Harnessing the Power of Innate Immunity in Vaccine against Tuberculosis

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“The Scientist must concern himself with what one will say about him in a century, rather than with current insults or compliments”

(Louis Pasteur, July 19, 1864)

Host responses to pathogens

1. Innate immunity

↓

2. Adaptive immunity

↓

3. Granuloma formation

↓

Dissemination & Death

M. tuberculosis

Vaccine against TB

T Cell Mediated Vaccine in TB

- 1960: Jacque Miller and Max Cooper discovered a subset of thymocytes is engaged in antigen recognition and responsible of delayed-type hypersensitivity.
- 1973:Robert North demonstrated that thymus-derived lymphocytes contribute to the containment of TB independent of antibodies
- Host deficient in T cells (e.g. HIV^+ patients) are more susceptible to TB
- The memory capacity of T cells

Virtually all vaccines against TB are targeting T cells

What about Innate Immunity?

Evidence of innate immunity in *Mtb* elimination

Approximately 20% of individuals living in hyperendemic of TB are TST negative and resistant to TB.

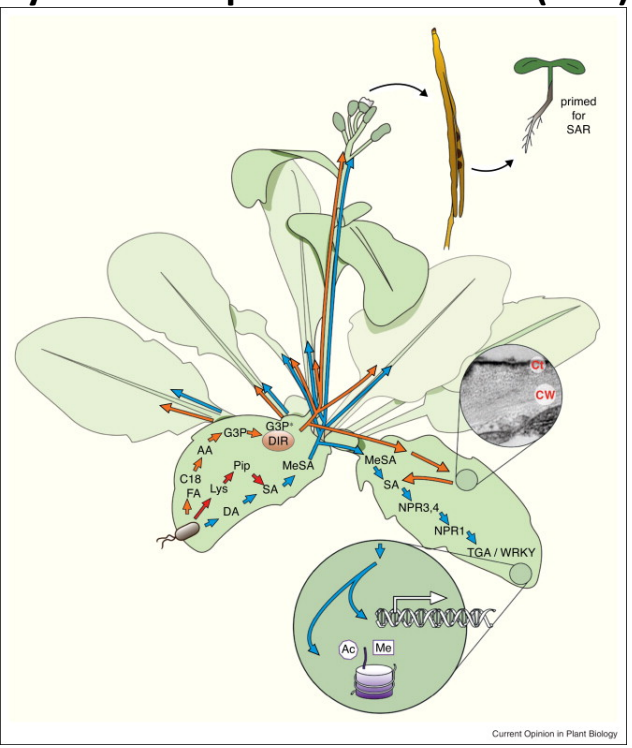
Approximately 30-50% of close household contacts of patients with active TB are TST negative and resistant to TB

Does innate immunity have memory-like capacity?

Cobat et al, JEM, 2009
Morrison et al, Lancet Infec Dis, 2008

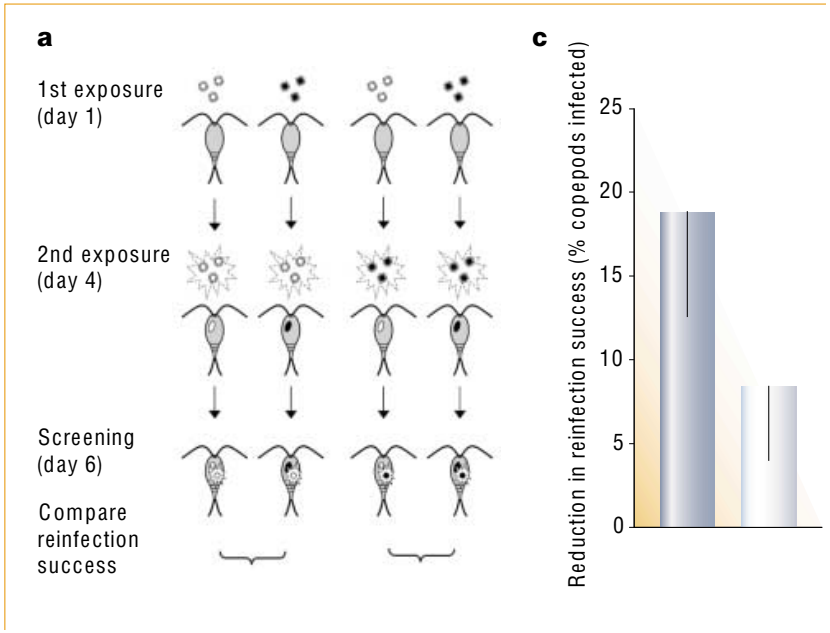
Innate Immunity is a major component of eliminating pathogens with memory-like capacity

Systemic Acquired Resistance (SAR)



SAR is a long distance signaling mechanism
Provides long-lasting resistance to 2nd infection

Invertebrate (Copepode)



Vertebrate (Humans)

Monocytes/Mac

Infection or vaccination

↓

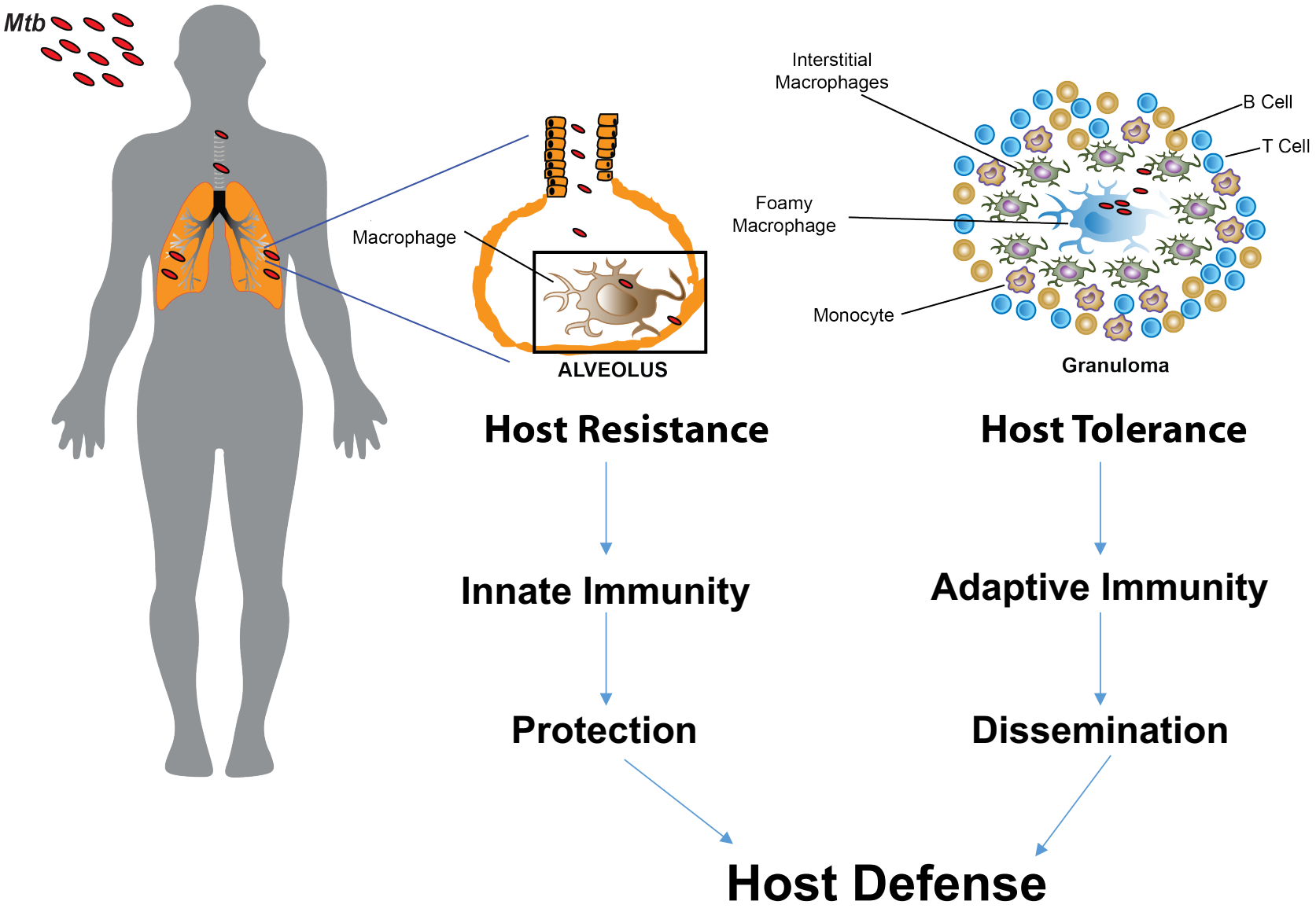
Epigenetic reprogramming in innate immune cells

↓

Trained Innate Immunity

Kachroo et al, Current Opinion in Plant Biology, 2013
Kurtz et al, Nature, 2003
Netea et al, Science, 2015

Immunity to *M. tuberculosis*

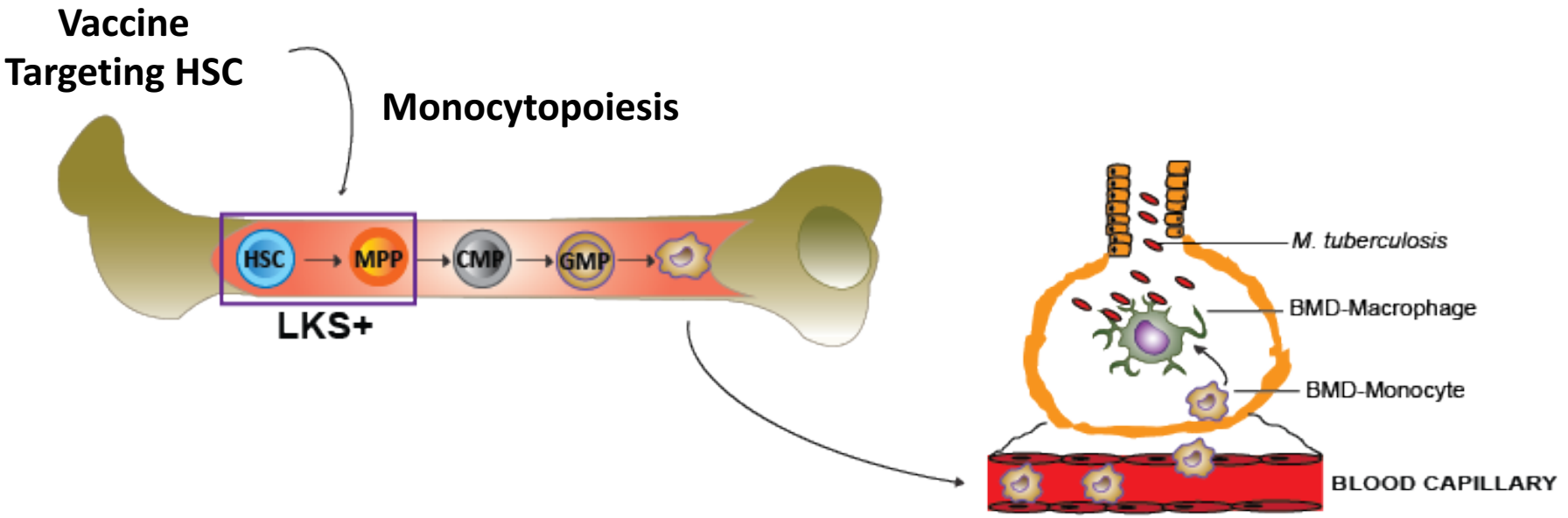


Divangahi & Behr, Am J Resp Crit Care Med, 2018

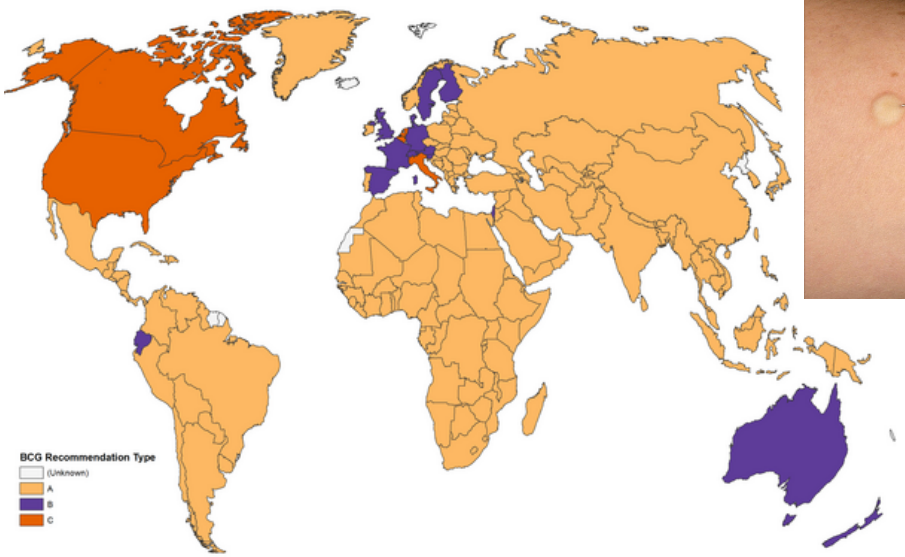
Jonathan Dunn (MSc)

Eva Kaufmann (PDF)

How can we harness the power of macrophages in protection against *Mtb*?


