SEQUENCE OF IMMUNE RESPONSE IN NON-CEREBRAL AND CEREBRAL EXPERIMENTAL MALARIA

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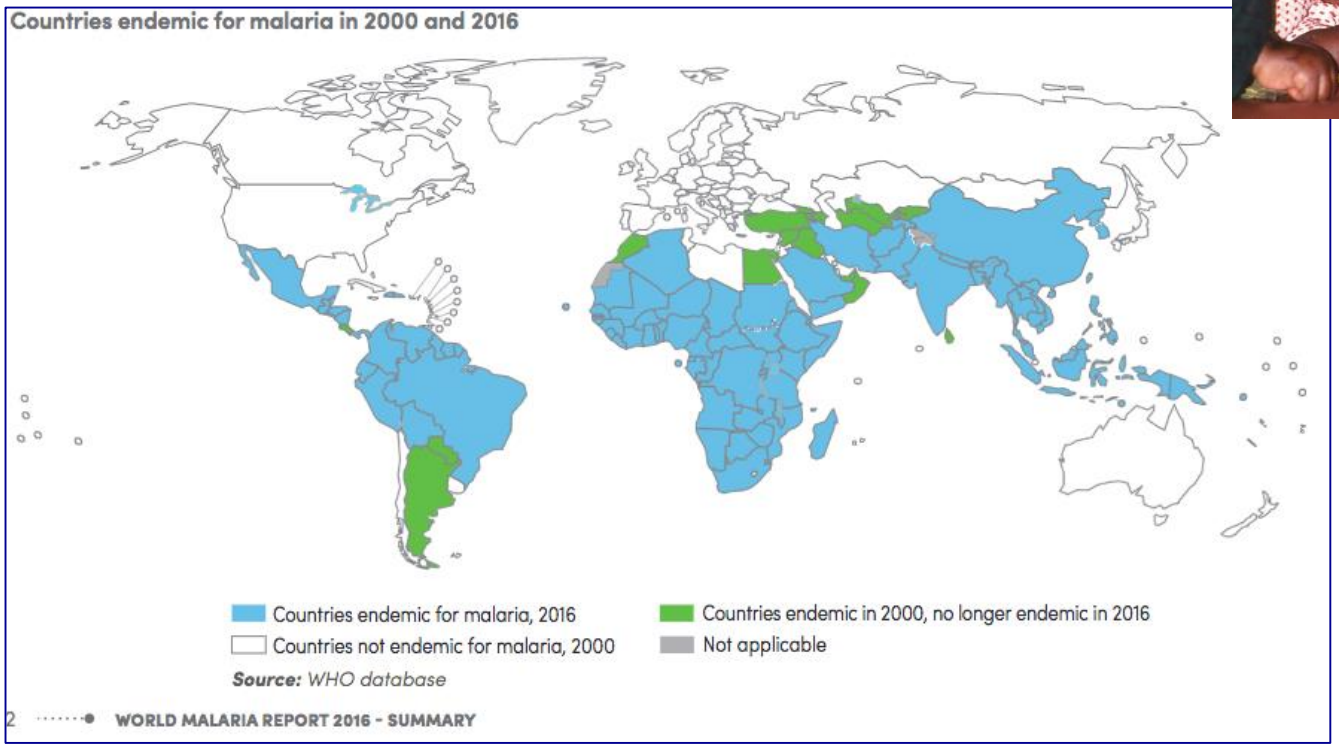
CHARACTERIZATION OF THE PROBLEM – **CEREBRAL MALARIA**

CEREBRAL MALARIA

ANEMIA



- 207 millions cases, resulting in 584,000-1,238,000 deaths, annually.

