Non-human primate malaria parasites: out of the forest and into the laboratory

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SUMMARY

The study of malaria in the laboratory relies on either the *in vitro* culture of human parasites, or the use of non-human malaria parasites in laboratory animals. In this review, we address the use of non-human primate malaria parasite species (NHPMPs) in laboratory research. We describe the features of the most commonly used NHPMPs, review their contribution to our understanding of malaria to date, and discuss their potential contribution to future studies.

Key words: malaria, primates, monkey, *Plasmodium knowlesi*, *Plasmodium cynomolgi*, *Plasmodium fieldi*, *Plasmodium inui*, *Plasmodium gonderi*, *Plasmodium simiovale*, *Plasmodium simium*.

EXPERIMENTAL MODELS FOR LABORATORY MALARIA RESEARCH

The study of malaria parasites may be broadly divided into two major disciplines; those that involve observation of human malaria parasites in their natural hosts in endemic areas, and those that rely on experimental manipulation of living parasites in the laboratory. The latter type of study involves either the manipulation of human malaria parasites, most commonly *Plasmodium falciparum*, in *in vitro* cultures of human blood or (uncommonly) in a permissible animal host, or the use of non-human malaria parasites in laboratory animals. Depending on the scope and purpose of the experiments, there will be advantages and disadvantages associated with each particular approach. When the aim of the laboratory scientist is to model most closely the natural situation of the malaria parasite, it is apparent that *in vitro* culture will often be far from satisfactory, as the physiological conditions in the blood of a living animal cannot be replicated accurately in a culture flask. Indeed, as the intricate interplay and vital association between *Plasmodium* and its host is fundamental to much of the biology of the malaria parasite, so removing it from the natural host will drastically alter its biology. That is not to say, of course, that *in vitro* studies are without merit, as they have been hugely important in informing a great deal regarding the biology of malaria parasites. But for certain types of studies, such as those that rely on maintenance of the whole life cycle of the parasites, and particularly those studies concerned with host–parasite interactions, there can be no satisfactory alternative to the use of non-human parasites in experimental animals.

Animal malaria parasite studies are not without their disadvantages and limitations. Some of the laboratory host–parasite combinations, such as the rodent malaria parasites and their *Mus musculus* hosts do not occur in nature, and so, as in the culture flask, the parasites find themselves in an environment somewhat removed from that in which they evolved. Furthermore, there are serious and profound ethical questions to be taken into consideration with the use of animals in any scientific research. Finally, non-human malaria parasites, although often sharing considerable biological and genetic similarity to their human counterparts, do differ from the human parasites in certain ways, and care must be taken when extrapolating results from one species to another.

The best animal models, from a purely scientific standpoint, are those in which the genetic and phenotypic distance between the parasite itself and whichever of the human parasites one wishes to model is small, along with a similarly close relationship between the experimental host animal and man. Ideally, the experimental host animal should also be the natural host. For studies of malaria parasites, the non-human primate parasites most closely fit this description. In this review, we will discuss solely malaria in non-human primates. We will highlight particular host–parasite pairings, and discuss their suitability for studies on particular aspects of human malaria.

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THE PRIMATE MALARIAS

The discovery that man was not the only primate to be infected with malaria parasites occurred early on in the history of modern malariology. In 1899, at around the same time that British and Italian parasitologists were discovering the role of the mosquito in vectoring malaria (Ross, 1897; 1898; Grassi *et al*. 1899), Alphonse Laveran described *Plasmodium kochi*, a parasite of African monkeys (Laveran, 1899). Now known as *Hepatocystis kochi*, this parasite, which has been found to predominantly infect African green monkeys, *Cercopithecus aethiops,* is a member of the genus Hepatocystis, a sister group to the *Plasmodium* spp of mammalian malaria parasites that do not undergo erythrocytic schizogony, maturing to gametocytes following initial invasion of red blood cells (Garnham, 1948).

The first *true* malaria parasite (i.e. belonging to the genus *Plasmodium* and undergoing erythrocytic schizogony) of non-human primates to be observed was *Plasmodium pitheci*, again by Laveran, just after the turn of the 20th Century (Laveran, 1905). This species was found in the blood of an orangutan, and is remarkable for being the first great ape parasite to be described (Halberstadter and Von Prowazek, 1907). At this time the first reports of malaria parasites infecting Southeast Asian macaques also appeared, with descriptions of *Plasmodium inui* and *Plasmodium cynomolgi* infecting *Macaca fascicularis*. Over the next 60 years, a further nine malaria parasite species infecting non-human primates in Southeast Asia were described, along with two parasites of New World monkeys from South America, one parasite of African green monkeys, and two parasites of lemurs from Madagascar (Table 1).