Vaccine
Targeting HSC
Monocytopoiesis
HSC
MPP
CMP
GMP
LKS+
M. tuberculosis
BMD-Macrophage
BMD-Monocyte
BLOOD CAPILLARY

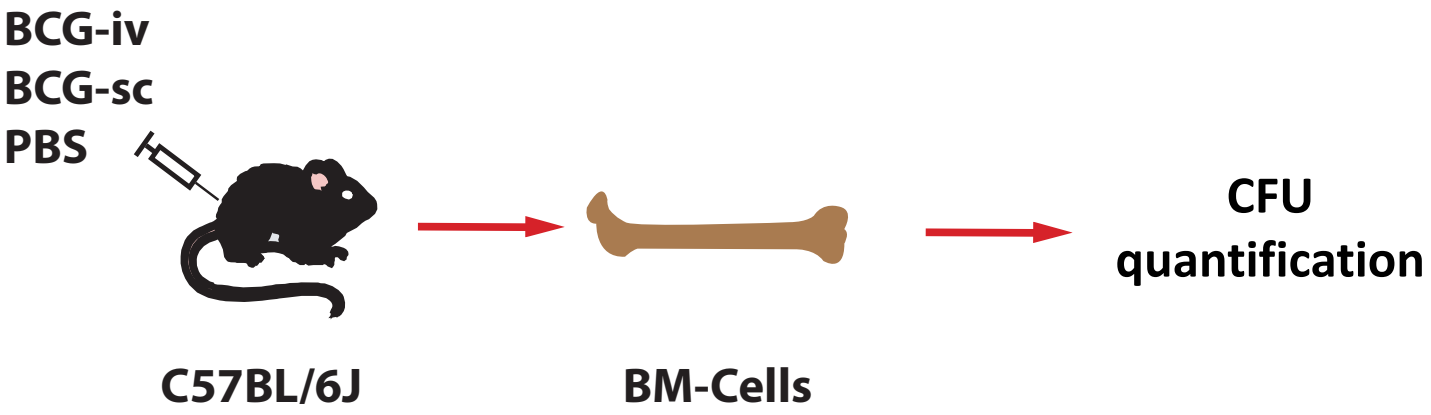
Bacille Calmette-Guérin (BCG)

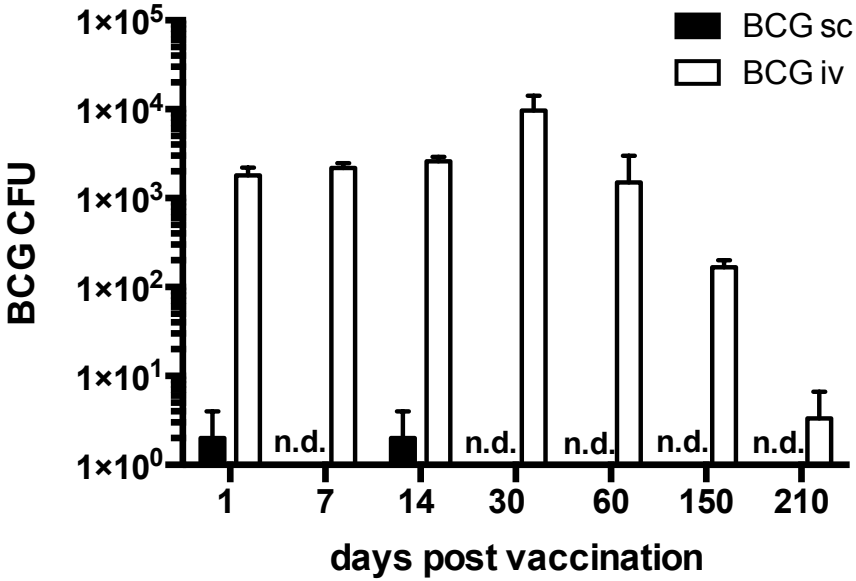


- **3 Billion people intradermally vaccinated with BCG**
- **Effective in early childhood however there is a lack of efficacy in protecting adults against TB**
- **The most prominent T cell antigens of *Mtb* (e.g. ESAT-6, CFP-10) are missing in BCG**
- **There is no direct link between BCG-specific T cells and protection against TB**

Zerling PLoS Med 2011
Behr Lancet Infect Dis 2002
Comstock Am J Resp Crit Care 1988

BCG Had NO Access in the BM after Subcutaneous Vaccination

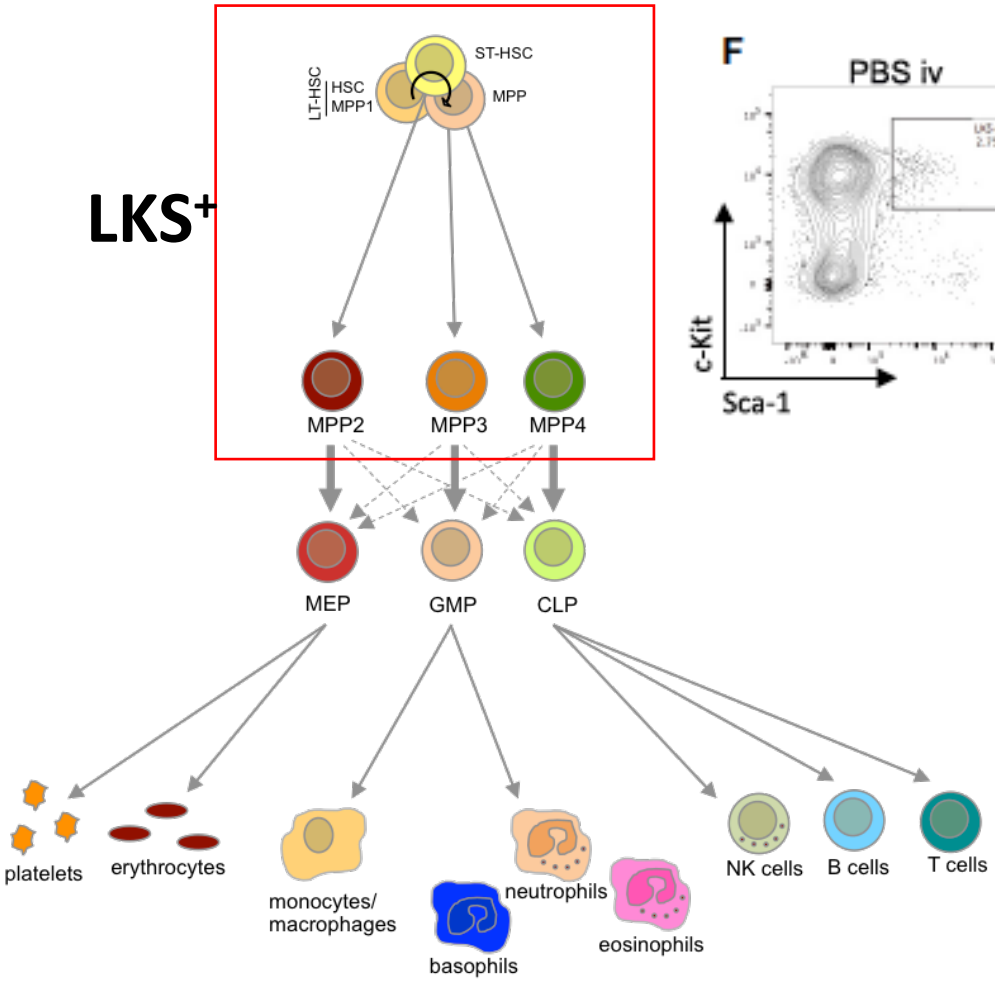


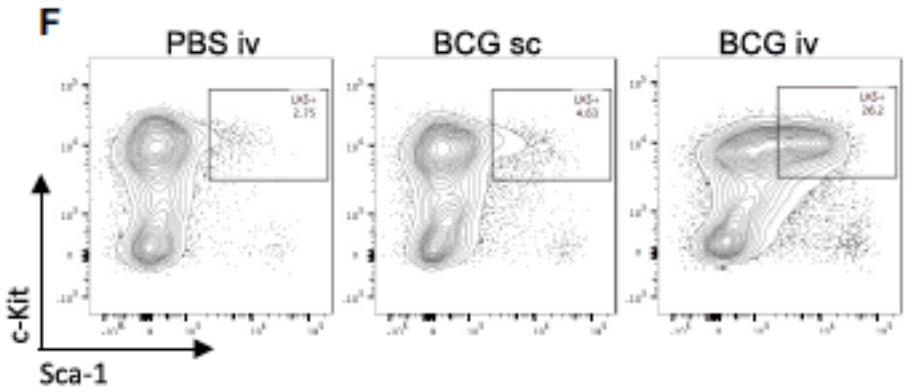


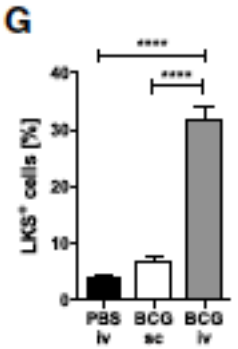
BCG-dose: 1x10^6 CFU

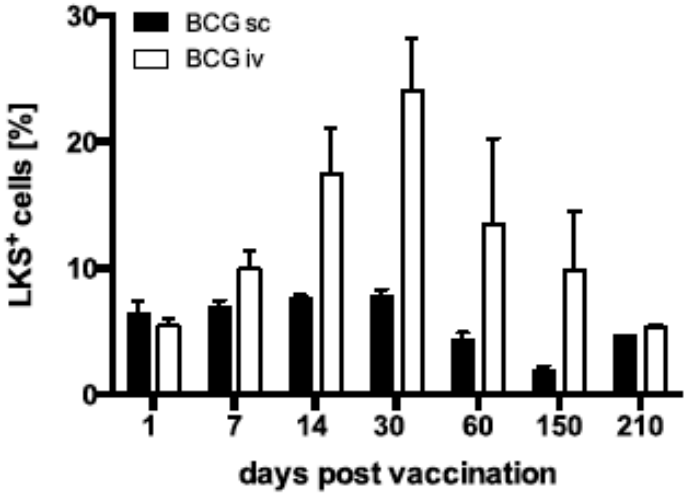
Kaufmann et al, Cell 2018

BCG-IV Vaccination Enhances Expansion of LKS+ Population in the BM









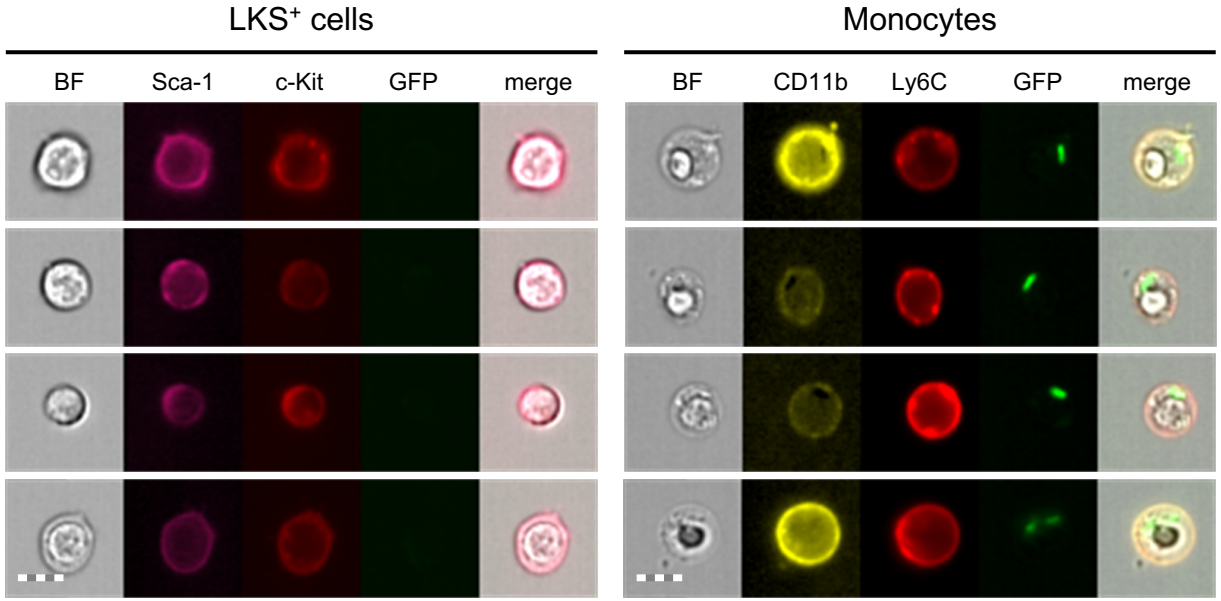
Gating Strategy: Single cells, Viable, lineage$^-$ (B220, Terr19, CD11b, CD4, CD8, CD5, Ly6c)

