A Case for the Replacement of Primates in Malaria Vaccine Research

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Malaria is a parasitic infection that kills 1–2 million people each year. Non-human primates (hereafter 'primates') have been used in malaria research for three decades. Here, evidence from a review is presented, which highlights the new and existing models and techniques that can be applied in malaria vaccine research as alternatives to the use of primates. This indicates that malaria represents a rational example of a biomedical field where primate use could be phased out in the short to medium term.

Primate Model Problems

Over the past 30 years of research, the relevance of the primate models has been questioned (1; 2), e.g. the first subunit malaria vaccine (Spf66), failed to show convincing protection during human clinical trials (3), despite initial positive indications in owl monkeys (4).

[1] **Heppner, D.G. *et al.*** (2001). *Trends Parasitol.* 17, 419–425; [2] **Riley, E.** (1997). *J. Pharm. Pharmacol.* 49(Suppl. 2), 21–27; [3] **Alessandro, U. *et al.*** (1995). *Lancet* 346, 462–467; [4] **Patarroyo, M.E. *et al.*** (1987). *Nature* 328, 629–632.

In Vitro Models

More than 10 years ago, an *in vitro* system was reported that provides a novel way in which to study the interactions between the human immune system and the malarial parasite (1). Indeed, studies on the human $CD4^+$ T-cell system may be an invaluable correlate of protective immunity to malaria, and could be a key model for use in the development of vaccines (2). It was also demonstrated that certain T-cell niches may react to specific parasite antigen (3), and thus have important implications for the selection of vaccine antigens.


http://www.histologia.cm-uj.krakow.pl/index.html

Similarly, although in the past it was impossible to study the developmental biology of the liver stages of the malarial parasite life-cycle *in vitro*, improvements in human liver cell culture mean that these cells can now facilitate comparative studies, and, with further development, may also provide a means of studying gene expression in sporozoites and of identifying novel liver-stage vaccine candidates (4). Recent developments in this field mean that it is now also possible to cultivate certain stages of the *P. vivax* life cycle *in vitro*, and work continues to achieve long-term cultivation (5).

[1] **Binh, V.Q. *et al.*** (1997). *Am. J. Trop. Med. Hyg.* 57, 594-600; [2] **Bergmann, E.S. *et al.*** (1997). *Cell. Immunol.* 180, 143–152; [3] **Toure-Balde, A. *et al.***(1996). *Infect. Immun.* 64, 744–750; [4] **Sattabongkot, J. *et al.*** (1994). *P. Natl. Acad. Sci. USA* 91, 9866–9870; [5] **Udomsangpetch, R. *et al.*** (2008). *Trends Parasitol.* 24, 85-88.

Genetically Modified Mouse Models

SCID (severe combined immunodeficiency) mouse models, implanted with human Hep G2 cells, are susceptible to infection by the mammalian parasite, *P. berghei* (1). These cells can therefore be used *in vitro* to increase understanding of the intra-hepatic stages of the parasite's life-cycle, thus eliminating the need for certain studies in primates.


http://www.lightmatter.net/gallery/albums.php

[1] **Butcher, G.A. *et al.*** (1993). *Exp. Parasitol.* 77, 257-60.

Genomics

Publication of the *P. falciparum* (1) and *P. yoelii* (2) genomes, and the launch of the *Plasmodium* database (3), have paved the way for genomics-related technologies, recombinant DNA and cell engineering, in order to reveal the genes and pathways involved in human malarial infections. This has begun to yield a number of possible targets for vaccine development (4). These developments are also leading to new techniques for studying the malarial parasite and its interactions, such as imaging technologies that allow the visualisation of individual malarial parasite molecules in living cells (5).

New technologies and post-genomic analysis can be used to explain species differences that have confounded the development of efficacious vaccines against human malarial infections. Such an approach can be used to address the fundamental question of whether primate models are relevant to human malaria. Indeed, *Nature* recently featured articles on the genomes of *P. vivax* (6) and *P. knowlesi* (7) that may provide further important insight.

[1] **Gardner, M.J. *et al.*** (2002). *Nature* 419, 498–511; [2] **Carlton, J.M. *et al.*** (2008). *Nature* 455, 757-763; [3] **Kissinger, J.C. *et al.*** (2002). *Nature* 419, 490-492; [4] **Winzeler, E.A.** (2008). *Nature* 455, 751-756; [5] **Gershon, D.** (2002). *Nature*, 419, 4–5; [6] **Carlton, J.M. *et al.*** (2002). *Nature* 419, 512–519; [7] **Pain, A. *et al.*** (2008). *Nature* 455, 799-804.

Conclusion

The current genetic focus highlights the specificity of the parasite to its human host, and may result in certain primate models becoming less and less relevant, e.g. a recently developed genetically modified whole parasite malaria vaccine is expected to be tested in a human-sporozoite challenge model (1).

There is a wealth of existing methods that could be implemented as primate replacements, as well as ongoing development of further cell-based models, genetic approaches and human-based testing. Therefore, malaria vaccine development represents a rational example of a target field, where, with appropriate investment in the development and validation of alternatives, primate use could realistically be phased out in the near future.

[1] Mueller, A.K. *et al* (2005). *Nature* 433, 164-167;

For further information on replacing primates in malaria and other fields of research please see the *Replacing Primates in Medical Research* report.

Available from: www.focusonalternatives.org.uk