INSIGHTS INTO THE IMMUNOPHATHOGENESIS OF MALARIA USING MOUSE MODELS

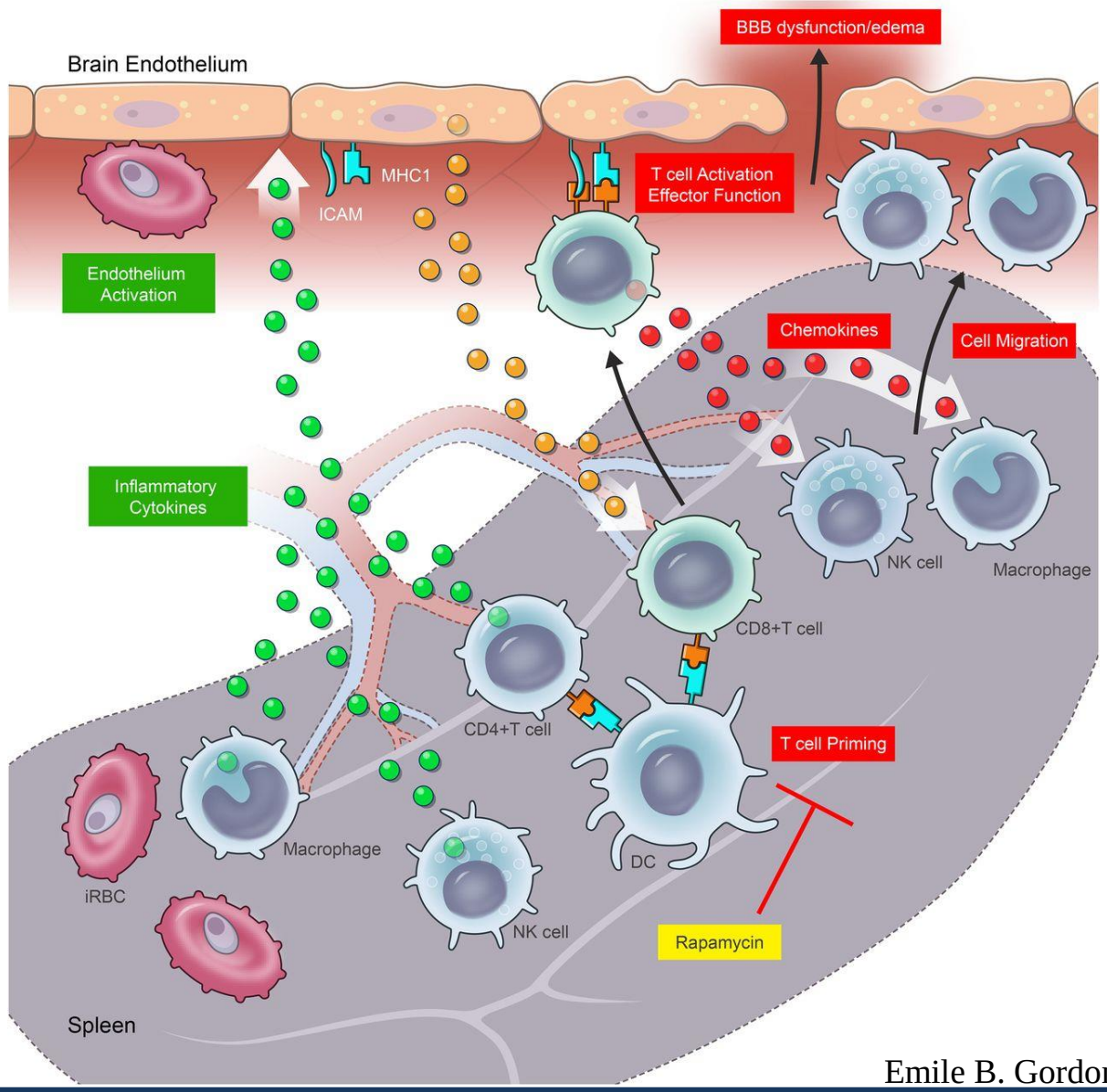
Table 1. Mouse models of malaria

Species; subspecies; clone	Organs of sequestration	RBC invasion preference	Mouse strain susceptibility to anaemia	Mouse strain susceptibility to CM
berghei ANKA	Brain, lungs and adipose tissue (Ref. 79)	Reticulocytes	C57BL/6: lethal CD-1: lethal C57BL/6J: non-lethal (Refs 159, 160)	C57BL/6: susceptible CBA: susceptible BALB/c: resistant (Ref. 3)
yoelii yoelii 17X	Brain (Ref. 26)	Reticulocytes and mature RBCs	BALB/c: non-lethal (Ref. 160)	Most strains resistant
yoelii yoelii 17XL		Reticulocytes and mature RBCs	BALB/c: lethal C57BL/6: lethal (Ref. 119)	Most strains susceptible
chabaudi chabaudi AS	Liver and brain (Refs 97, 101)	Mature RBCs	A/J: lethal C57BL/6: non-lethal (Ref. 121)	C57BL/6 IL-10 KO: susceptible (Ref. 161)
chabaudi chabaudi AJ	Liver (Ref. 98)	Mature RBCs	BALB/c: non-lethal (Ref. 121)	
chabaudi adami DS		Mature RBCs	C3H: lethal C57BL/6: non-lethal (Ref. 128)	
chabaudi adami DK		Mature RBCs	BALB/c: non-lethal C3H: non-lethal (Ref. 128)	
vinckei vinckei		Mature RBCs	BALB/c: lethal (Ref. 120)	

Abbreviations: IL, interleukin; KO, knockout; RBC, red blood cell.

Lamb T., et al. *Expert Reviews in Mol. Medicine*, 2006

STRONG ACTIVATION OF CD8$^+$ AND CD4$^+$ T CELLS IN SPLEEN DURING EXPERIMENTAL CEREBRAL MALARIA



Emile B. Gordon et al. *mBio*, 2015

WHAT DETERMINE IF THE HOST IMMUNE RESPONSE WILL EITHER DRIVE OR PREVENT THE DEVELOPMENT OF CEREBRAL MALARIA?

AIM

- Investigate the balance of the immune response between hosts with different genetic background (susceptible and resistant) following infection with *Plasmodium berghei*-ANKA.

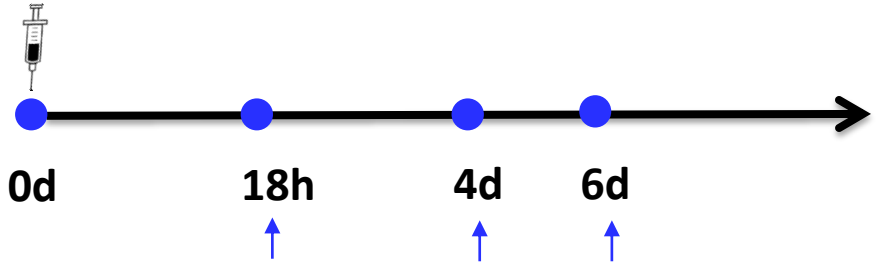
EXPERIMENTAL MODEL OF CEREBRAL AND NON-CEREBRAL MALARIA

CM-Susceptible
C57BL/6

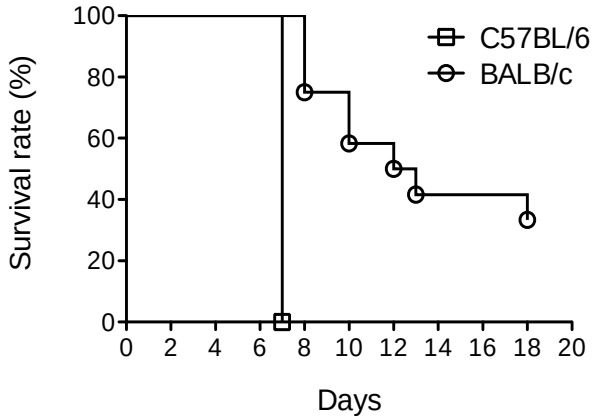
CM-Resistant
BALB/c

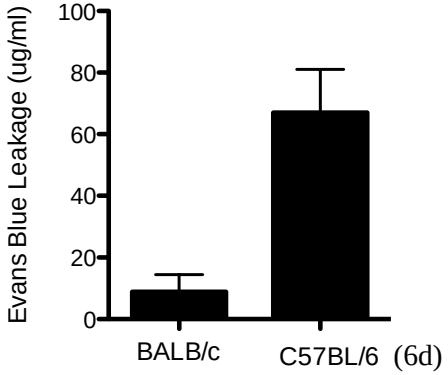
Experimental Design

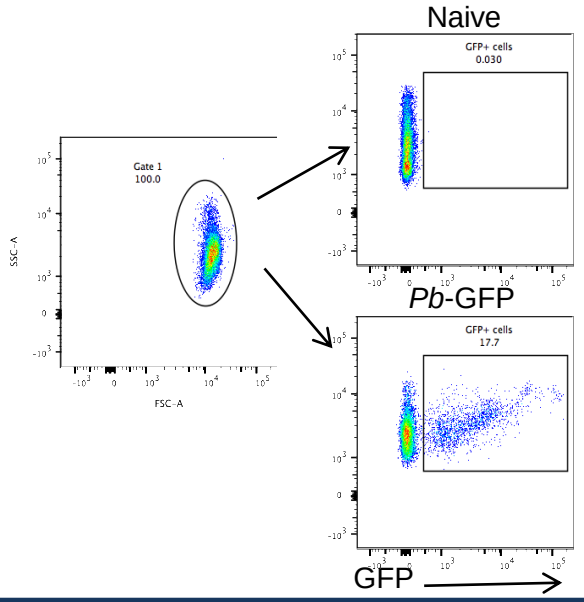
1x10^6 *P. berghei* ANKA-GFP+ erythrocytes/i.p.