The malaria parasites of the great apes have a more convoluted history than those infecting monkeys. Following the discovery of *P. pitheci* in 1905, it was not until 1920 that malaria parasites of African great apes were observed, firstly by Reichenow, and then by Blacklock and Adler (Reichenow, 1920; Blacklock and Adler, 1922). Both these reports detailed the observation that there existed in chimpanzees three distinct species of malaria parasite that were broadly comparable to the human malaria parasites *P. falciparum, Plasmodium malariae* and *P. vivax*. These were later termed *Plasmodium reichenowi, Plasmodium rodhaini* and *Plasmodium schwetzi*, respectively (Table 1).

For the next 90 years, our understanding of the great ape malaria parasites changed very little, with the exception of the addition of a second parasite of the orangutan, *Plasmodium silvaticum* in 1972 (Garnham *et al*. 1972). Then, in 2009 the field once again opened up with a number of papers reporting the discovery of a plethora of new malaria parasite species (Ollomo *et al*. 2009; Rich *et al*. 2009; Duval *et al*. 2010; Krief *et al*. 2010; Prugnolle *et al*. 2010) of apes in Africa. Following a brief period of some confusion, a landmark paper that proved that *P. falciparum* had become a human parasite as a result of a host switch from gorillas consolidated our current understanding of the diversity and host preferences of the malaria parasites of great apes (Liu *et al*. 2010).

These newly described species are closely related to *P. falciparum* of humans, and belong to the subgenus Laverania. Of these, three species, *Plasmodium reichenowi, Plasmodium gaboni* (also named *Plasmodium blillbrayi)* and *Plasmodium billcollinsi* are found predominantly in chimpanzees, and three, *Plasmodium praefalciparum, Plasmodium adleri* and *Plasmodium blacklocki* in gorillas (Table 1). There has also been a 'rediscovery' in great apes of parasites closely related to *P. vivax* and *P. malariae* (Krief *et al*. 2010; Liu *et al*. 2010, 2014). The former species has now been formally named *Plasmodium carteri* (Loy *et al*. 2016) in honour of Richard Carter, who has long argued that *P. vivax* has had a longer association with humans in Africa than it has in Southeast Asia (Carter, 2003). A recent genome sequencing project (Sundararaman *et al*. 2016) focused on *P. reichenowi* and *P. gaboni* has highlighted their distinct nature as separate species, as well as evolutionary developments that allowed *P. falciparum* to infect humans.

To date there are 27 *Plasmodium* malaria parasites of non-human primates described in the literature. It is likely that this number will increase with further surveys of wild primate populations. Below we consider these species in the context of their utility as experimental models for human malaria, and highlight the significant advances in malariology achieved through their use.

NON-HUMAN MALARIA PARASITES IN THE LABORATORY

The following sections focus on the use of non-human primate malaria parasites (NHPMPs) in laboratory research.

Subgenus *Laverania*

The subgenus Laverania originally consisted of just two species; *P. falciparum* and *P. reichenowi*, characterized by their crescent shaped gametocytes. Since 2009, numerous additional members of this subgenus have been described. To date, these have been described and classified based solely on sequencing of DNA, and so remain poorly characterized at the morphological and phenotypical level.

Plasmodium reichenowi

Plasmodium reichenowi was the second malaria parasite species of chimpanzees to be described after

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Table 1. The non-human primate malaria parasites, their geographical origin and dates of first observation

