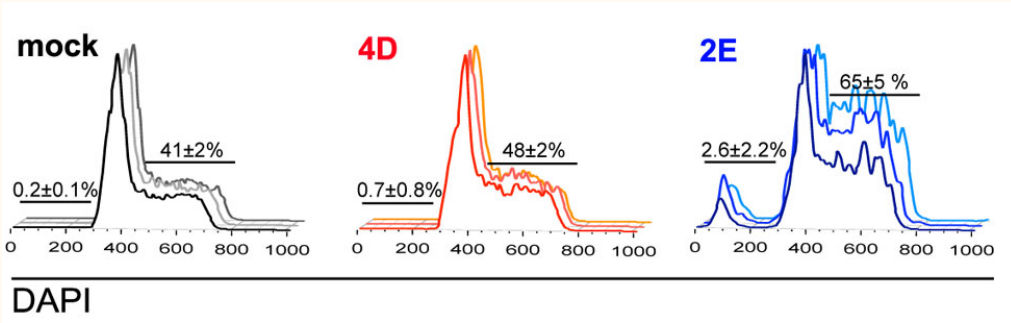




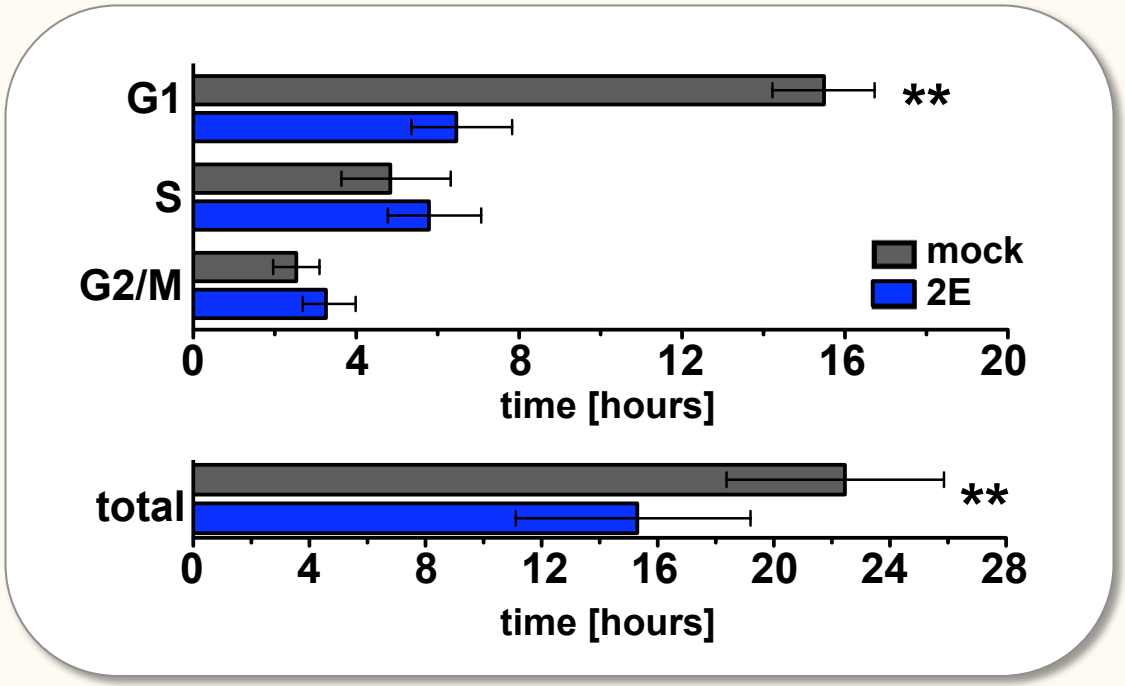


2E dramatically accelerates transit through G1

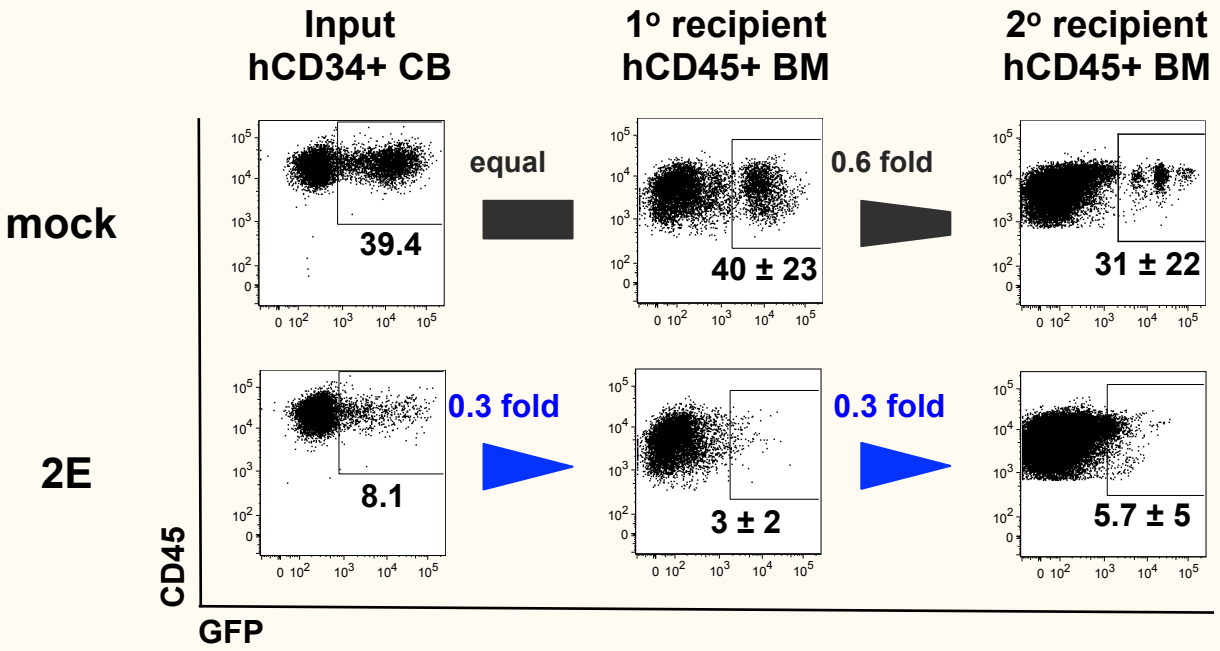


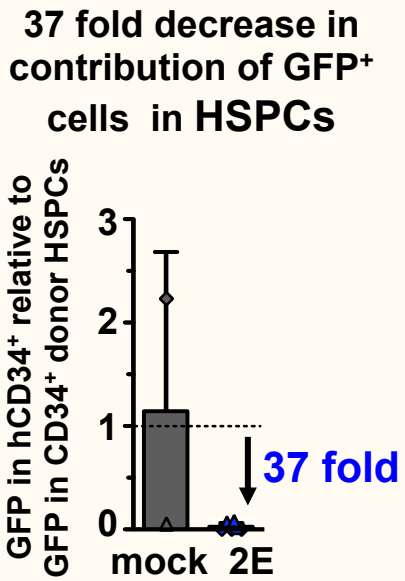


3-5 d after transduction

