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Rodent malaria models: insights into human disease and parasite biology

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The use of rodents as model organisms to study human disease is based on the genetic and physiological similarities between the species. Successful molecular methods to generate transgenic reporter or humanized rodents has rendered rodents as powerful tools for understanding biological processes and host-pathogen interactions relevant to humans. In malaria research, rodent models have been pivotal for the study of liver stages, syndromes arising from blood stages of infection, and malaria transmission to and from the mammalian host. Importantly, many *in vivo* findings are comparable to pathology observed in humans only when adequate combinations of rodent strains and *Plasmodium* parasites are used.

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Introduction

Malaria is responsible for over 400,000 deaths worldwide, most of whom are children under the age of five [1]. Although over 100 species of *Plasmodium* exist and can infect multiple vertebrates including reptiles, birds, and other mammals, only five species are known to affect humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*. While the severity of complications caused by infections with each species differs greatly, all five of them cause significant morbidity and/or mortality.

Animal models have been invaluable throughout the history of malaria research, including birds, non-human primates, rodent species, and bats. The use of rodents as model organisms to study human biology is largely-based on the biological similarities between the species (reviewed in Ref. [2]). These genetic similarities, together with the availability of a plethora of inbred and outbred mouse strains with varied immunological makeup and powerful genetic methods for generating transgenic mice such as CRISPR/Cas9, make rodents an invaluable tool for research. Moreover, the increased use of humanized mouse models and xenografted mice, has further led to successful *in vivo* investigations of human malaria pathology, host-pathogen dynamics, and anti-malarial drug efficacy. The main characteristics of the five most studied rodent strains is presented in Table 1 and in Supplementary Table 1.

Four *Plasmodium* species infecting African rodents, that have been extensively used in *in vivo* rodent research are *Plasmodium berghei*, *Plasmodium chabaudi*, *Plasmodium yoelii*, and *Plasmodium vinckei*. Advantages of the rodent malaria models include ease of genetic manipulation through a combination of efficient transfection and various available tools for forward and reverse genetics, which have facilitated the generation of a large number of parasite mutants [3]. In addition, resources such as PlasmoGem [4•,5••,6], a repository of barcoded vectors, offer the opportunity for large-scale production and genetic screening of parasite mutants, making *in vivo* studies much more time-efficient while reducing the numbers of mice used.

Pre-erythrocytic stages and link to blood stages

Pre-erythrocytic parasite stages have traditionally been studied using the rodent models *P. berghei* and *P. yoelii*. Main reasons are that experimental research of liver stages in humans is ethically problematic, and that the general biology of human and rodent *Plasmodium* species is relatively comparable (Table 2). Although splenectomised chimpanzees can be infected with *P. falciparum* and *P. vivax*, and *P. cynomolgi* serves as a robust non-human primate model, few laboratories in the world can afford liver stage research on monkey *Plasmodium* parasites.

Inhibition of parasite development across stages

Rodent and human parasites share many features in pre-erythrocytic stages in terms of invasion, development and egress (Table 2). It was recently shown that highly-specific plasmepsin IX and X inhibitors block *P. falciparum* egress from, and invasion of erythrocytes [7,8]. However, only by using the rodent *P. berghei* model it could be shown that plasmepsin IX and X-inhibitor 49c is

Table 1

Characteristics of main mouse and rodent *Plasmodium* models, and their combined pathology outcomes.

	Mouse strain characteristics	*P. berghei*	*P. yoelii*	*P. chabaudi*	*P. vinckei*
Parasite strain characteristics		Generally inducing severe pathology. Lines including NK65, ANKA, and K173, differ in pathology.	Widely used for studying receptors for erythrocyte binding. Lines including *17X* and *YM* differ in pathology.	Important model for investigation of drug resistance, immune evasion, sequestration, and antigenic variation. Produces non-lethal, chronic infection.	*P. vinckei* is the most widely distributed amongst the rodent *Plasmodium* species. It shows a preference for mature RBCs.
Balb/c 	Inbred strain. Prototypical Th2 response mouse. Increased levels of cytokines and chemokines upon LSP and TLR2-ligand challenges. Increased acute phase proteins.	**Lethality:** Yes **MA:** yes **SMA:** Anaemia with hyperparasitemia. **S:** yes **ALI/ARDS:** Pulmonary oedema remains confined. Not severe. **PM:** yes, lethal to pregnant rodents.	**Lethality:** Yes (YM) **SMA:** Anaemia and splenomegaly. Hyperparasitemia. **ALI/ARDS:** PyXL-infected mice develop interstitial pneumonia and oedema. **IMM:** 17X results in chronic infection which resolves in 35-40 days. **PM:** Placental iRBC accumulation.	**Lethality:** No **SMA:** PcCB causes severe anaemia unrelated to parasitemia. **ALI/ARDS:** Limited lung pathology after 20 days of infection. **IMM:** Model for antigenic switching *in vivo*. Immunity to homologous challenges. **PM:** Placental iRBC accumulation.	**Lethality:** Yes **ALI/ARDS:** Pulmonary pathology at high parasitemia.
C57BL/6 	Inbred strain. Prototypical Th1 response mouse. Activated macrophages produce higher levels of TNFa and IL12.	**Lethality:** Yes **ECM:** PbANKA is main model for ECM, but sequestration index of iRBCs is low. **ALI/ARDS:** Infection with PbNK65 result in severe ARDS with a 90% incidence. Most similar to human ALI/ARDS. **PM:** All strains represent good experimental systems to study PM pathogenesis.	**Lethality:** Yes **ALI/ARDS:** Limited lung pathology compared to *P. berghei* infections. **PM:** Placental iRBC accumulation. **IMM:** Py17X results in variable outcomes of lethality. Widely used to validate vaccine approaches.	**Lethality:** No **ALI/ARDS:** Limited lung pathology compared to *P. berghei* infections. **PM:** Females lose embryos half-way through their pregnancy. **SMA:** Resistant to infection. Develop moderate levels of peak parasitemia, followed by clearance.	**Lethality:** Yes; Does not develop ECM. Other phenotypes not as widely studied.
DBA/2 	Oldest of all inbred strains. Significant genetic disparity with C57BL/6 strain. Have haemolytic complement (C5) deficiency.	**Lethality:** Yes **ALI/ARDS:** PbANKA infection considered a model of ALI/ARDS (50% incidence). Recapitulates human syndrome – pulmonary oedema, haemorrhaging, hypoxemia.	**Lethality:** Yes **ALI/ARDS:** Limited lung pathology compared to *P. berghei* infections. Reduced hemozoin.	**Lethality:** No **SMA:** Resistant to infection. Develop moderate levels of peak parasitemia, followed by clearance.	**Lethality:** Yes Other phenotypes not as widely studied.