Region	Parasite	Subgenus	Date first observed	Host	Reference
Asia	*Plasmodium pitheci*	*Plasmodium*	1905	Orangutan (*Pongo pygmaeus*)	Halberstadter and von Prowazek (1907)
	Plasmodium inui	*Plasmodium*	1905	Macaque (*Macaca fascicularis*)	Halberstadter and von Prowazek (1907)
	Plasmodium cynomolgi	*Plasmodium*	1905	Macaque (*Macaca fascicularis*)	Mayer (1907)
	Plasmodium eylesi	*Plasmodium*	1965	Gibbon (*Hylobates lar*)	Warren *et al*. (1965)
	Plasmodium hylobati	*Plasmodium*	1939	Gibbon (*Hylobates lensciscus*)	Rodhain (1941)
	Plasmodium jefferyi	*Plasmodium*	1964	Gibbon (*Hylobates lar*)	Warren *et al*. (1966)
	Plasmodium youngi	*Plasmodium*	1964	Gibbon (*Symphalangus syndactylus*)	Eyles *et al*. (1964)
	Plasmodium fieldi	*Plasmodium*	1962	Macaque (*Macaca nemestrina*)	Eyles *et al*. (1962*a*)
	Plasmodium simiovale	*Plasmodium*	1965	Macaque (*Macaca sinica*)	Dissanaike *et al*. (1965*a*)
	Plasmodium coatneyi	*Plasmodium*	1965	Macaque (*Macaca mulatta*)	Eyles *et al*. (1962*b*)
	Plasmodium fragile	*Plasmodium*	1965	Macaque (*Macaca radiata*)	Dissanaike *et al*. (1965*b*)
	Plasmodium knowlesi	*Plasmodium*	1932	Macaque (*Macaca fascicularis*)	Sinton and Mulligan, (1932)
	Plasmodium silvaticum	*Plasmodium*	1972	Orangutan (*Pongo pygmaeus*)	Garnham *et al*. (1972)
America	*Plasmodium brasilianum*	*Plasmodium*	1908	Cacajao (*Cacajao calvus*)	Gonder and Von Berenberg-Gossler (1908)
	Plasmodium simium	*Plasmodium*	1951	Howler monkey (*Alouatta fusca*)	da Fonseca (1951)
Africa	*Plasmodium gonderi*	*Plasmodium*	1908	Mangaby (*Cercocebus atys*)	Sinton and Mulligan (1933)
	Plasmodium schwetzi	*Plasmodium*	1920	Chimpanzee (*Pan troglodytes*)	Brumpt (1939)
	Plasmodium rodhaini	*Plasmodium*	1939	Chimpanzee (*Pan troglodytes*)	Brumpt (1939)
	Plasmodium carteri	*Plasmodium*	2016	Chimpanzee (*Pan troglodytes*)	Loy *et al*. (2016)
	Plasmodium reichenowi	*Laverania*	1922	Chimpanzee (*Pan troglodytes*)	Sluiter *et al*. (1922)
	Plasmodium gaboni	*Laverania*	2009	Chimpanzee (*Pan troglodytes*)	Ollomo *et al*. (2009)
	Plasmodium billcollinsi	*Laverania*	2010	Chimpanzee (*Pan troglodytes*)	Krief *et al*. (2010)
	Plasmodium praefalciparum	*Laverania*	2011	Gorilla (*Gorilla gorilla*)	Rayner *et al*. (2011)
	Plasmodium adleri	*Laverania*	2011	Gorilla (*Gorilla gorilla*)	Rayner *et al*. (2011)
	Plasmodium blacklocki	*Laverania*	2011	Gorilla (*Gorilla gorilla*)	Rayner *et al*. (2011)
Madagascar	*Plasmodium lemuris*	*Vinckeia*	1963	Lemur (*Lemur collaris*)	Huff and Hoogstral (1963)
	Plasmodium girardi	*Vinckeia*	1952	Lemur (*Lemur fulvus rufus*)	Bück *et al*. (1952)

P. schwetzi. Morphologically similar to *P. falciparum*, it shares the same length of erythrocytic cycle as well as several other biological features such as crescent-shaped gametocytes (Bray, 1956). Its genome has been fully sequenced and reveals strong synteny with *P. falciparum*, including conserved organisation of the hypervariable *var* genes involved in immune evasion (Otto *et al*. 2014). It has also provided valuable insights into the recent evolutionary rise of *P. falciparum* (Sundararaman *et al*. 2016). The high degree of conservation between the two species has also made *P. reichenowi* a comparative model to study the evolution of *P. falciparum* and its adaptation to the human host, particularly at the antigenic level (Wanaguru *et al*. 2013; Zilversmit *et al*. 2013; Otto *et al*. 2014).

While *P. reichenowi* can readily infect a wide range of anopheline vectors (Collins *et al*. 1986*a*), it is restricted to chimpanzees as its vertebrate host (Martin *et al*. 2005). Thus, *in vitro* culturing, using protocols adapted from *P. falciparum*, plays an important role in the study of this parasite (Kocken *et al*. 2000). Still, the use of a relatively fastidious and ethically sensitive animal model limits the scope of studies possible with *P. reichenowi*. Furthermore, the fact that chimp-adapted *P. falciparum* can establish an infection not only in splenectomized chimpanzes, but also in chimpanzees with intact immune systems (Taylor *et al*. 1985) further highlights the rather peripheral role played by *P. reichenowi* as a human malaria model.

Other species of the Laverania subgenus

Six *Laverania* gorilla and chimpanzee parasites, *P. gaboni* (referred to as *P. billbrayi* by Krief *et al*. (2010)), *P. billcollinsi, P. adleri, P. blacklocki, P. praefalciparum* have recently been described in addition to *P. reichenowi* from the earlier literature (Table 1). These species, whilst of potential use in comparative genomics (Pacheco *et al*. 2013; Boundenga *et al*. 2015; Larremore *et al*. 2015; Roy, 2015; Sundararaman *et al*. 2016), are not (to date) utilized in laboratory studies due to important practical limitations. Firstly, collection of blood samples from Great Apes is difficult as they are protected species. Secondly, maintaining parasites in laboratory conditions would either involve the keeping of Great Apes in captivity, a situation which is no longer deemed ethically acceptable, or the adaptation of the parasites to *in vitro* culture, preferentially in human blood.

Subgenus Plasmodium

All other malaria parasites of prosimians, except those infecting lemurs (which fall into the subgenus *Vinckeia*), are classified into the subgenus *Plasmodium*.