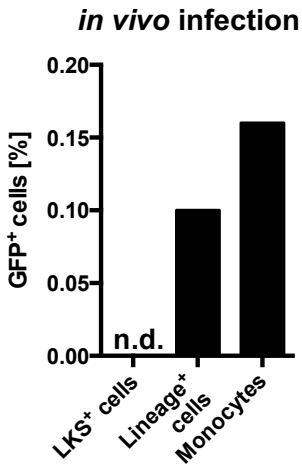
LKS: Lineage Committed Cells, **c-Kit** Proliferation, **Sca-1** Regulating Self-renewal

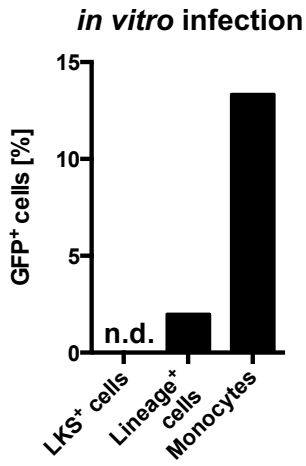
Long-term HSCs (LKS$^+$ CD150$^+$ CD48$^-$) and **Short-term HSCs** (LKS$^+$CD150$^+$CD48$^+$)

Kaufmann et al, Cell 2018

BCG does not infect LKS$^+$ cells



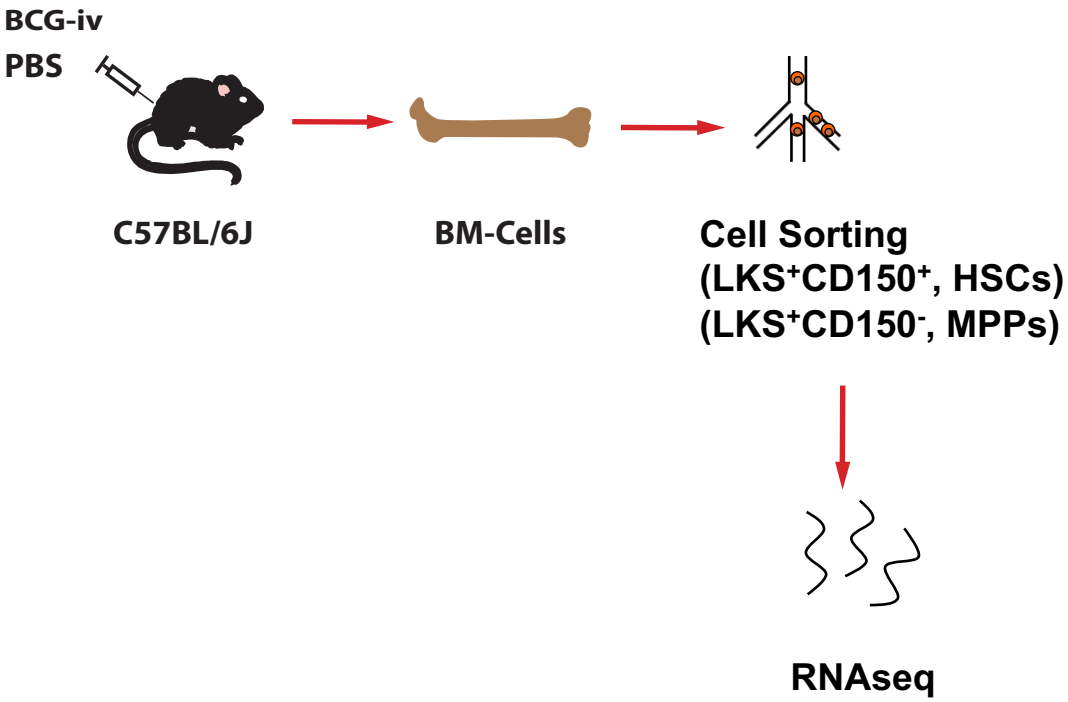


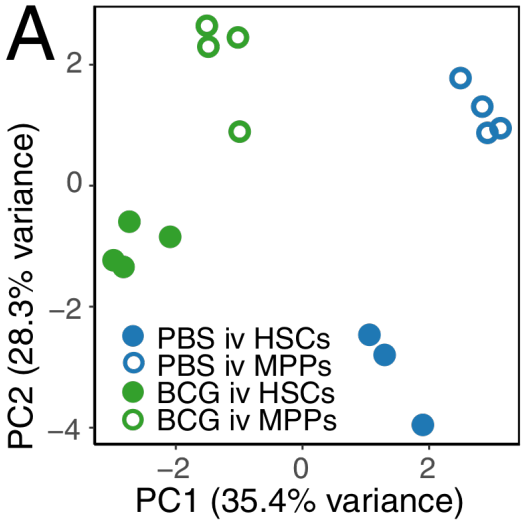


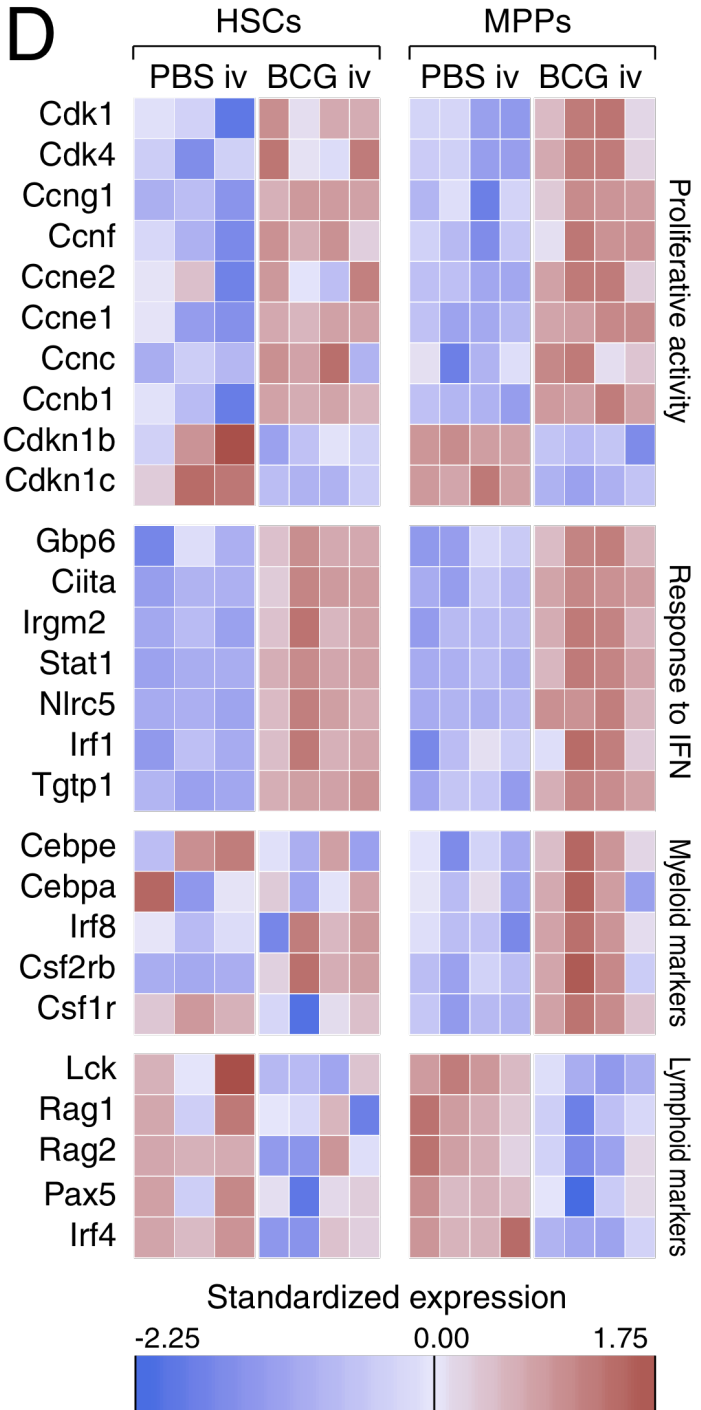
Kaufmann et al, Cell 2018

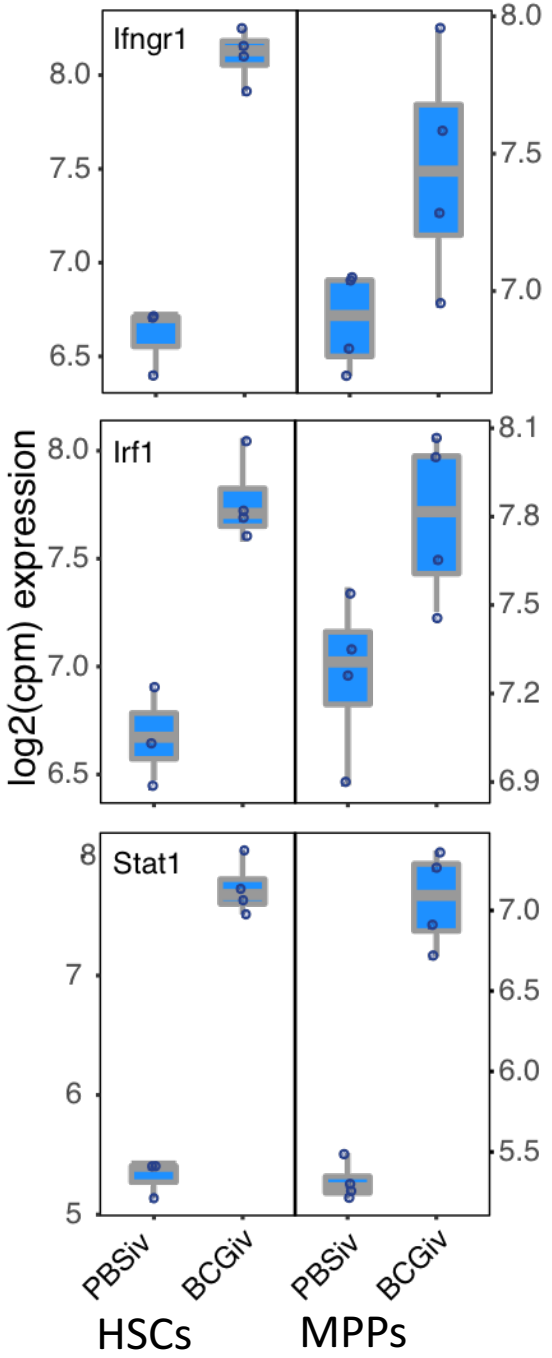
Dr. Luis Barreiro

Comparison of the transcriptome of BCG iv-educated vs. uneducated HSCs



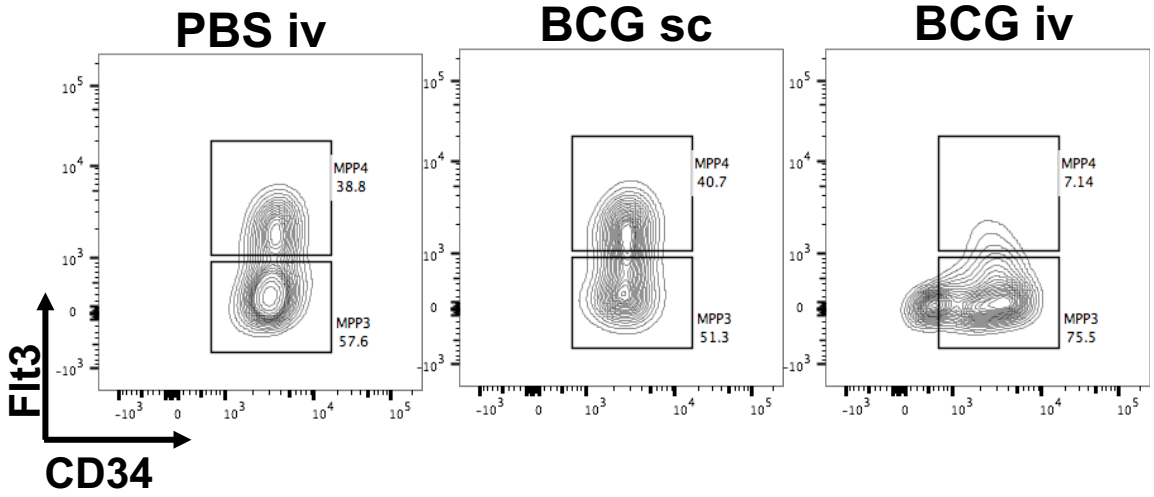


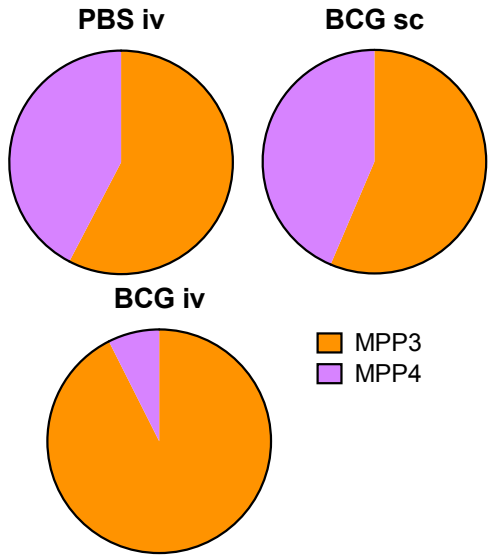


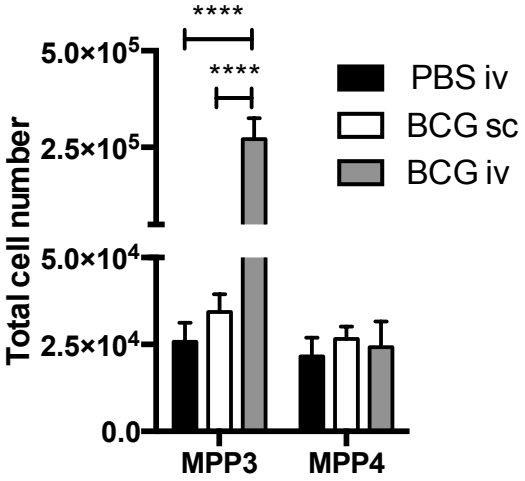


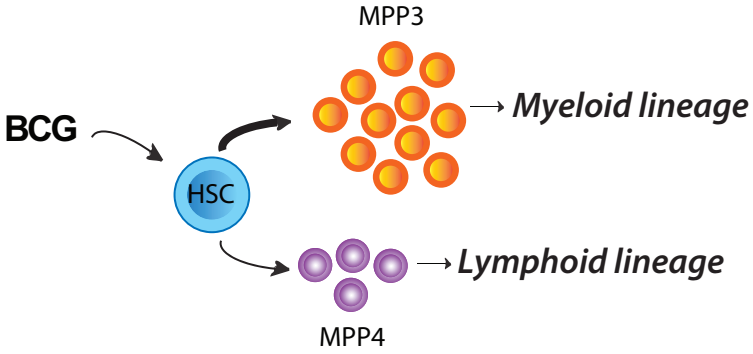
Kaufmann et al, Cell 2018

BCG-iv vaccination biases the expansion of myeloid progenitors



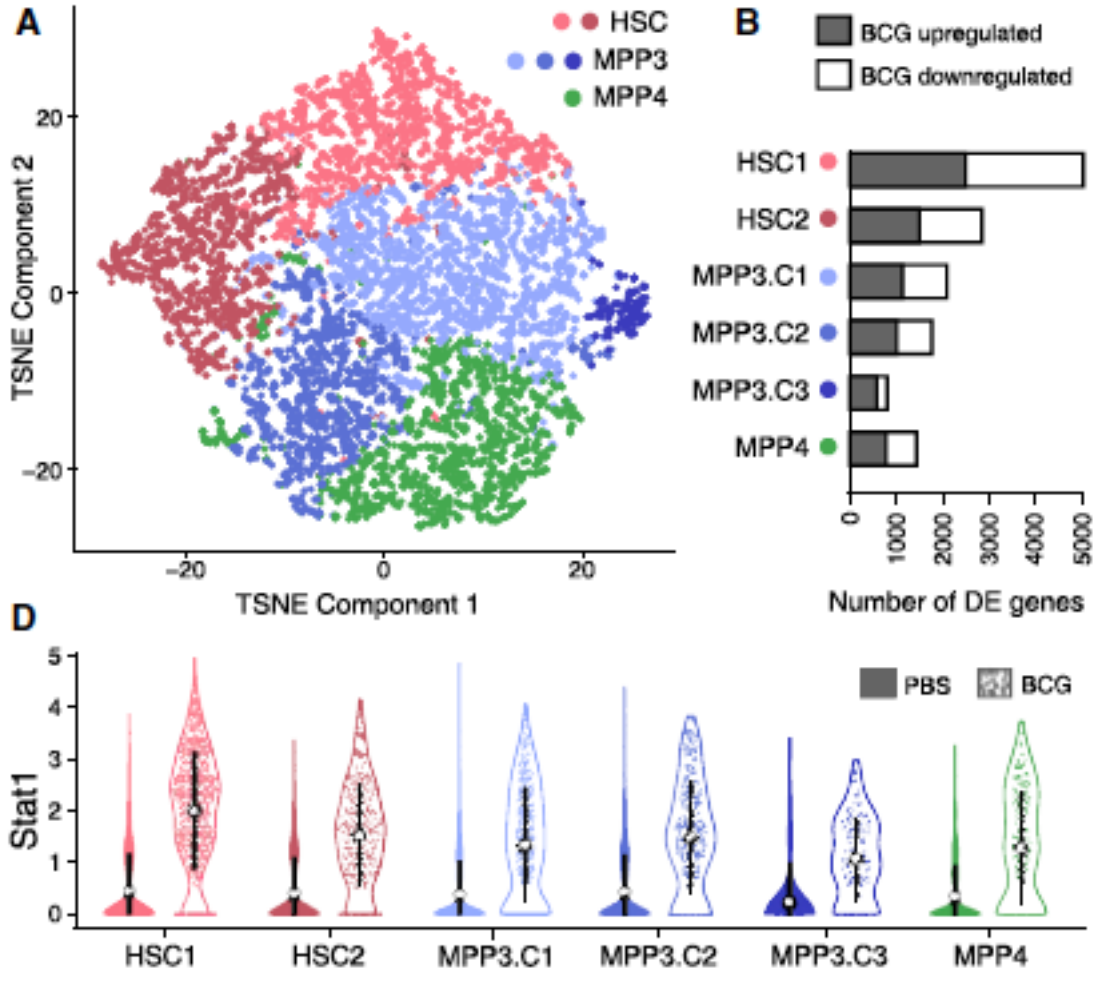


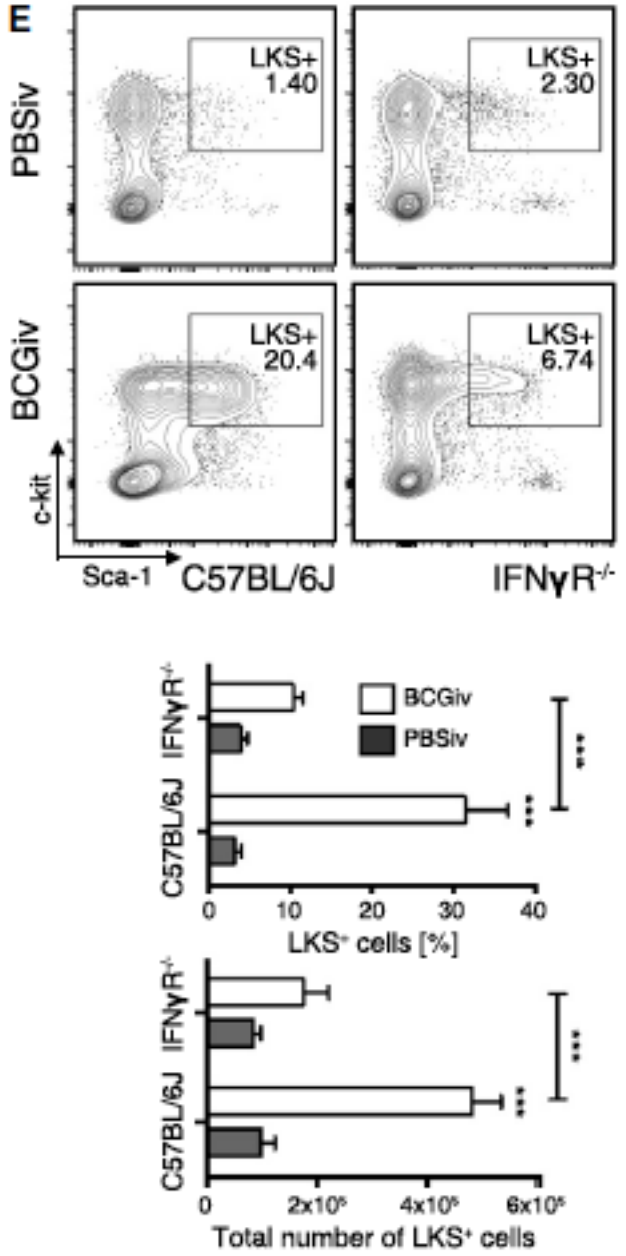




Long-term HSCs (LKS$^+$ CD150$^+$ CD48$^-$) and **Short-term HSCs** (LKS$^+$CD150$^+$CD48$^+$)
MPP (LKS$^+$CD150$^-$CD48$^-$) **MPP3** (MPP$^+$CD34$^+$Flt3$^-$) **MPP4** (MPP$^+$CD34$^+$Flt3$^+$)