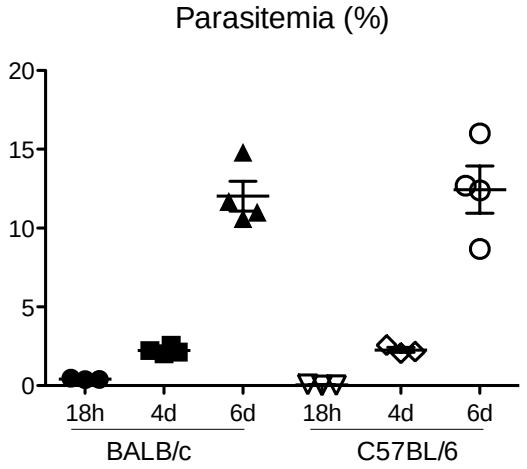


PARASITEMIA, SURVIVAL AND CEREBRAL VASCULAR LEAKAGE DURING INFECTION WITH *P. berghei* ANKA





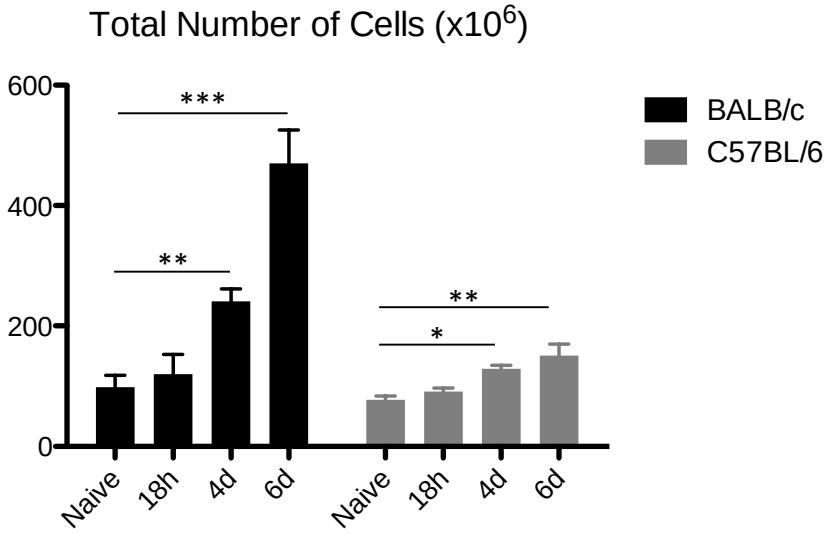




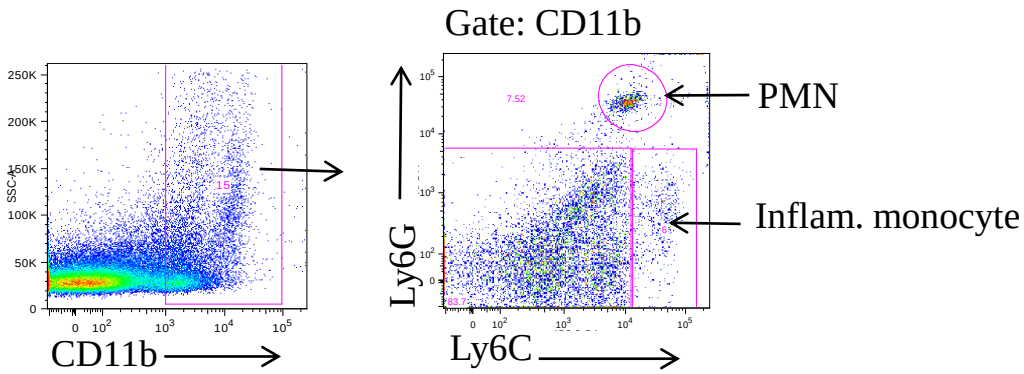
SPLENIC CELLULARITY OF *P. berghei* ANKA-INFECTED BALB/c AND C57BL/6

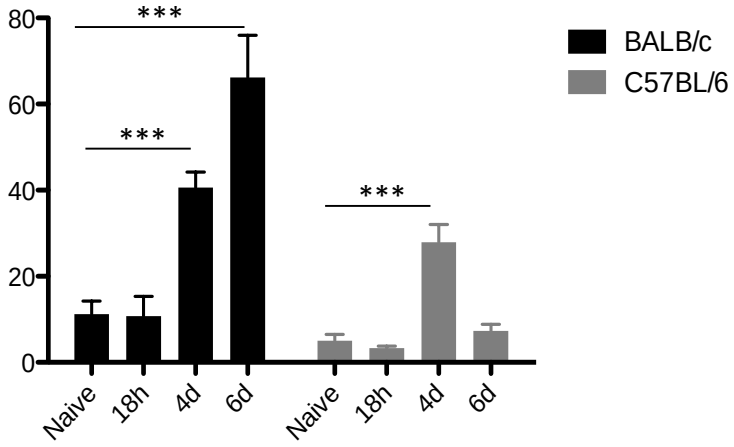
CM-Resistant
BALB/c

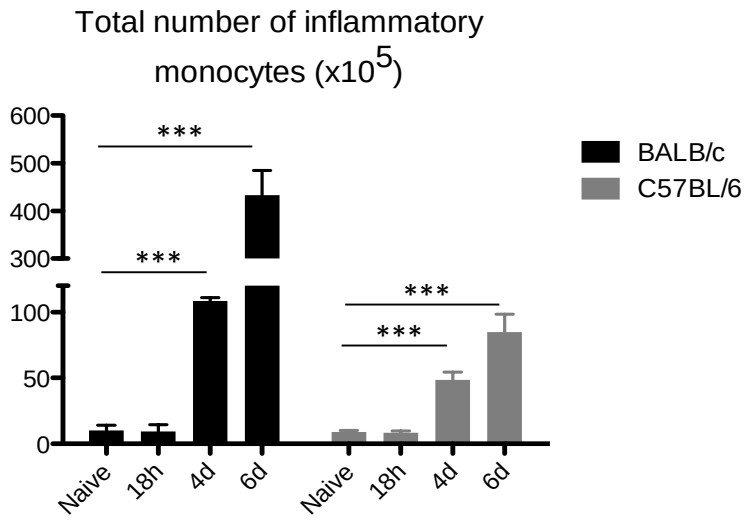
CM-Susceptible
C57BL/6



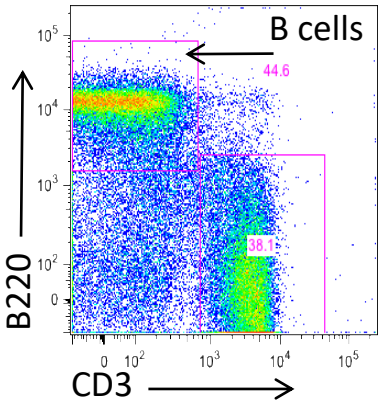
CHANGES IN MYELOID CELL POPULATIONS FOLLOWING *P. berghei* ANKA INFECTION