Plasmodium knowlesi

Plasmodium knowlesi is probably the most thoroughly characterized and widely used non-human primate malaria parasite species. It is certainly the species most utilized in experimental laboratory studies of malaria, many of which have contributed enormously to malariology. The contribution of this species to our understanding of malaria parasite biology is immense, and the literature pertaining to it enormous. We will attempt to outline some of the major advancements achieved using *P. knowlesi*, but advise the reader that this is a selective and in no way exhaustive treatment of the subject.

First described in 1932, laboratory investigations of malaria parasite biology using this species were underway by the close of the decade. Initial *in vivo* work involved studies on immunity and drug responses (Coggeshall, 1940; Coggeshall and Kumm, 1938; Eaton and Coggeshall, 1939), and this was shortly followed by investigations of parasite cell biology (McKee *et al*. 1946; Shen *et al*. 1946; Morrison and Jeskey, 1947). A workable *in vitro* culture system was established for *P. knowlesi* during the mid 1960s (Polet, 1966), and this led to its use in studies on malaria parasite cellular biology (Polet and Barr, 1968; Polet and Conrad, 1969; Skelton *et al*. 1969). A major breakthrough was achieved with the establishment of continuous *in vitro* cultivation of malaria parasites by Trager and Jensen in 1976, was soon adapted to *P. knowlesi* (Butcher, 1979), and huge advances in the understanding of the ultrastructure of parasite invasion of erythrocytes were subsequently carried out using *P. knowlesi in vitro* (Aikawa *et al*. 1978; Haynes *et al*. 1988; Johnson *et al*. 1980; Miller *et al*. 1988; Barnwell *et al*. 1989).

Antigenic variation, a major immune evasion mechanism employed by malaria parasites, was first described in *P. knowlesi*. Antigenic variation involves a parasite strain expressing different alleles of genes encoding antigenic proteins over the course of an infection in order to escape antibody mediated immune clearance. This phenomenon was first described in *P. knowlesi* by Brown and Brown (1965), using the schizont agglutination test developed in this same species by Eaton (1938). They showed that during a chronic *P. knowlesi* infection in a Rhesus macaque, successive waves of parasitaemia were composed of serologically distinct parasites. They went on to further characterize this phenomenon (Brown *et al*. 1968), work which eventually led to the identification of the variant antigen proteins themselves (Howard *et al*. 1983).

Plasmodium knowlesi was has also been fundamental to malaria vaccine studies, in which protection has been elicited against asexual blood forms (Collins *et al*. 1977; Mitchell, 1977; Mitchell *et al*. 1977), gametocytes (Gwadz and Green, 1978;

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Gwadz and Koontz, 1984) and sporozoites (Gwadz *et al*. 1979; Moser *et al*. 1978; Nardin *et al*. 1979).

Another landmark advancement in malariology involving the use of *P. knowlesi* was the discovery, in the laboratory of Professor Louis Miller at the NIH in the USA, of the Duffy erythrocyte receptor's role in malaria parasite invasion. Miller and colleagues first showed that Duffy negative erythrocytes were refractory to invasion by merozoites of *P. knowlesi* (Miller *et al*. 1975), an observation which led to experiments that proved the absolute requirement of Duffy for erythrocyte invasion by the related human malaria parasite *P. vivax* (Miller *et al*. 1976), and explained the absence of this parasite from vast swathes of western and central Africa where *P. vivax* is almost totally absent (Culleton *et al*. 2008). This work led directly to the identification of malaria parasite invasion ligands (Haynes *et al*. 1988; Miller *et al*. 1988; Adams *et al*. 1990; Fang *et al*. 1991), a topic addressed in more detail in a previous review (Culleton and Kaneko, 2010).

Also noteworthy is the landmark paper by Dvorak and colleagues in 1975, who captured the first moving images of the invasion of erythrocytes by merozoites using *P. knowlesi* (Dvorak *et al*. 1975).

Plasmodium knowlesi is not, however, a perfect non-human primate malaria model for experimental studies. It is, for example, difficult to transmit to mosquitoes in the laboratory; sporozoites in the salivary glands of two of the most commonly used laboratory vector mosquitoes, *Anopheles stephensi* and *Anopheles gambiae*, were observed too rarely to support effective transmission (Murphy *et al*. 2014). Sporozoites were also completely unable to colonise the salivary glands of *Anopheles freeborni* mosquitoes (Rosenberg, 1985). Indeed, only the salivary glands of mosquitoes of the Leucosphyrus group of *Anopheles* appear to be suitable for colonization by *P. knowlesi* sporozoites. Unfortunately, one of the most effective vectors for transmitting *P. knowlesi, Anopheles dirus*, can be particularly fastidious to maintain in the laboratory, requiring constant forced mating. However, alternative, less fastidious vectors, such as *Anopheles cracens* have been proposed (Murphy *et al*. 2014), and may offer a route to genetic crossing and forward genetics studies.