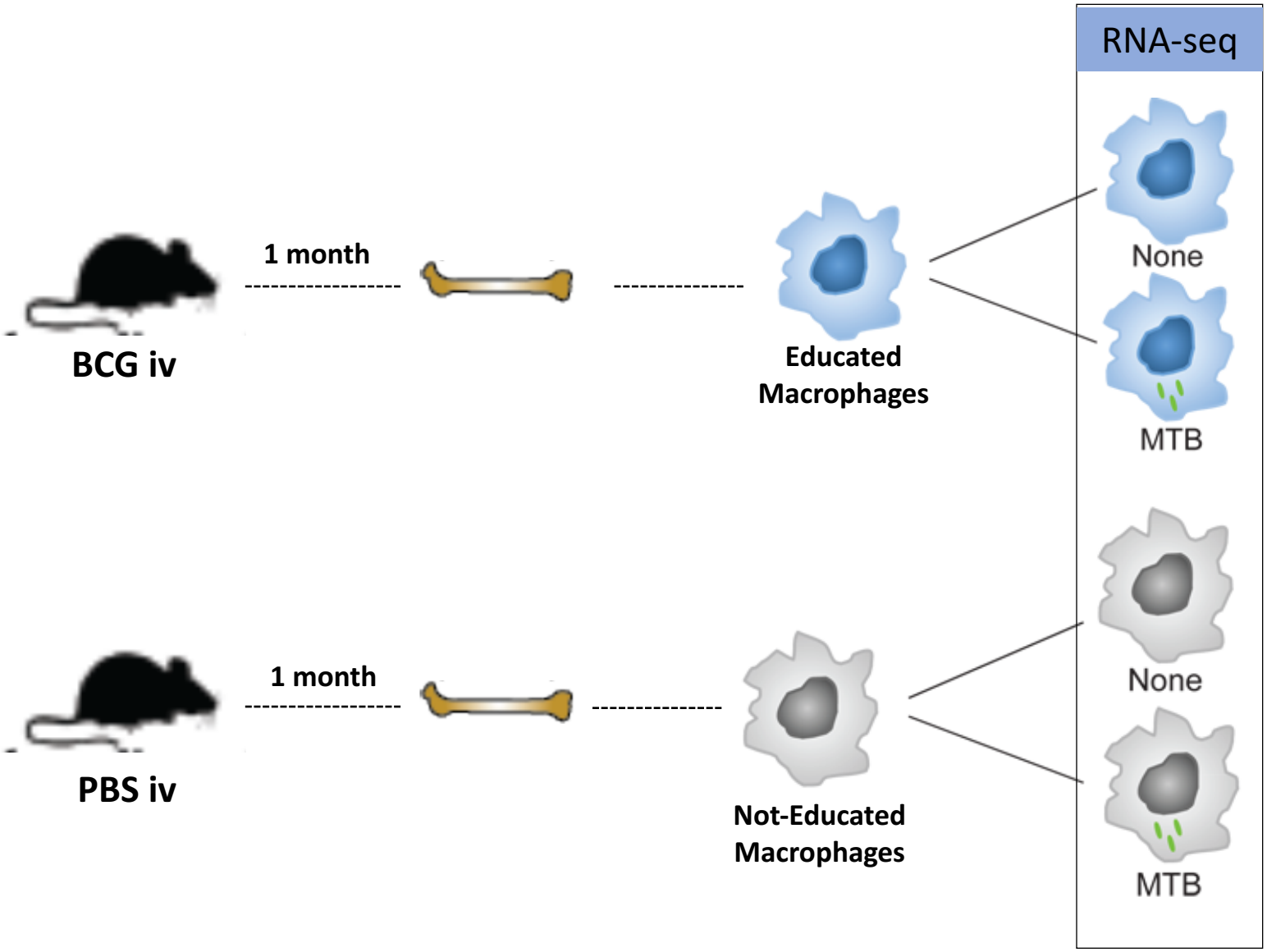
Kaufmann et al, Cell 2018



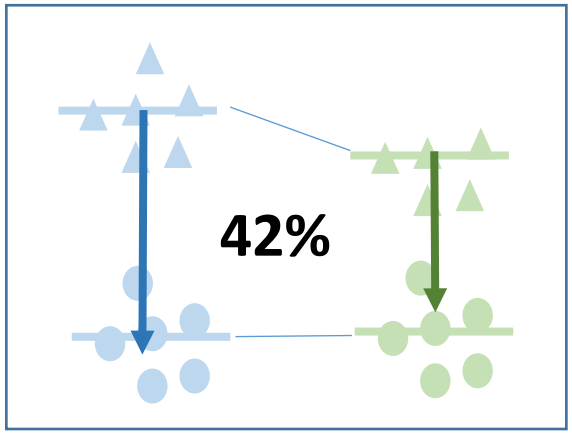


Kaufmann et al, Cell 2018

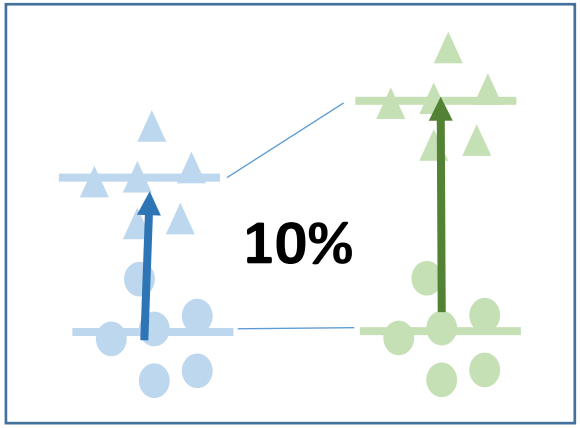
Comparison of the transcriptome of educated vs uneducated macrophages