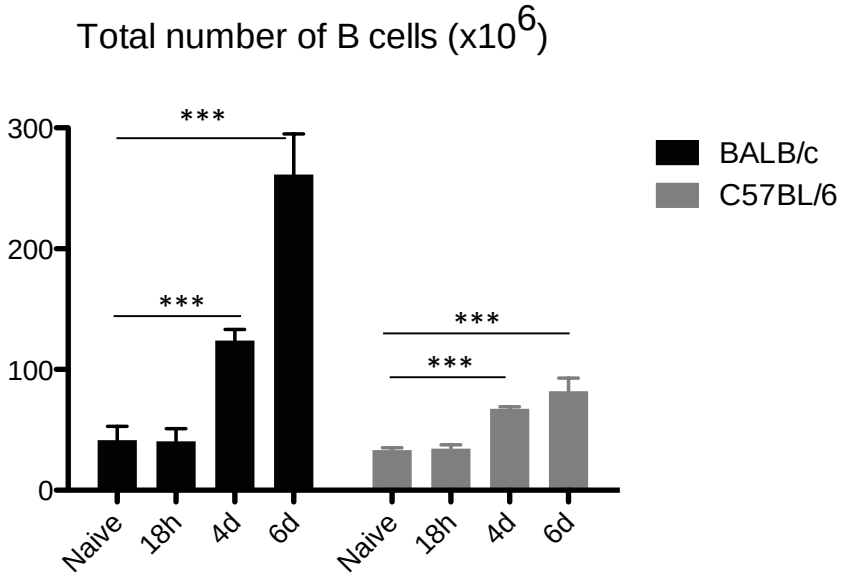




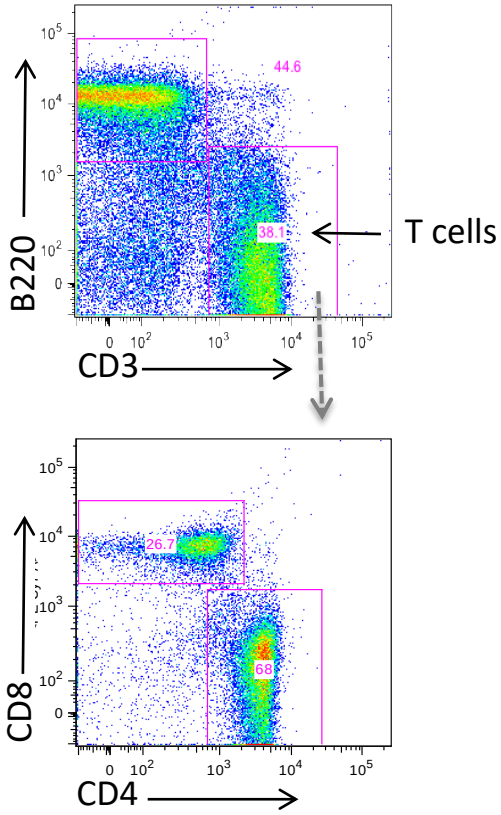


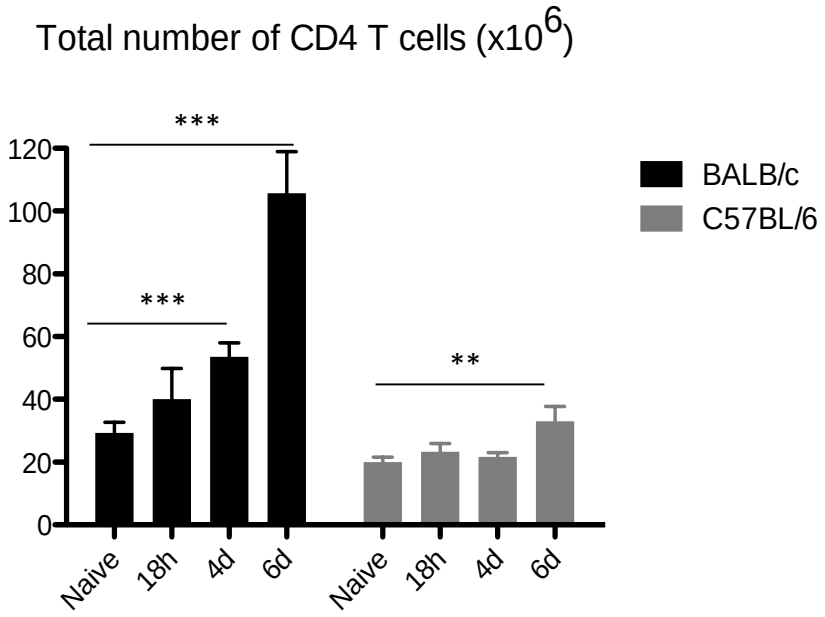
EXPANSION OF SPLENIC B CELL DURING *P. berghei* ANKA INFECTION



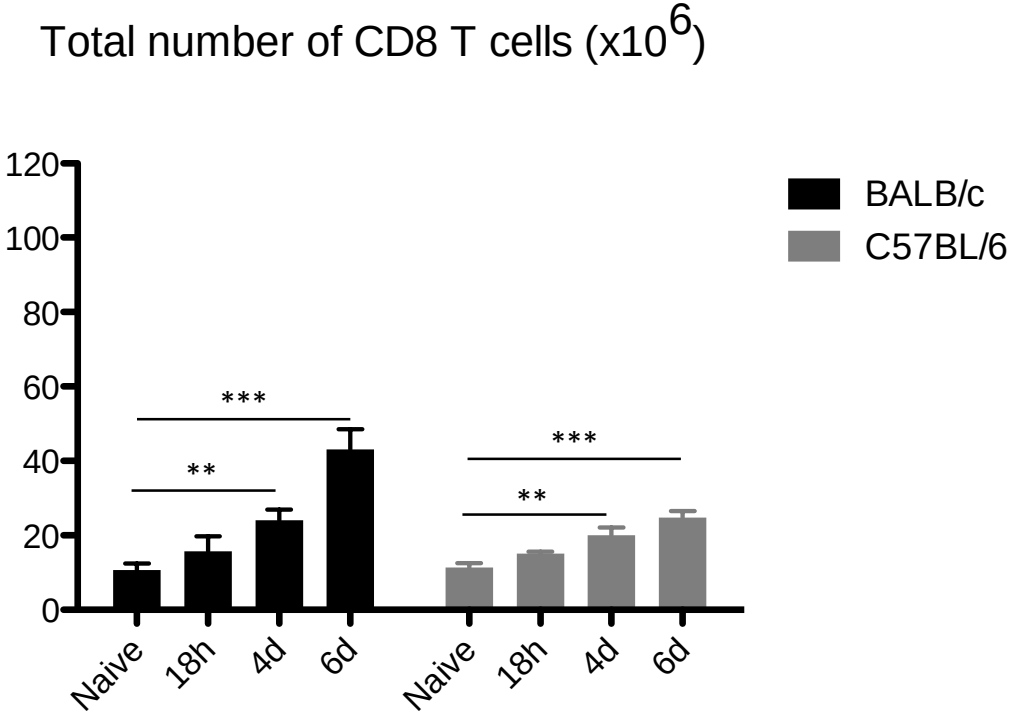


P. berghei ANKA INFECTION LEADS TO AN INCREASE IN THE NUMBER OF SPLENIC CD4$^+$ T CELLS

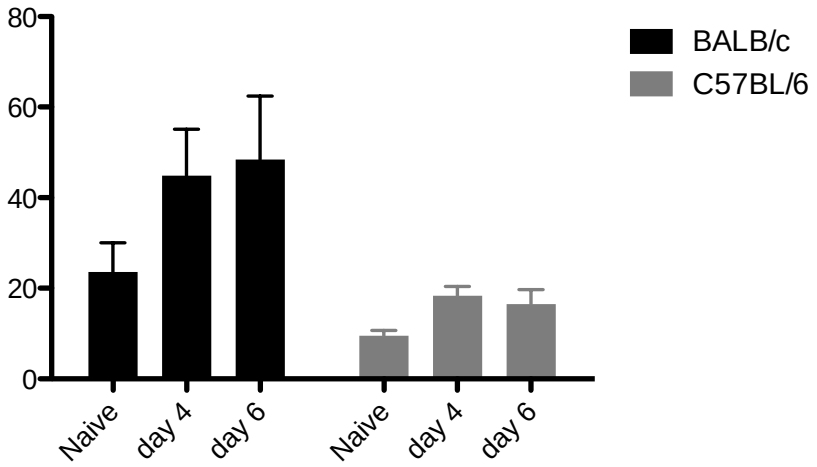


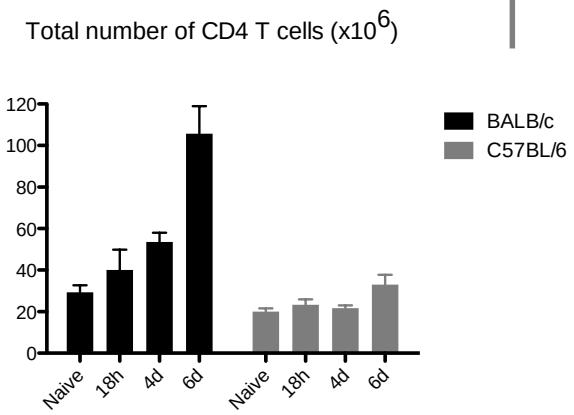


NUMBER OF SPLENIC CD8$^+$ T CELLS FOLLOWING INFECTION WITH *P. berghei* ANKA



NUMBER OF SPLENIC CD4^{+} FOXP3^{+} REGULATORY T CELLS FOLLOWING INFECTION WITH *P. berghei* ANKA





ROLE OF CD4$^+$ FOXP3$^+$ REGULATORY T CELLS FOLLOWING INFECTION WITH *P. berghei* ANKA

Limited Role of CD4$^+$Foxp3$^+$ Regulatory T Cells in the Control of Experimental Cerebral Malaria

Christiane Steeg, Guido Adler, Tim Sparwasser, Bernhard Fleischer and Thomas Jacobs