There are considerable biological differences between *P. knowlesi* and the other human malaria parasite species. Human malaria is usually classified according of the amount of time required by the parasite to undergo a complete shizogonic replication cycle in the blood. The four major species fall into two categories: tertian (48–50 h cycle, including *P. falciparum, P. vivax* and *P. ovale*) and quartan (72 h cycle, *P. malariae*). *Plasmodium knowlesi*, however, has a distinct 24 h cycle, which is one factor that leads to its high virulence in man (Mideo *et al*. 2013). *Plasmodium knowlesi* is an excellent resource for experimental studies on malaria due to the wealth of literature dedicated to it as well as the availability of a high quality genome (Pain *et al*. 2008). However, other NHPMPs may be more appropriate when studying particular phenotypes, especially those of relevance to human malarial disease.

In 2004, a large outbreak of *P. knowlesi* in humans in Borneo elevated this species from a useful model for malaria to a pathogen of direct importance to human health (Singh *et al*. 2004).

Quartan malaria parasites

Plasmodium brasilianum. *Plasmodium brasilianum* is the most closely related sister-species to the human parasite *Plasmodium malariae*. Like *P. malariae* it is a quartan parasite and undergoes its full erythrocytic cycle in 72 h (Von Berenberg-Gossler, 1909). It is found in tropical areas of South America where its natural hosts include a variety of New World Monkeys (Deane and de Almeida, 1967; Marinkelle and Grose, 1968; Baerg, 1971; Collins *et al*. 1985; Wedderburn *et al*. 1985). It can be transmitted by various laboratory mosquito vectors, including both *A. stephensi* and *A. gambiae* (Collins *et al*. 1985).

Recent evidence has indicated that *P. brasilianum* can infect humans in the wild (Lalremruata *et al*. 2015) and this, coupled with the cross-reactivity of *P. malariae*-specific monoclonal antibodies against *P. brasilianum* (Cochrane *et al*. 1985), suggests a close relationship between the two species. Indeed, there is evidence to suggest that *P. brasilianum* is a strain of *P. malariae* that has adapted to infect new world monkeys relatively recently (Ayala *et al*. 1999; Collins and Jeffery, 2007). This fact renders it somewhat obsolete as a model for *P. malariae*, as the human parasite itself also readily infects new world monkeys (Collins and Jeffery, 2007). However, the *P. brasilianum* genome could offer valuable insights on its origins and adaptations, and would be useful for comparative genomics (Rayner, 2015).

Plasmodium inui. *Plasmodium inui* is the only major NHPMP other than *P. brasilianum* with a quartan life cycle (Coatney *et al*. 1966). Initially thought to be closely related to *P. malariae* and used as a model for it, phylogenetic evidence has revealed its inclusion in the clade of primate malaria parasites that includes *P. vivax* (Mitsui *et al*. 2010). Indeed, immunological evidence had previously suggested its separate nature from the *P. malariae* subgroup (Kamboj and Cochrane, 1988). Originally isolated from a Javan *Macaca fascularis, P. inui* can infect a wide range of monkeys, including the Platyrrhini of the New World (Collins *et al*. 2009*b*) and can be transmitted by several species of mosquito commonly kept in the

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laboratory (Collins *et al*. 2007). It is also infectious to humans, which marks it as a potential zoonotic disease of medical significance (Coatney *et al*. 1966). Unlike other quartan malaria parasite species, *P. inui* has been adapted to *in vitro* culture (Nguyen-Dinh *et al*. 1980). Despite its closer phylogenetic relatedness to *P. vivax* than to *P. malariae*, *P. inui* has recently been used to model human quartan malaria nephrotic syndrome in monkeys (Nimri and Lanners, 2014).

Plasmodium vivax clade malaria parasites

Plasmodium cynomolgi. *Plasmodium cynomolgi* is, after *P. knowlesi*, the most well characterized and often used NHPMP in experimental malariology. Like *P. knowlesi*, this species also has the capacity to infect man in nature (Ta *et al*. 2014), although there is currently little evidence to suggest that this occurs frequently. It is closely related to the human malaria parasite *P. vivax* and shares with it some crucial features that make it well suited as a model for *vivax* malaria. Like *P. vivax*, *P. cynomolgi* has a 48 h erythrocytic cell cycle (Wolfson and Winter, 1946) and, crucially, it also produces hypnozoites, the dormant liver stages that can cause relapse (Krotoski *et al*. 1982*a*). It was, in fact, in *P. cynomolgi* that hypnozoites were first described, a discovery that took place some 34 years after the same species was used for the first description of exoerythrocytic stages of a mammalian malaria parasite (Shortt and Garnham, 1948). It offers an ideal model to study both the biological properties of the hypnozoite stages, and the testing of potential treatments to remove them (Deye *et al*. 2012; Dembélé *et al*. 2014; Joyner *et al*. 2015).

Originally isolated from a Javan macaque, it can also infect Platyrrhini monkeys (Collins *et al*. 1975, 1999), which are more tractable laboratory species. Furthermore, *P. cynomolgi* blood stages (Nguyen-Dinh *et al*. 1981), as well as liver stages (Millet et al. 1987, 1988), can be routinely maintained *in vitro*, making it a more appealing model when ethical and financial considerations regarding the use of monkeys as test animals are considered.