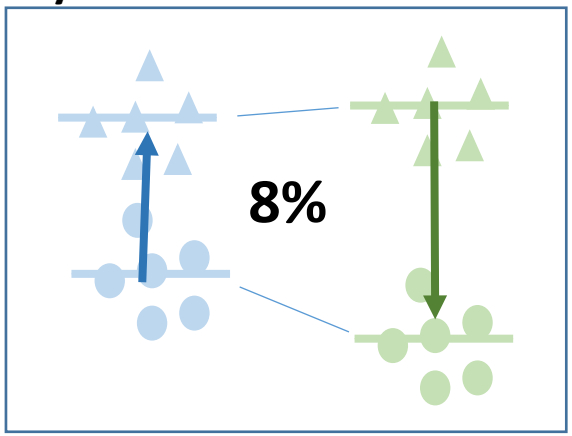
Down-regulation damped by BCG-iv



Up-regulation enhanced by BCG-iv

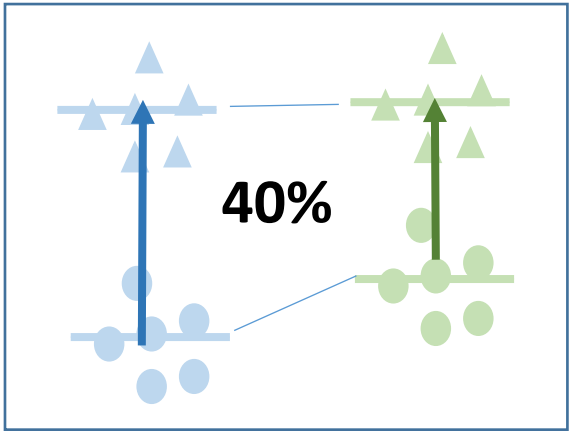


Down-regulation enhanced by BCG-iv



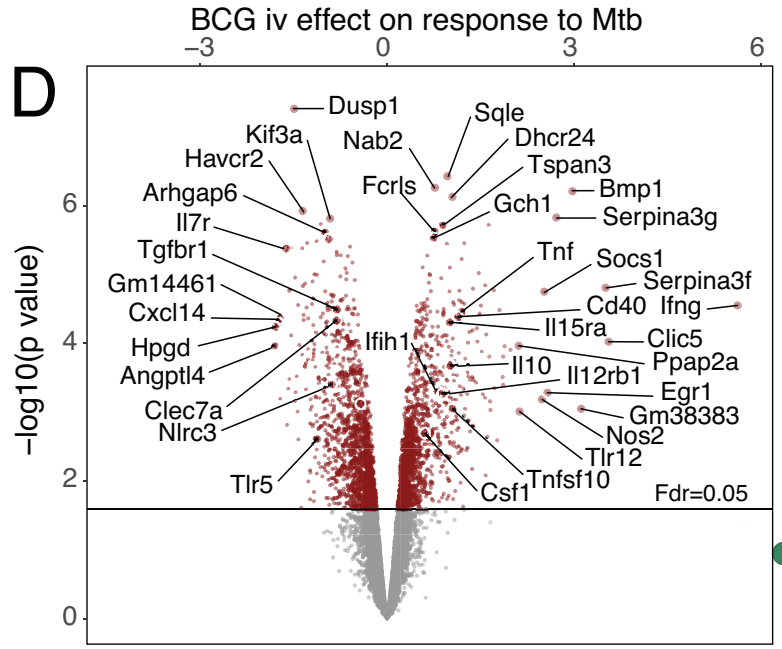
Not-Educated Educated

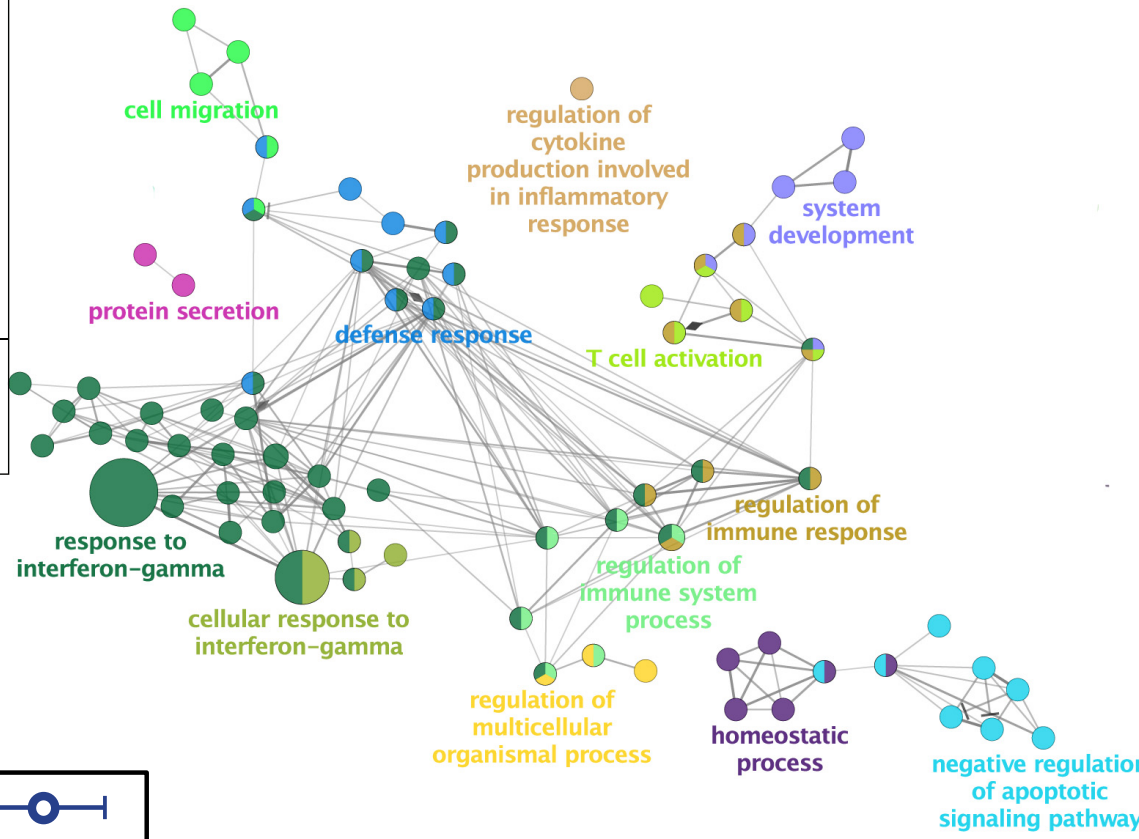
Up-regulation damped by BCG-iv

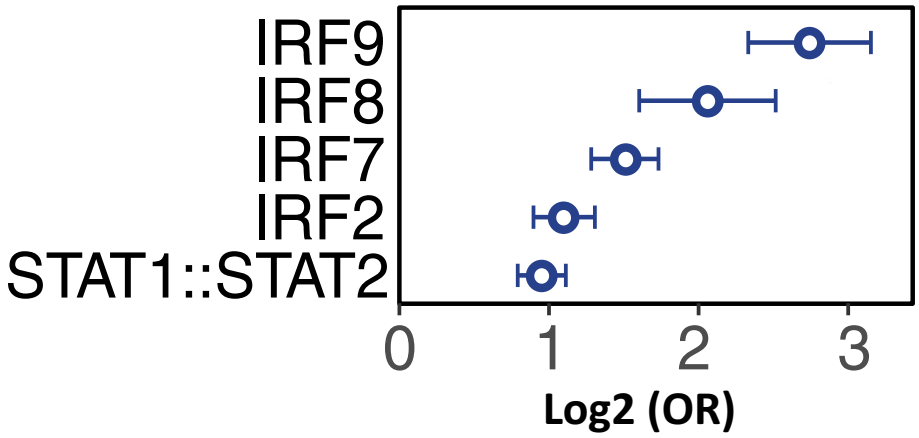


Not-Educated Educated

Kaufmann et al, Cell 2018

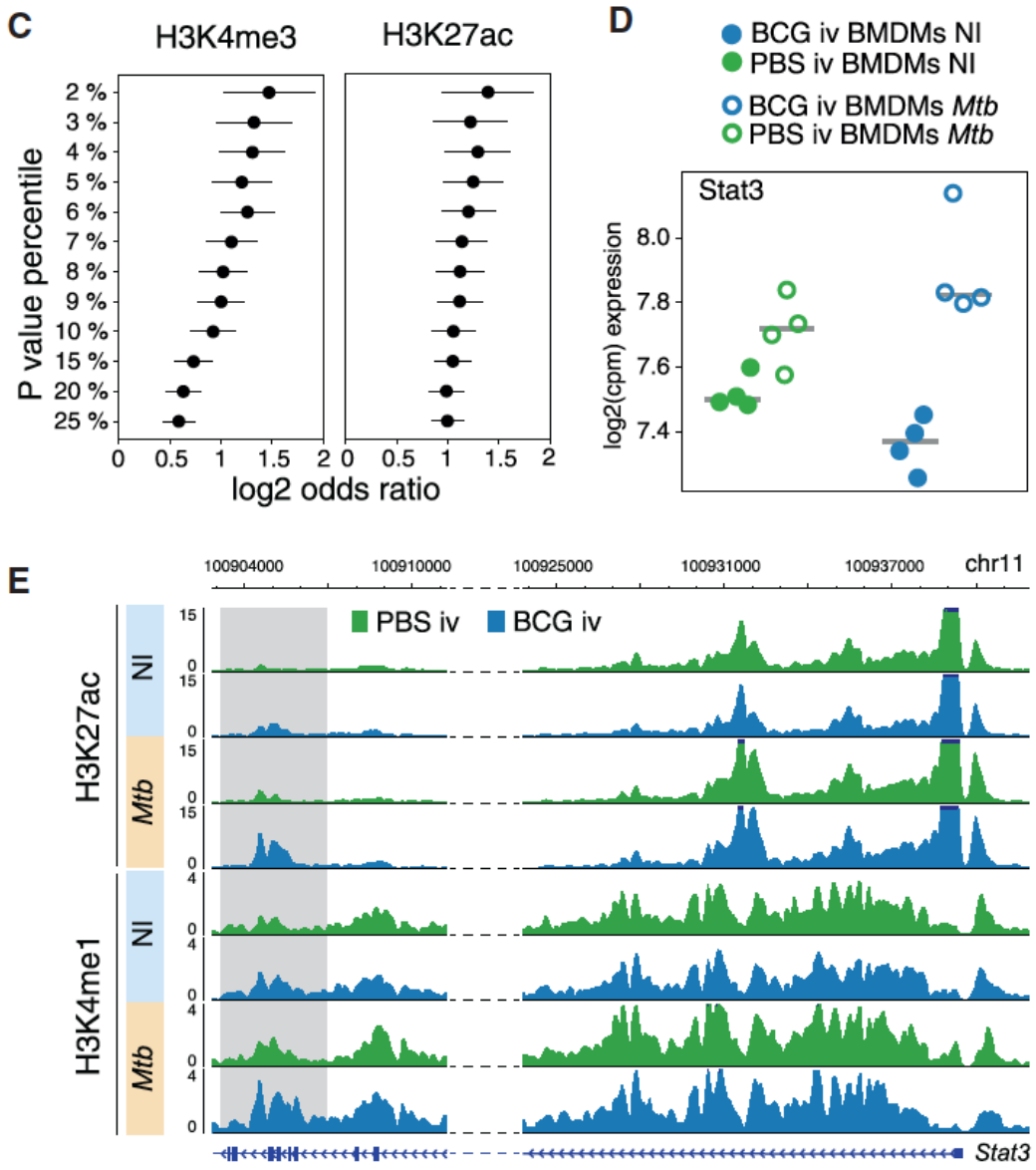






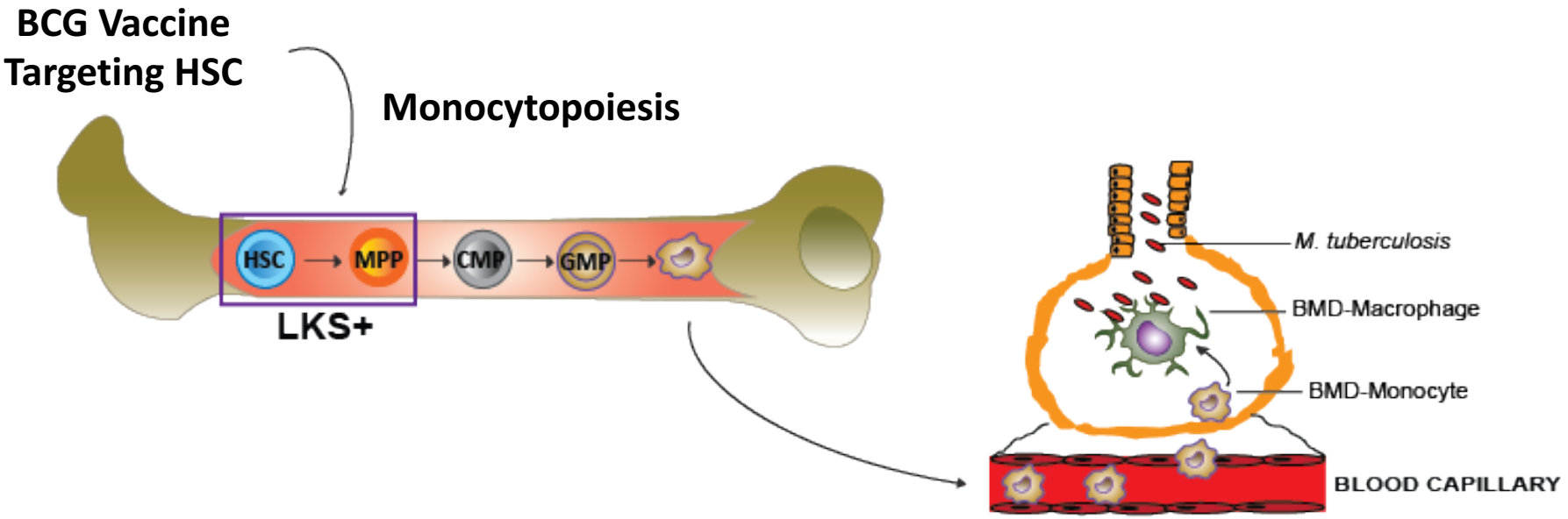
Kaufmann et al, Cell 2018