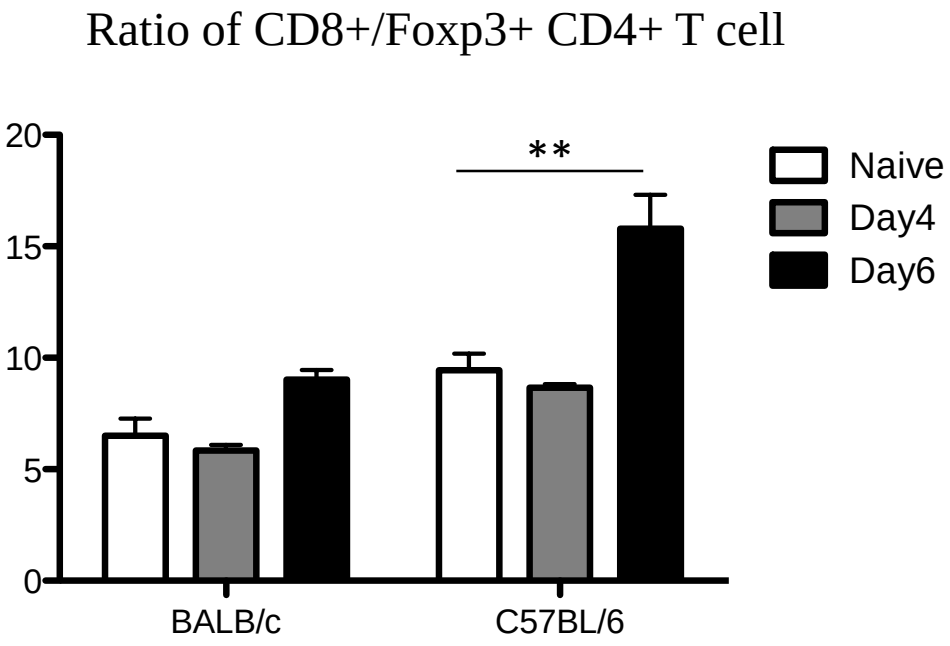
J Immunol December 1, 2009, 183 (11) 7014-7022; DOI: https://doi.org/10.4049/jimmunol.0901422

PLoS Pathog. 2010 Dec; 6(12): e1001221. PMCID: PMC3000360
Published online 2010 Dec 9. doi: 10.1371/journal.ppat.1001221

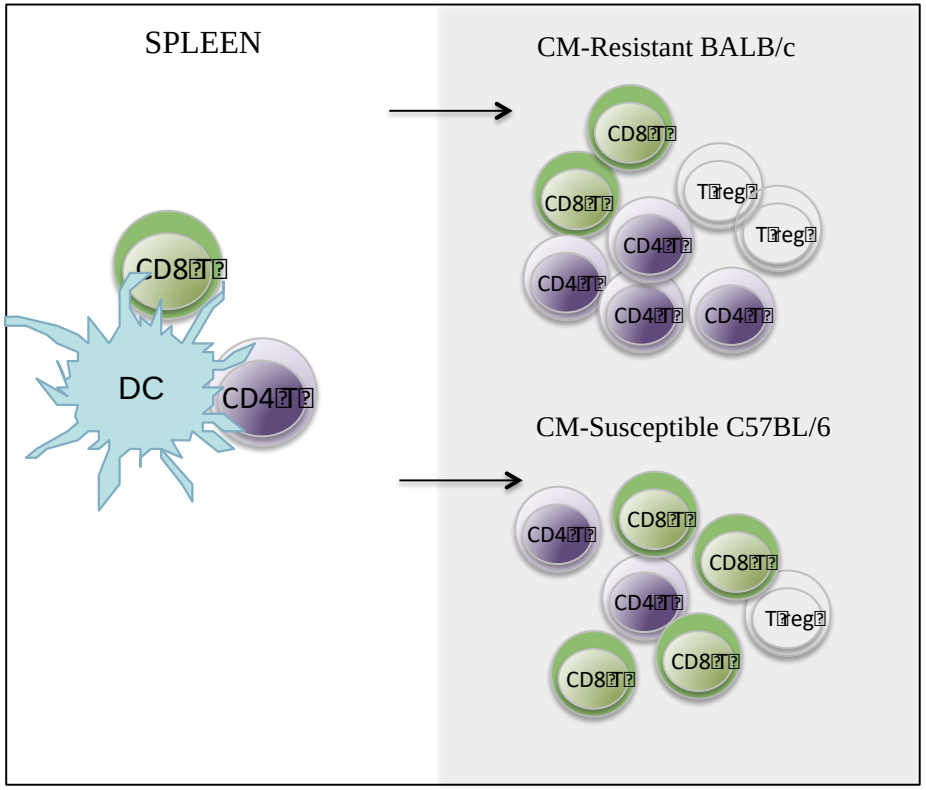
CD4$^+$ Natural Regulatory T Cells Prevent Experimental Cerebral Malaria via CTLA-4 When Expanded In Vivo

Ashraful Haque,[1,*] Shannon E. Best,[1] Fiona H. Amante,[1] Seri Mustafah,[1] Laure Desbarrieres,[1] Fabian de Labastida,[1] Tim Sparwasser,[2] Geoffrey R. Hill,[3] and Christian R. Engwerda[1]

LARGE PROPORTION OF ENDOGENOUS CD8^{+} T / REGULATORY T CELLS IN *P. berghei*-INFECTED C57BL/6 MICE



TAKE HOME MESSAGE



- The kinetic of myeloid cell recruitment to and expansion of lymphoid cells in the spleen revealed a different inflammatory process in CM-susceptible and CM-resistant hosts.

- This study reveals an unbalanced proportion of $CD8^+$ T cells and regulatory T cells in C57BL/6 mice that can contribute to the development of cerebral malaria