Plasmodium cynomolgi is less restricted than *P. knowlesi* in terms of mosquito vector transmissibility. Beside the natural vectors *A. cracens* and *A. dirus* (Cheong *et al*. 1965; Vythilingam *et al*. 2008), it can also be transmitted by *Anopheles farauti* (Nace *et al*. 2004) and by species commonly maintained under laboratory conditions, such as *A. gambiae* and *A. stephensi* (Collins *et al*. 2009*a*).

In addition to relapse, *P. cynomolgi* has been used to study a wide variety of medically relevant phenotypes and general malaria biology, for which there is an extensive body of literature.

Several studies related to malaria immunity have been carried out with *P. cynomolgi*. The activation of components of the immune system during infections have been studied (Praba-Egge *et al*. 2002; Li *et al*. 2012), while the parasite has also been used as a model for malaria-HIV co-infections (Koehler *et al*. 2009). The genome of *P. cynomolgi* contains orthologues of the *vir*-gene family, which in *P. vivax* are responsible for immune evasion (Prajapati and Singh, 2014). Strain-specific immunity, a trait found both in human and rodent malaria (Ciuca *et al*. 1934; Jarra and Brown, 1985), has been observed in *P. cynomolgi* (Wijayalath et al. 2008, 2012). Additionally, *P. cynomolgi* has also been used to test the efficacy of potential vaccination strategies (Millet et al. 1992, 1995; Barnwell *et al*. 1999; Bhardwaj *et al*. 2003; Dutta *et al*. 2005).

The species has been studied to understand the interactions between *Plasmodium* and its vector. Studies on refractoriness to infections and its genetic basis in mosquitoes have been carried out (Collins *et al*. 1986*b*; Zheng *et al*. 1997, 2003), as well as experiments aimed at understanding factors determining infectivity to mosquitoes (Naotunne *et al*. 1990, 1991).

Plasmodium cynomolgi has also been regularly used to test the activity of various novel anti-malarial drugs (Puri and Dutta, 2003; Deye *et al*. 2012; McNamara *et al*. 2013; Ohrt *et al*. 2014; Zeeman *et al*. 2016).

Plasmodium cynomolgi has also been included in several studies on malaria evolution and genetic diversity (Nishimoto *et al*. 2008; Cornejo *et al*. 2014; Luo *et al*. 2015; Sutton *et al*. 2016), especially since the publication of three assembled and annotated draft reference genomes (Tachibana *et al*. 2012).

The existence of optimized protocols for transfection studies (Kocken *et al*. 1999; Voorberg-van der Wel *et al*. 2013) further facilitates experimental work with the species.

Plasmodium coatneyi. *Plasmodium coatneyi* is a tertian malaria species closely related to *P. knowlesi* and found primarily in macaques of SE Asia (Fooden, 1994). It is transmitted by Asian Anopheline mosquitoes such as *A. dirus* and *A. freeborni*, although transmission through *A. stephensi* and *A. gambiae*, while less efficient, has been demonstrated (Collins *et al*. 2001). New world monkeys appear to be susceptible to the liver stages of the parasite, although evidence for successful establishment of the erythrocytic cycle is lacking (Sullivan *et al*. 2005). The liver stages of *P. coatneyi* have also been successfully cultured *in vitro* (Millet *et al*. 1990).

Plasmodium coatneyi displays phenotypes with striking similarities to those associated with malignant *falciparum* malaria in humans, such as the presence of knob protrusions on the surface of infected erythrocytes, cytoadherence to the vascular endothelium, rosetting and the induction of ‘cerebral

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malaria' (Kilejian *et al*. 1977; Udomsangpetch *et al*. 1991; Kawai *et al*. 1993, 1995; Maeno *et al*. 1993; Sein *et al*. 1993; Smith *et al*. 1996). It also provides a valuable model to study the multisystemic dysfunction associated with severe malaria in monkeys (Moreno *et al*. 2013) and has been used in studies involving co-infections with schistosomiasis (Semenya *et al*. 2012).

An non-annotated draft genome project is currently available at the PlasmoDB website (http://www.plasmodb.org/common/downloads/Current_Release/PcoatneyiHackeri/) thus providing some framework for genetic studies with this parasite species.

Plasmodium simium. *Plasmodium simium* is the most closely related NHPMP to *P. vivax*. Indeed, there is now strong evidence that it may represent an adaptation of *P. vivax* to transmission and growth in New World monkeys following a host switch (Ayala *et al*. 1999; Goldman *et al*. 1993; Mu *et al*. 2005; Tazi and Ayala, 2011). As expected by its phylogenetic location, *P. simium* shares many features with its human counterpart, including the presence of an extensive repertoire of *vir*-genes involved in immune evasion (Prajapati and Singh, 2014), the expression of a Duffy binding protein that interacts with a host Duffy antigen receptor for chemokines (DARC) (Camargos Costa *et al*. 2015) and a tertian erythrocytic cycle (Deane *et al*. 1966).