BCG-educated macrophages are epigenetically reprogrammed to respond to *Mtb*



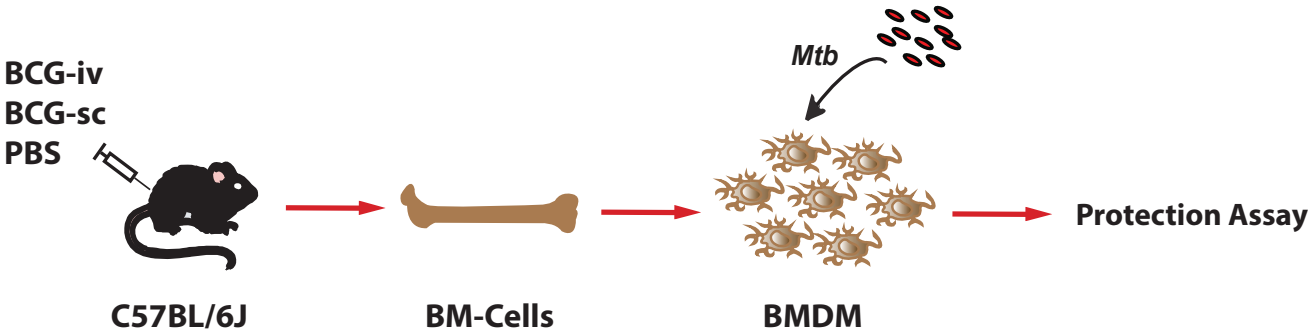
Kaufmann et al, Cell 2018

BCG-induced transcriptional changes in HSCs is transmitted to macrophages

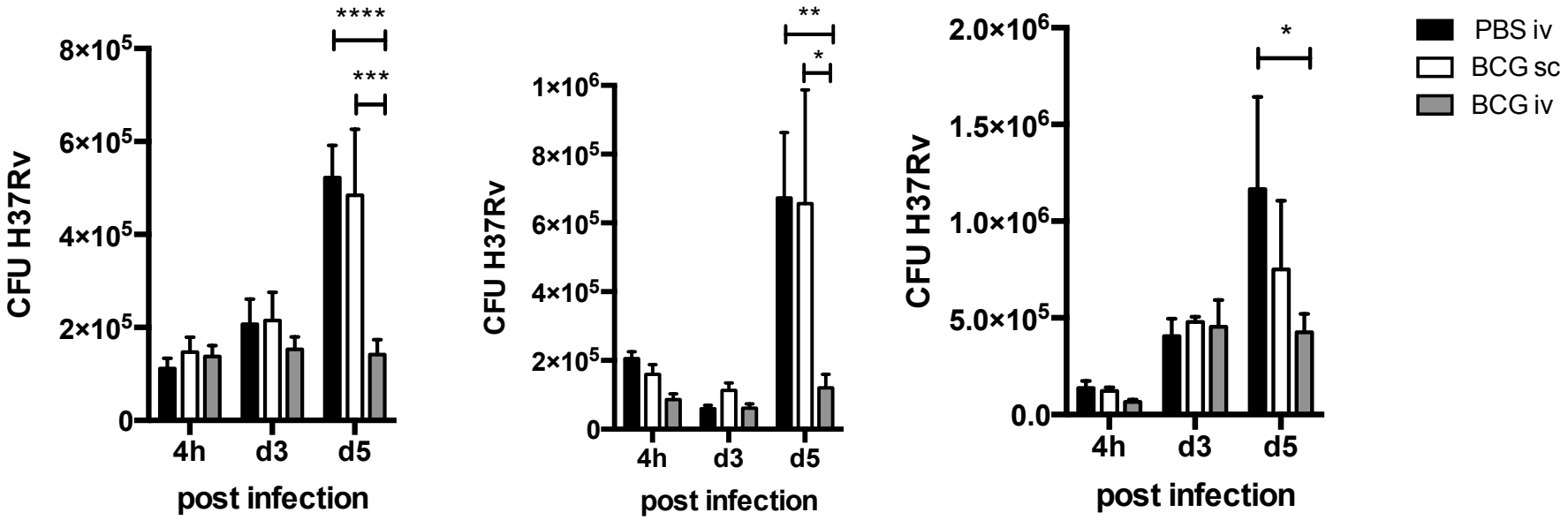


Good or Bad?

Educated BMDMs provide significant protection against *in vitro Mtb* infection

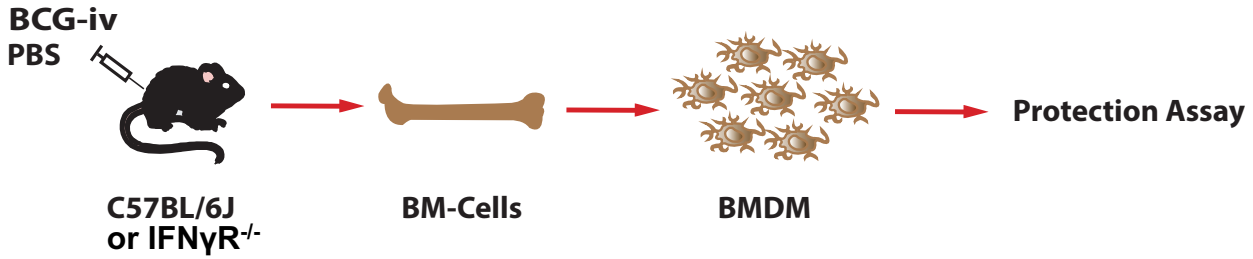


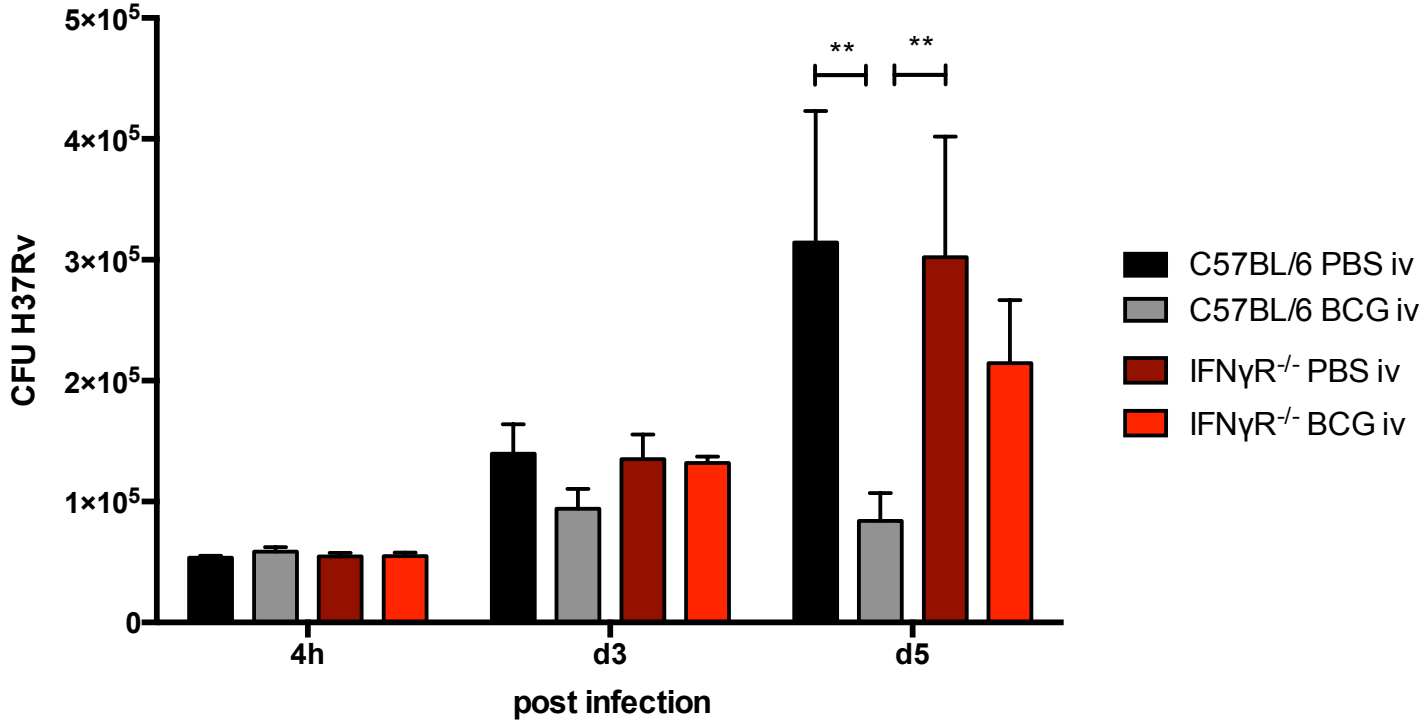
1 month post BCG vacc. **2 months post BCG vacc.** **5 months post BCG vacc.**