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FAPERJ
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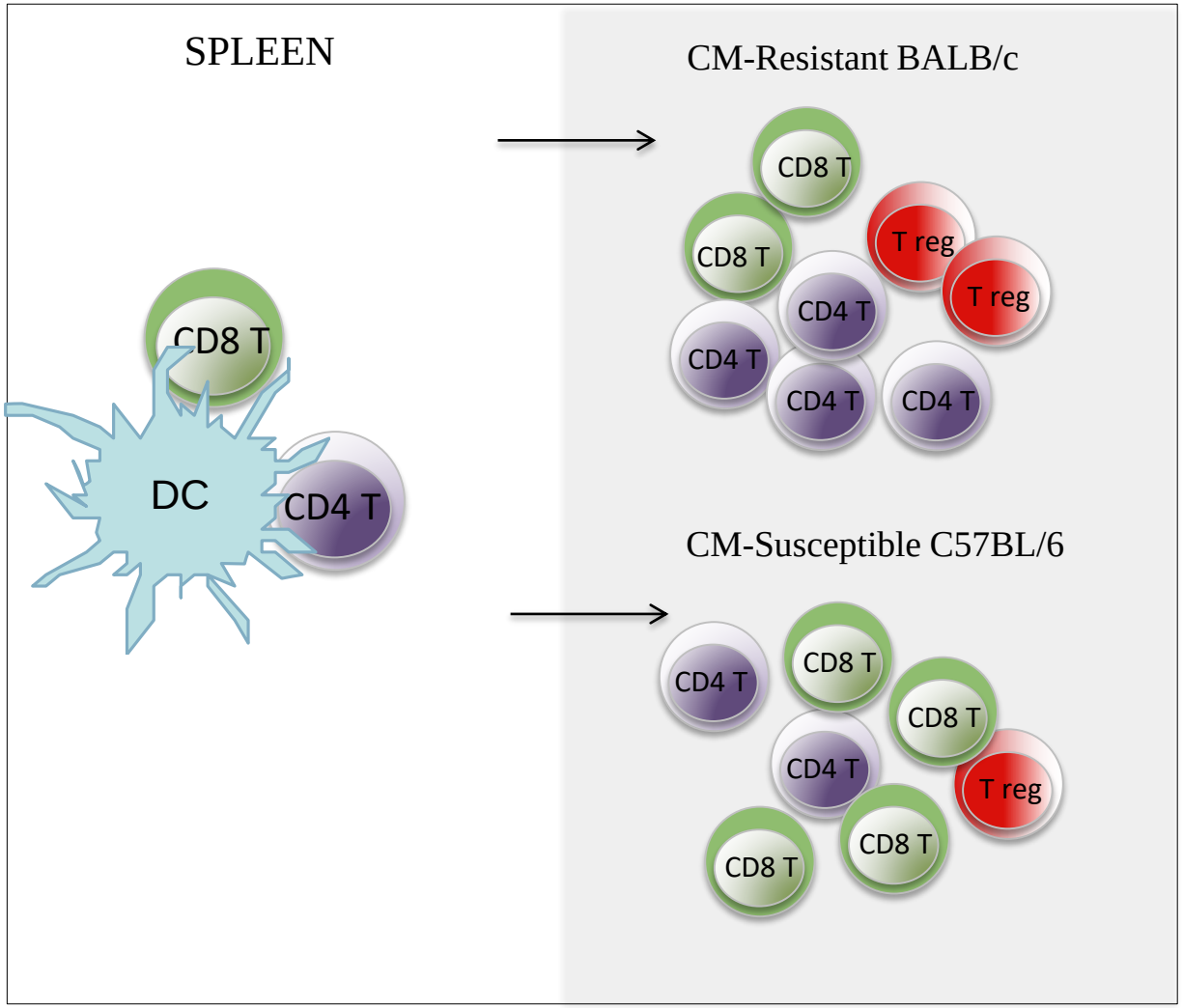
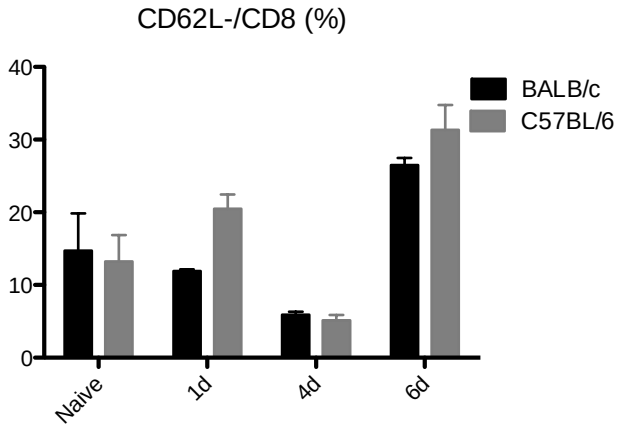
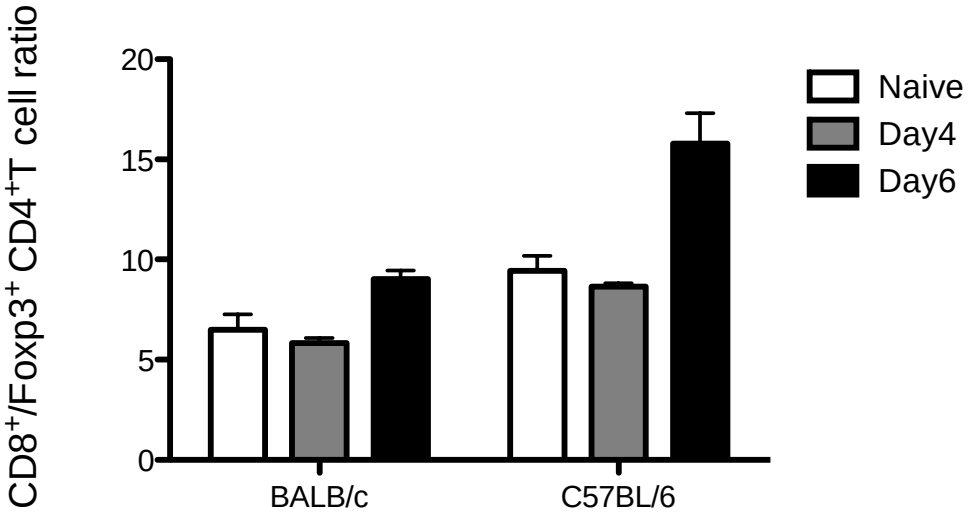
WORKING HYPOTHESIS

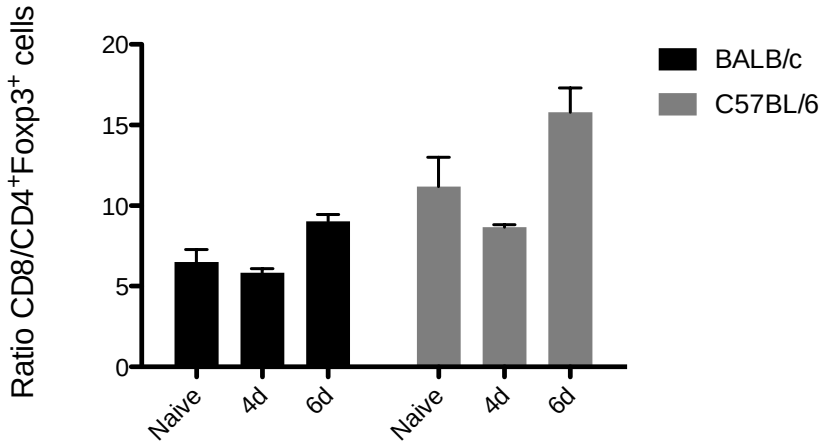


LIFE CYCLE – *Plasmodium sp.*



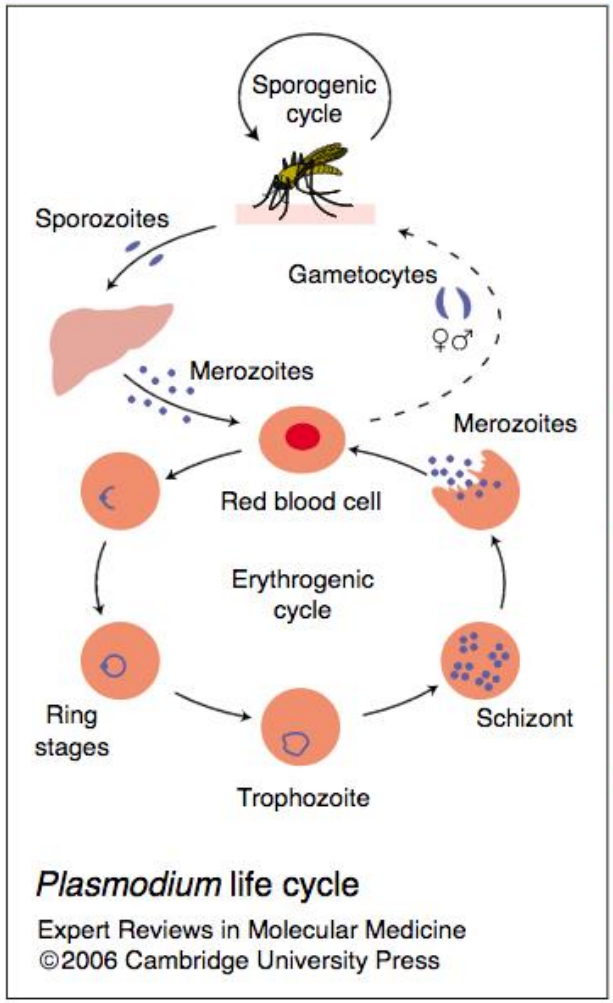

CD8+/Foxp3+ CD4+T cell ratio
20
15
10
5
0
BALB/c
C57BL/6
Naive
Day4
Day6

LIFE CYCLE – *Plasmodium sp.*



LIFE CYCLE – *Plasmodium sp.*

The blood stage of plasmodium infection is the symptomatic;



Lamb T., et al. *Expert Reviews in Mol. Medicine*, 2006

- Cerebral malaria (CM) is a life-threatening sequela of human infected with Plasmodium falciparum (Miller et al, Nature, 2002). OR, Cerebral malaria is the most complication of Plasmodium falciparum infection.OR, Malaria remais a significant global heath problem with 207 millions cases, resulting in 584,000-1,238,000 deaths, annually. A high proportion of these deaths are due to cerebral malaria (CM), a neuropathology induced primarily by the species Plasmodium falciparum.