Its natural hosts are the Platyrrhine monkeys of South America (Collins *et al*. 1973, 1987; Deane *et al*. 1966) and it can be transmitted by a variety of mosquito vectors, including the commonly used laboratory species *A. stephensi* (Collins *et al*. 1979*b*). Occasional cases of naturally acquired human infections have been reported (Deane *et al*. 1966), although such observations should be viewed with caution due to the difficulty of distinguishing *P. simium* from *P. vivax* in the pre molecular biology era.

Due to its close relationship to *P. vivax, P. simium* has been proposed as a model to study the efficacy of vaccine candidates (Collins *et al*. 2005). No genome, which could provide valuable information both on its origins and on host adaptations, is currently available.

Plasmodium fragile. *Plasmodium fragile* is a tertian NHPMP species originally isolated from monkeys of the Indian subcontinent (Ramakrishman and Mohan, 1961; Dissanaike *et al*. 1965*a*). Laboratory induced infections have demonstrated its capacity to establish infections in New World Monkeys, but it appears somewhat more restricted in vector infectivity and its development has only been successfully observed in *A. dirus* (Collins *et al*. 1990, 1974, 2006). However, other species from the *Anopheles leucosphyrus* group (to which *A. dirus* belongs) have been observed to transmit *P. fragile* (Sallum *et al*. 2005). Two strains of the parasite are currently available with one having lost the ability to produce infective gametocytes in the host (Collins *et al*. 2006). Additionally, a protocol to grow the parasite *in vitro* exists (Chin *et al*. 1979).

Like *P. falciparum* and *P. coatneyi, P. fragile* infected red blood cells adhere to blood vessels (Fremount and Miller, 1975) and have been shown to form rosettes; a phenomenon typically associated with *P. falciparum* infections in humans (David *et al*. 1988). Indeed, *P. fragile* infections in monkeys have been used as a model for human cerebral malaria (Fujioka *et al*. 1994).

Plasmodium fragile has been adopted as a model to study malaria vaccines (Collins *et al*. 1979*a*; Fujioka *et al*. 1994), as well as major surface antigens (Nguyen-Dinh *et al*. 1988; Peterson *et al*. 1990). Like major human malaria species, *P. fragile* also evades the immune system by undergoing antigenic switching (Handunnetti *et al*. 1987). More recently, various aspects of HIV and malaria co-infections have been studied using *P. fragile* and the Simian Immunodeficiency Virus as models (Trott *et al*. 2011, 2013; Frencher *et al*. 2013). Finally, *P. fragile* has been used to test the activity of antimalarial drugs (Tripathi *et al*. 1997; Puri and Dutta, 2003).

While less studied than *P. knowlesi* or *P. cynomolgi, P. fragile* displays several interesting phenotypes that have made it a relatively popular model for human malaria, despite the reliance on the relatively fastidious *A. dirus* vector for transmission. Its adaptation to *in vitro* culture also makes it an ideal parasite for future genome sequencing and genome editing studies.

Other vivax-type NHPMPs

There are several other species of monkey malaria belonging to the *P. vivax* clade that have been less studied than those described above. These include *Plasmodium simiovale, Plasmodium fieldi, Plasmodium hylobati* and *Plasmodium gonderi*. *Plasmodium fieldi* and *P. hylobati* were originally detected in SE Asia, whereas *P. gonderi* is of African origin (Mitsui *et al*. 2010).

Plasmodium simiovale, like *P. vivax* and *P. cynolomgi*, produces hypnozoites (Cogswell *et al*. 1991) and the full-life cycle can be maintained in Old World monkeys using *A. dirus* and *A. maculatus*, but not *A. stephensi* mosquito vectors (Collins and Contacos, 1979). *In vitro* cultures of the exo-erythrocytic cycle are also possible (Millet *et al*. 1994), but no evidence of adaptation of the parasite to growth in *in vitro* blood culture or in Platyrrhine monkeys is available.

Plasmodium gonderi can be transmitted by various Anopheline vectors, including *A. stephensi*, is infective to Old World monkeys (Collins and Contacos, 1980) and can be cultivated *in vitro* (Guo *et al*.

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1983; Millet *et al*. 1990). Like *P. simiovale* it induces relapse in infected monkeys (Collins and Contacos, 1971) and the exoerythrocytic stages have been cultured *in vitro* (Millet *et al*. 1994). However, no complete life-cycle infections could be maintained in more tractable Platyrrhine monkeys (Sullivan *et al*. 2002).

Plasmodium hylobati has been generally neglected and attempts at growing the parasite in Platyrrhine monkeys failed (Collins *et al*. 1981).