Kaufmann et al, Cell 2018

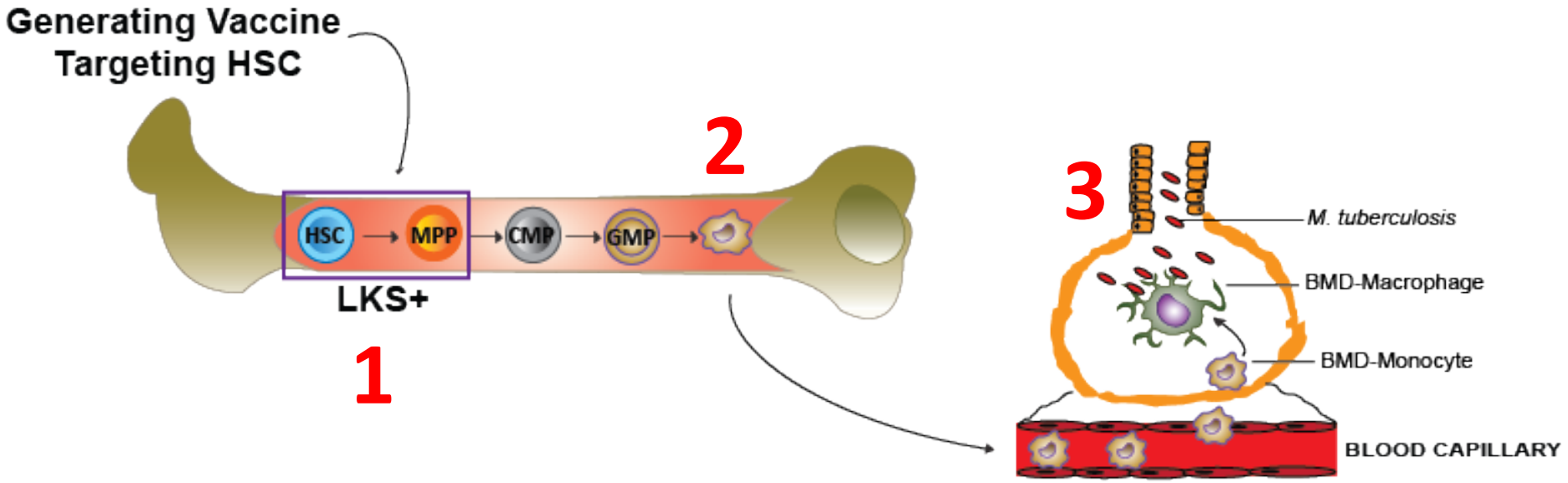
BMDMs form BCG iv-vaccinated IFNγR$^{-/-}$ mice are not protected against *Mtb* infection *in vitro*



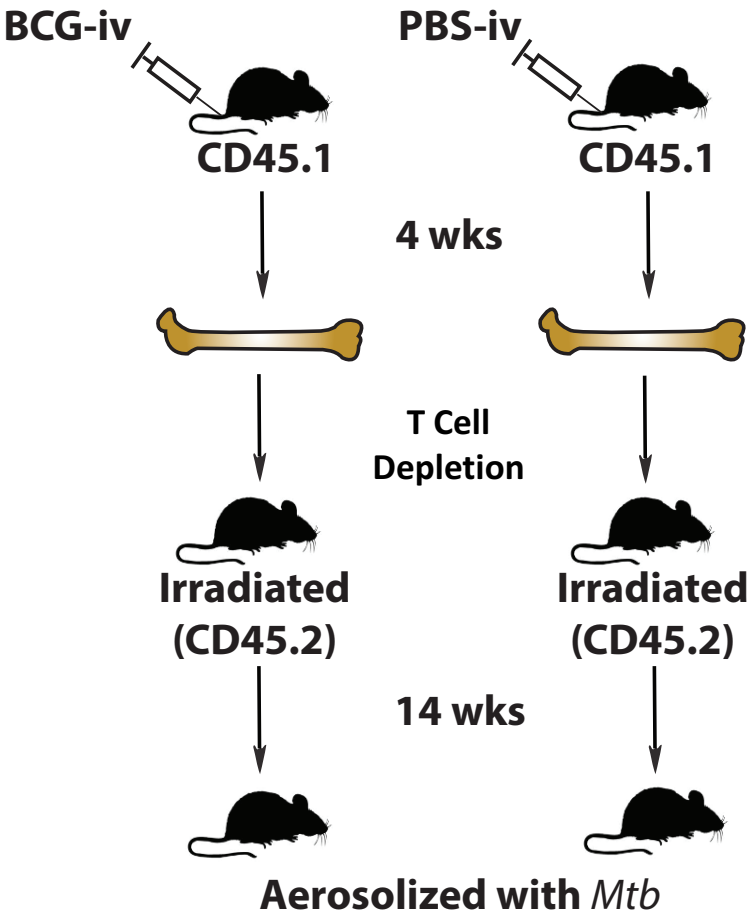


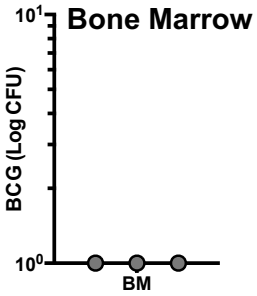
Kaufmann et al, Unpublished data

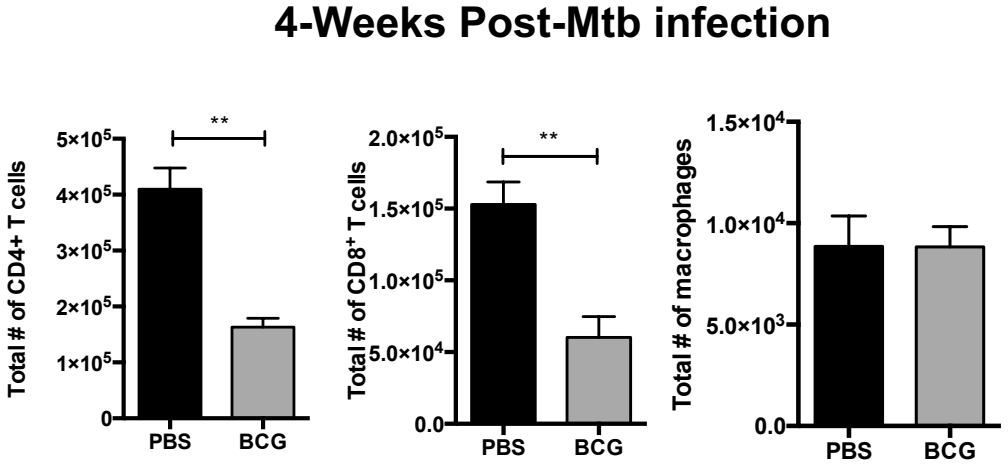
Does the BCG-iv reprogramming of HSCs generate protective monocytes/macrophages that are sustainable *in vivo*?



(1) Chimeric Model

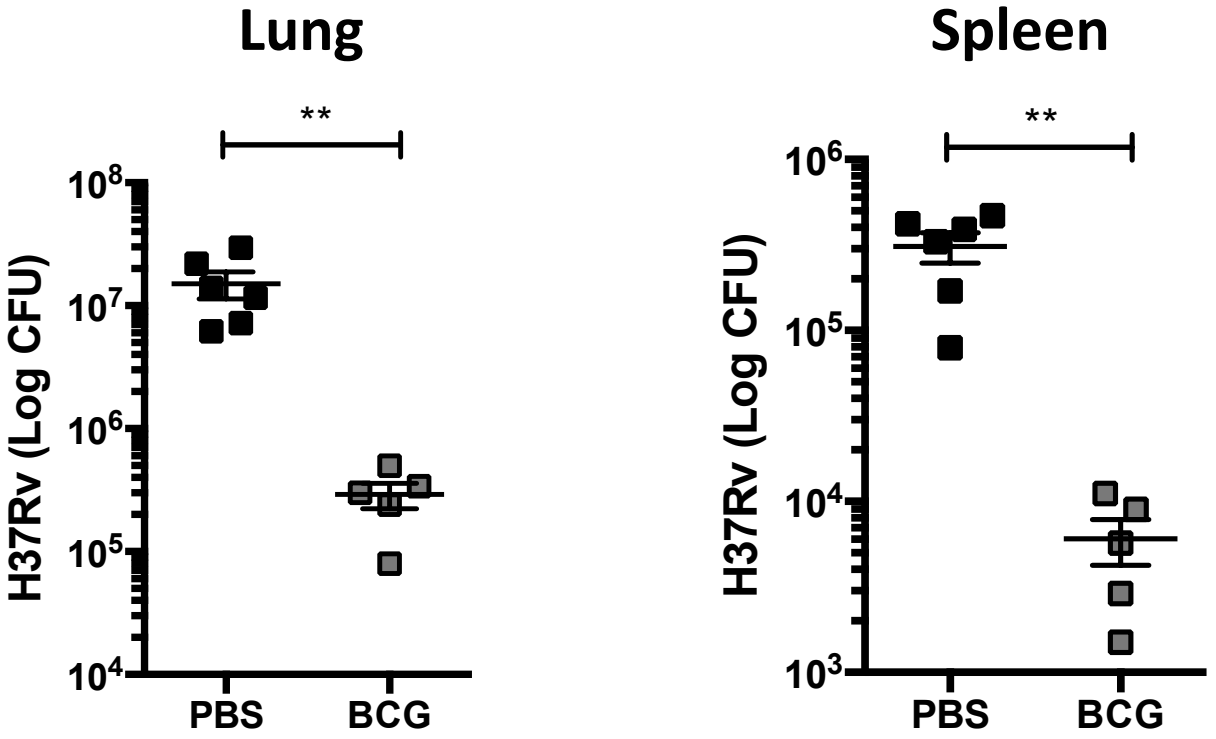




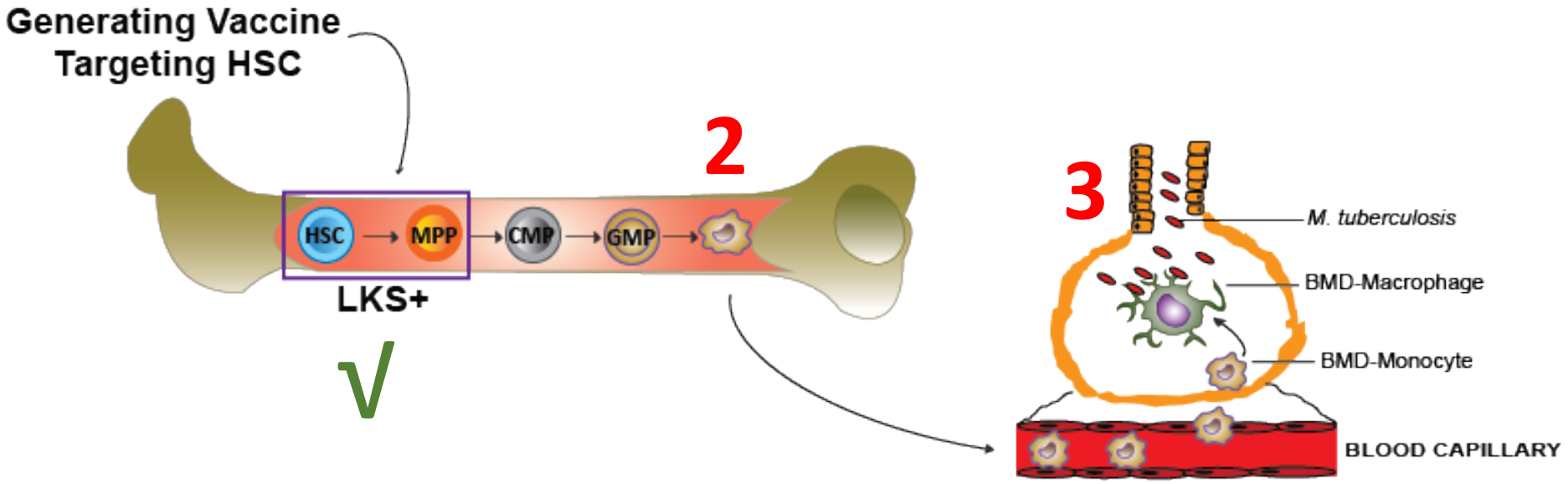


Kaufmann et al, Cell 2018

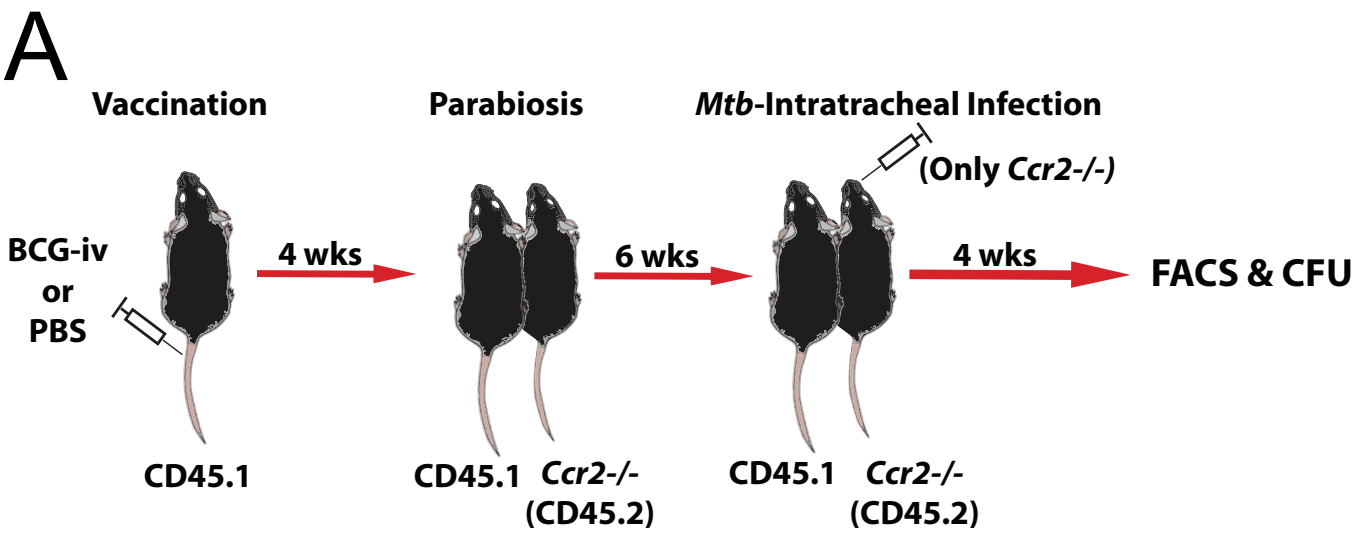
The protective capacities of the HSCs are sustainable *in vivo*