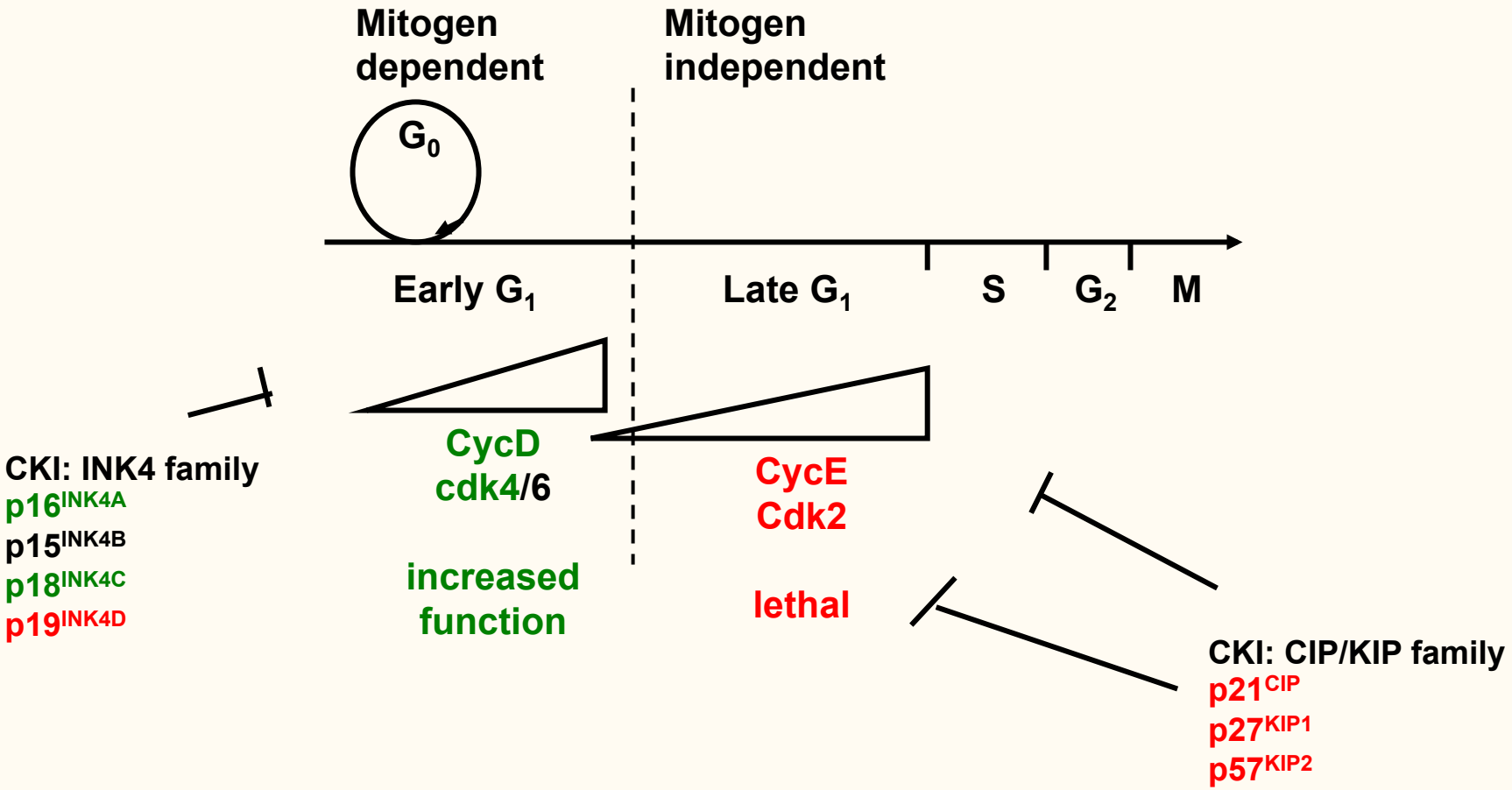


2E confers a competitive disadvantage to human HSPCs





Progression through early cell cycle phases determines fate of human HSCPs



A balanced transit through early and late G1 phase is a key regulator for human HSPC function.