USE OF NON-HUMAN PRIMATES INFECTED WITH HUMAN MALARIA

Both major human malaria parasite species, *P. falciparum* and *Plasmodium vivax*, can grow and replicate in non-human primates (usually splenetcomized) with varying degrees of success (Young *et al*. 1975). Splenectomized chimpanzees have been used to produce genetic crosses between *P. falciparum* strains for genetic studies. An initial cross between strains 3D7 and Hb3, produced by Walliker and colleagues (Walliker *et al*. 1987) led to the discovery of mutations associated with pyrimethamine resistance (Peterson *et al*. 1988). A second cross (between strains Dd2 and Hb3) was performed to study the basis of chloroquine resistance (Wellems *et al*. 1990), which later led to the discovery of mutations in the chloroquine resistance transporter gene (crt) and their association with drug resistance (Fidock *et al*. 2000). The same cross was also used to uncover the genetic basis of sulfadoxine resistance (Wang *et al*. 1997). More recently, what is presumed to be the last ever malaria cross to be produced in chimpanzees, was conducted using an artemisinin-resistant strain of *P. falciparum* (Miles *et al*. 2015).

Human malaria parasite infections in monkeys have been used to discover parasite antigens. One of the most prominent studies involved the discovery of a new family of reticulocyte-specific ligands expressed by *P. vivax* merozoites infecting splenectomized squirrel monkeys (Galinski *et al*. 1992). Homologues of these genes were found in other malaria parasite species, including *P. falciparum* (*P. falciparum* reticulocyte-binding protein homologues, PfRh) and are essential for red blood cell invasion (Cowman and Crabb, 2006). A more recently discovered member of this family, PfRh5 (Baum *et al*. 2009), has recently been tested in a vaccine trial in *Aotus* monkeys and showed strong, strain-transcending protective immunity (Douglas *et al*. 2015). Indeed, *Aotus* monkey models represent a useful model for testing the efficacy of putative malaria vaccines (Herrera *et al*. 2002; Curtidor *et al*. 2015).

Testing of novel antimalarial compounds also relies heavily on the use of *P. vivax*- and *P. falciparum*- infected monkeys (Powers and Jacobs, 1972; Rossan *et al*. 1975; Bitonti *et al*. 1988; Nayar *et al*. 1997; Wengelnik *et al*. 2002; Ye *et al*. 2013). Indeed, many efforts have been undertaken to adapt strains of human malaria to growth in monkeys for the purpose of drug testing (Herrera *et al*. 2002; Obaldía *et al*. 2009).

Relapse in *P. vivax* and other malaria parasite species is caused by the hypnozoite stage. This stage was originally discovered in rhesus macaques infected with *P. cynomolgi* (Krotoski *et al*. 1982*a*) and later demonstrated in chimpanzees infected with *P. vivax* sporozoites (Krotoski *et al*. 1982*b*). Non-human primate hosts are still crucial to understand both hypnozoite biology and genetics and also to develop novel antimalarial treatments (Joyner *et al*. 2015).

Concluding remarks

Plasmodium knowlesi and, to a lesser extent, *P. cynomolgi* are the two most commonly used NHPMP species used in experimental laboratory research on malaria. This is justified by their zoonotic potential (particularly in the case of *P. knowlesi*, which may represent a fifth species of human malaria), their adaptation to *in vitro* culture and to growth in Platyrrhine monkeys, the availability of reference genomes and of established protocols for transfection studies.

However, while *P. cynomolgi* shares many features with *P. vivax*, none of the other macaque species share such a close phenotypic similarity to severe *P. falciparum,* with the possible exception of *P. knowlesi* in certain hosts (Cox-Singh and Culleton, 2015). Unfortunately, the strict host specificity of most Laverania species severely constrains their development as model organisms. However, among the less studied NHPMP species, there are alternative models for severe and cerebral malaria that bear striking similarities with *P. falciparum* infections, such as *P. fragile* and *P. coatneyi*. Both species can be maintained *in vitro*, while *P. fragile* can also be maintained in Platyrrhine monkeys and a draft genome exists for *P. coatneyi*. No genome project is currently available for *P. fragile*, which is rather surprising given the existence of a strain incapable of producing infective gametocytes, a phenotype of prominent biological interest.

While *P. cynomolgi* represents the model most suited to study *P. vivax, P. simium,* due to its close relationship to and possible derivation from *P. vivax*, could provide valuable insights into the evolution of zoonosis and host adaptation.

Finally, *P. brasilianum* and *P. inui* represent potential models for quartan malaria, though the capacity of *P. malariae* to establish infection in Platyrrhine monkeys makes their development less essential. Nonetheless, *P. brasilianum* represents a possible adaptation of *P. malariae* to Platyrrhine monkeys and the assembly and annotation of its genome could provide answers to the questions surrounding its origin.

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To conclude, while the use of *P. knowlesi* as the major malaria model in monkeys is justified by resource availability, ease of use and zoonotic threat, other NHPMPs deserve attention for their capacity to model various and diverse aspects of human malaria. As with all scientific endeavour, picking the right tools for a particular experiment is crucial and, with the diversity of phenotypes provided by the NHPMPs, we are blessed with a well-stocked tool shed.

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