Kaufmann et al, Cell 2018

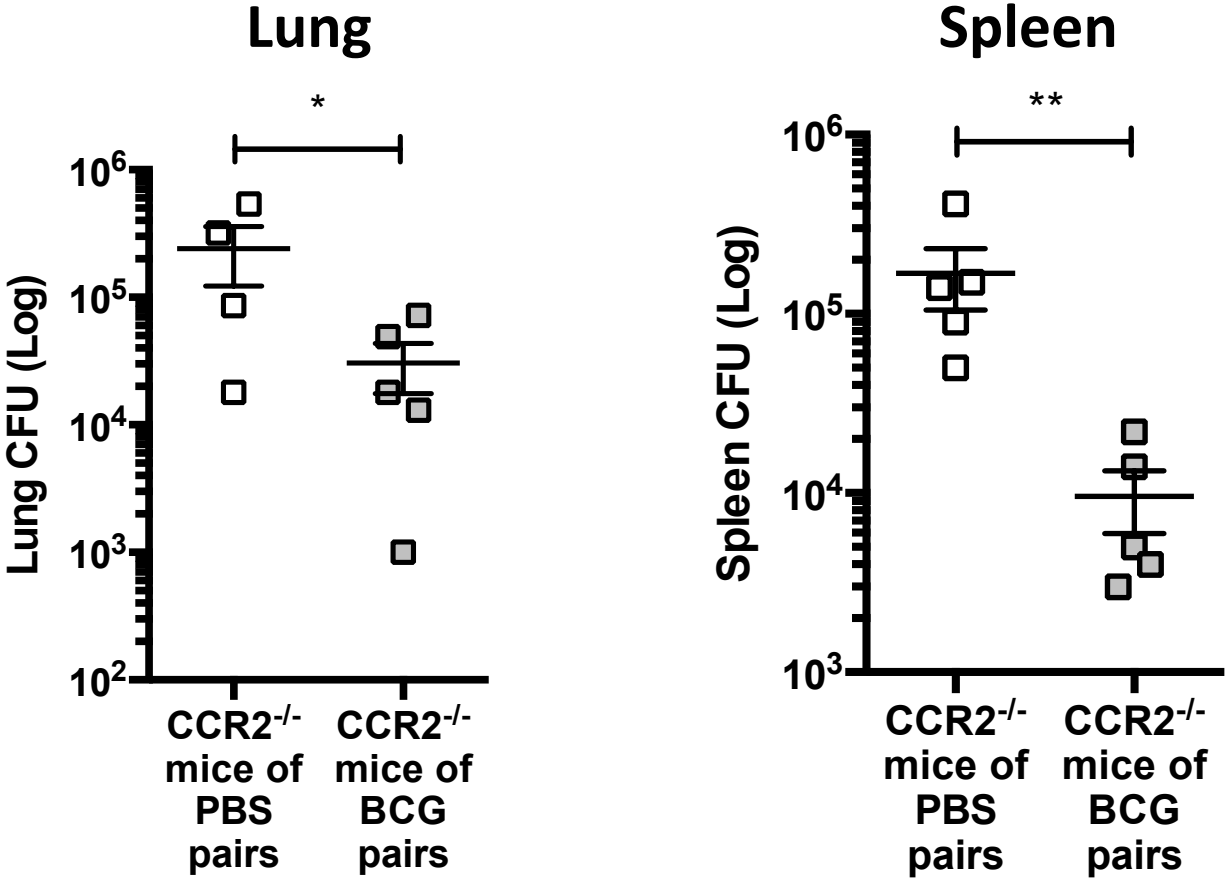

Generating Vaccine
Targeting HSC
HSC
MPP
CMP
GMP
LKS+
√
2
3
M. tuberculosis
BMD-Macrophage
BMD-Monocyte
BLOOD CAPILLARY

(2) Parabiosis Model



Kaufmann et al, Cell 2018

Recruitment of the BCG-educated monocytes provides significant protection against *Mtb* infection



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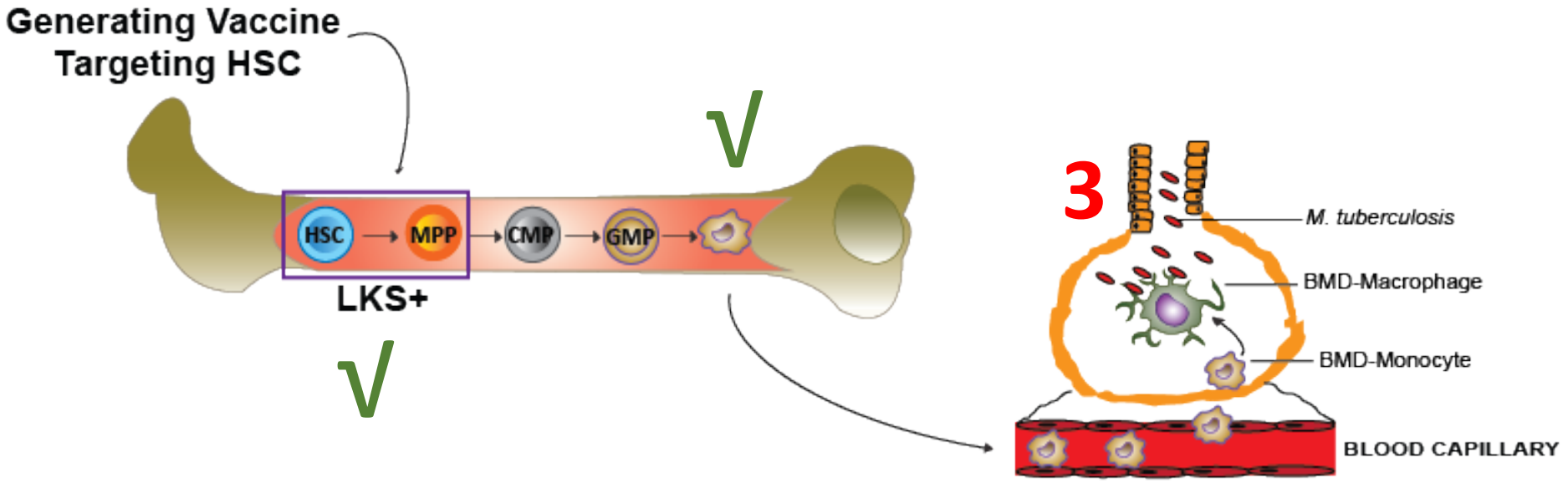
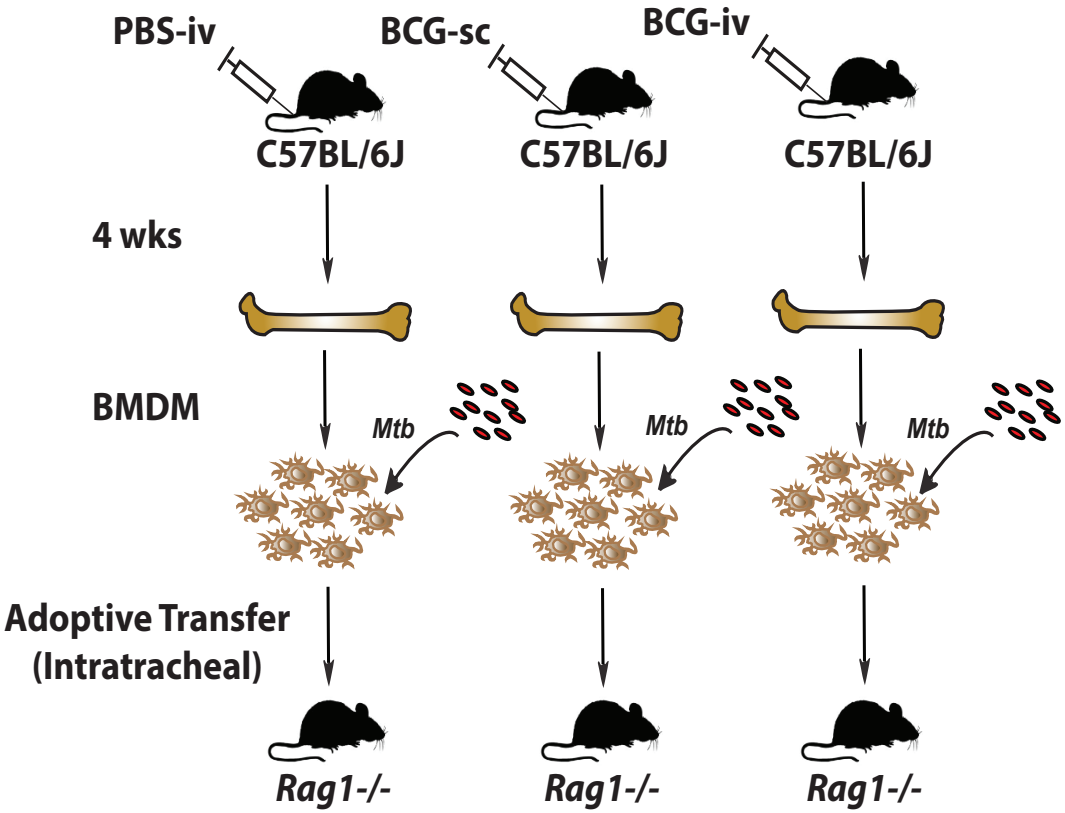
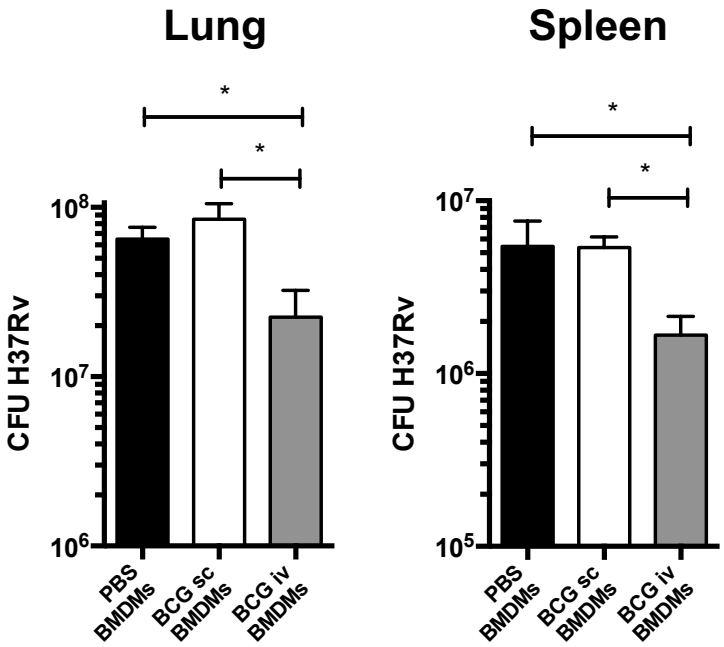

Generating Vaccine
Targeting HSC
HSC
MPP
CMP
GMP
LKS+
√
√
3
M. tuberculosis
BMD-Macrophage
BMD-Monocyte
BLOOD CAPILLARY

(3) Adoptive Transfer Model





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