- This hypothesis suggests that CM is the result of an over- vigorous immune response (reviewed in Clark and Rockett[30]) originally evolved for the protection of the host, producing endothelial cell damage and alterations in blood–brain barrier (BBB) permeability[5] or other manifestations that affect central nervous system (CNS) function, such as nitric oxide production.

Cerebral malaria (CM) is a life-threatening sequela of human infected with Plasmodium falciparum (Miller et al, Nature, 2002). OR, Cerebral malaria is the most complication of Plasmodium falciparum infection.OR, Malaria remais a significant global heath problem with 207 millions cases, resulting in 584,000-1,238,000 deaths, annually. A high proportion of these deaths are due to cerebral malaria (CM), a neuropathology induced primarily by the species Plasmodium falciparum.

Infection of susceptible C57BL/6 mice with Plasmodium berghei ANKA is an experimental model of CM that shares several characteristics with human disease (Jennings et al, Infect. Immun, 1998).

The blood stage of PbA infection induces a strong activation of CD8 T cells as well CD4 cells in spleen and blood, leading to an increased number of activated T cells. OR, CD8+ T cells are a key immune cells type responsible for development of cerebral pathology during malaria infection.

HOW MY REASERCH FIT IN THE TRANSLATIONAL MEDICINE? I WOULD SAY, IT FIT WELL…THE IMPLICATION OF THIS WORK ARE VERY MUCH TRANSLATIONAL… A greater understanding of the parasitological and immunological events leading to development of CM would aid the development of improved therapeutical options to treat the condition.

The roles played by the host immune response in either driving or preventing CM are unclear. It is possible that the immune response could be over-exuberant in some CM-patients or lethargic in others, the balance of witch may depend on the patient's and the parasite's genetic background
Various studies clearly demonstrated a role for T cells and B cells for the genesis of CM.

Infection of C57BL/6 mice with PbA causes CM in the majority of infected mice, that usually die between days 7 and 9 pi.

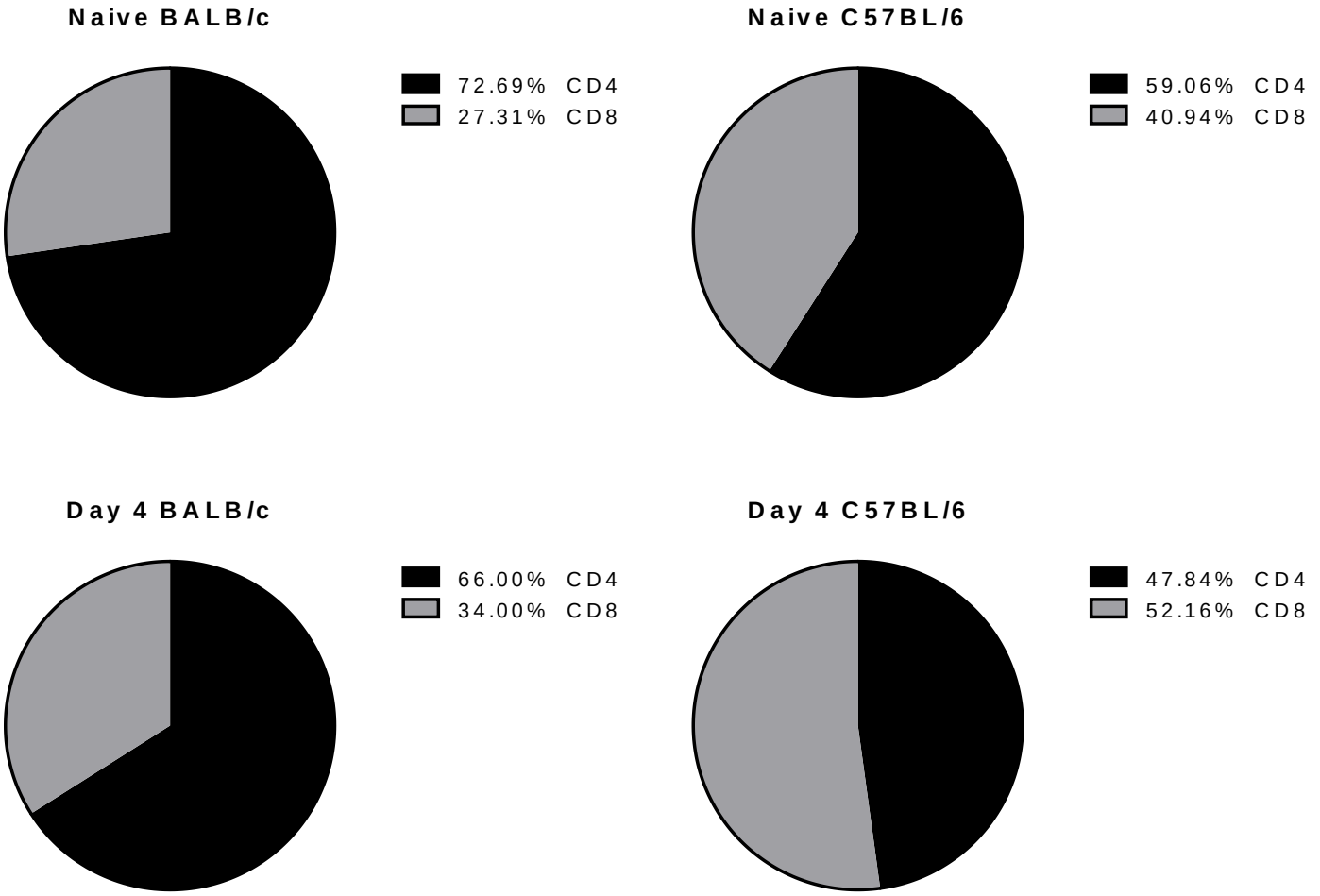
To further study the role of T reg during the course of malaria, C57BL/6 and BALB/c mice were infected with PbA.

The reason why PbA causes CM in C57BL/6 but not in BALB/c mice is an area of active investigation.

The pathogenic CD8+ T cells are primed in the spleen before migrating to the brain, however the relative importance of this event in development of CM remains undefined.

During malaria infection, the spleen has been shown to be th emais lymphoid organ involved in immune response development. While in certain others models of mutine malaria, splenectomy aggravates the infection by prolonging and increasing peak parasitemia, splenectomized infected with PbA are protected from ECM.

PORCENTAGEM DE CÉLULAS CD4 E CD8 NO BAÇO DOS CAMUNDONGOS BALB/c E C57BL/6 INFECTADOS COM *P. berghei* ANKA



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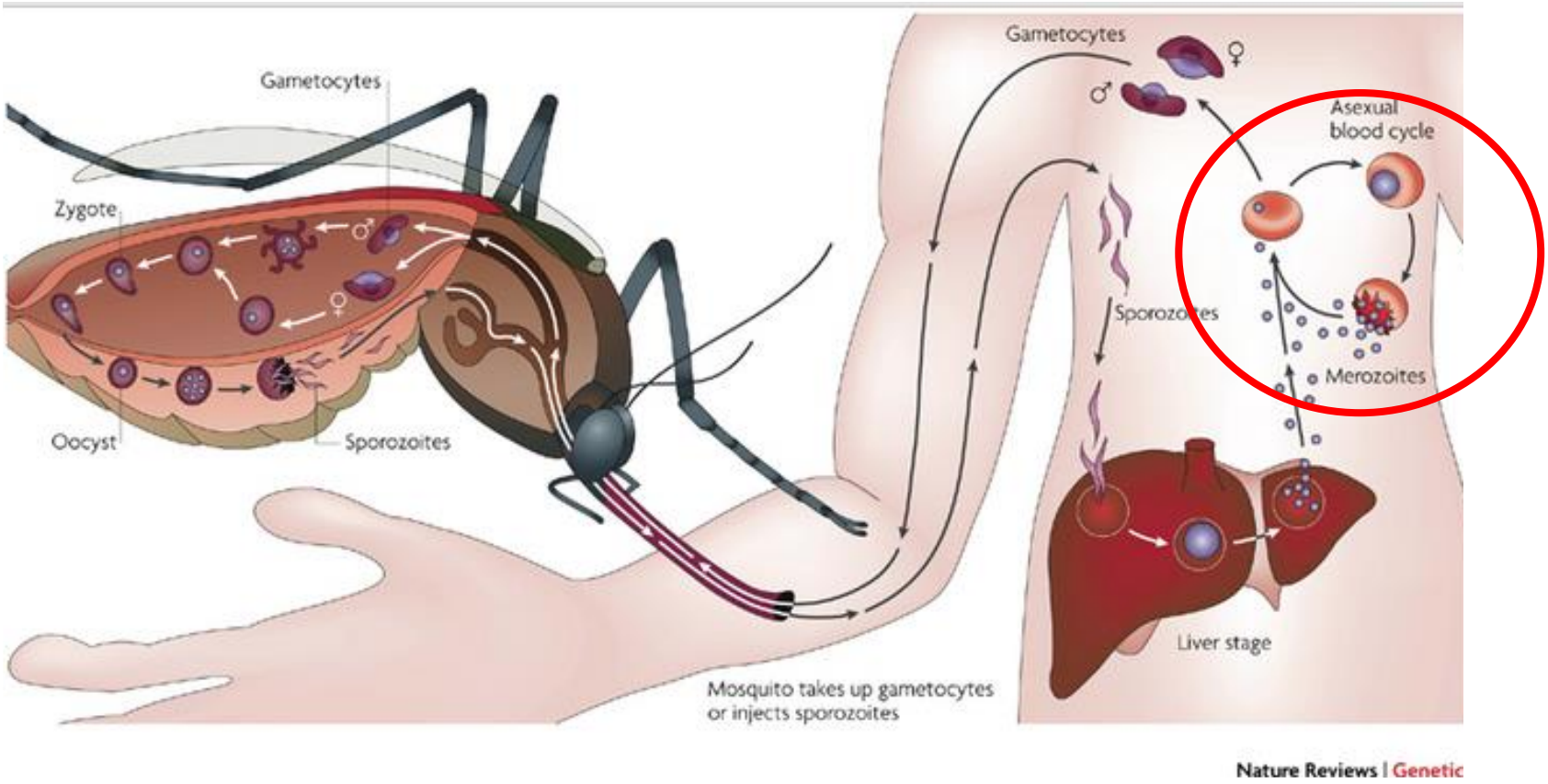
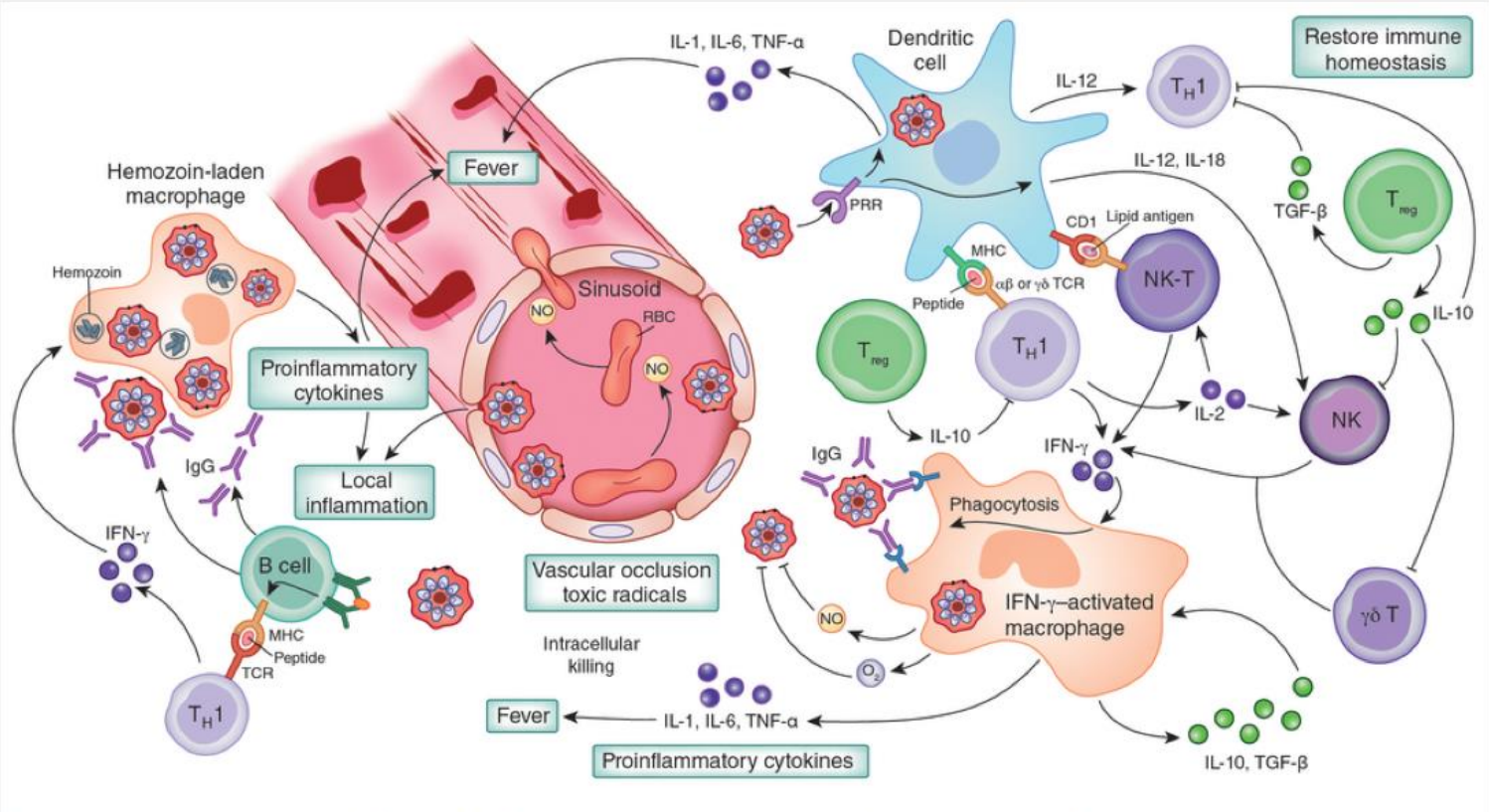


Su, X., et al. *Nature Reviews Genetics*, 2007

IMMUNE RESPONSE– *Plasmodium sp.*



Ann Stewart, V. *Nat Med*, 2013