Is there a Role for Autoimmunity in Immune Protection against Malaria?

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Much remains to be known about the mechanisms involved in protective immunity against malaria and the way it is acquired. This is probably the reason why, in spite of so much progress, it has not yet been possible to develop an anti-malaria vaccine able to induce parasite specific antibodies (Ab) and/or T-cells.

It has been considered in the early 80s that the induction of efficient protection against the blood stage forms of *Plasmodium falciparum* would not be possible without simultaneously eliciting an autoimmune (AI) response against erythrocytes, even at the price of inducing an AI pathology. Despite the description of the reciprocal relationship, i.e. the protective effect of malaria on the development of AI diseases – demonstrated since 1970 – no effort has been made to verify the possible involvement of the AI response in protection against malaria.

With this end in view – and in the light of the knowledge acquired in autoimmunity and the existence of the so called “natural” (not associated with pathology) autoantibodies – we propose to examine the hypothesis that the participation of the AI response (not necessarily restricted to autologous erythrocyte antigens) in the immune protection against malaria is possible or even necessary.

Key words: malaria - *Plasmodium* - autoimmunity - autoantibodies - immune protection - premunition - vaccination

Immunology arose as an individualised discipline at the end of the XIX century with the works of Pasteur, establishing the basis of reproducibility and the rational basis for the expansion of vaccination: the artificial process of immunisation against infectious diseases. This strategy was based on the observation that several viral and bacterial diseases affect individuals only once: after primo-infection the individual was “exempt from the charge” of a second infection (etymology of the words “immune” and “immunity”).

During the first half of the XX century, a significant number of bacterial and viral vaccines was produced by technologies that progressed only slowly. To take an example: the vaccine that permitted the eradication of smallpox at the end of the 70s was, in reality, achieved by inoculation, in man, of the virus of the cowpox bovine disease (the vaccinia) that presents the property of cross-protection with human smallpox. Such procedure was not safe and was even capable of inducing secondary reactions, some of which being very severe.

This methodology has been progressively replaced by the use of killed, inactivated or attenuated live pathogens. Progresses in biochemistry, immunology and molecular biology during the last years allowed the use of vaccines composed of purified or recombinant proteins. The lesson resulting from this technological development, however, is that (with the exception of tetanous toxoid) we have only learnt to produce vaccines corresponding to diseases for which there is a “natural” – disease induced – immunity. We left to “later on” (and the “later on” never arrived!) the production of vaccines for diseases against which nature does not know (or knows very imperfectly) how to immunise. Among them one can easily include parasitic diseases – by definition, due to organisms very well adapted to their hosts. From an immunological point of view, this adaptation includes, among other parasite “escape-mechanisms” (intracellular parasitism, immunosuppression, polyclonal lymphocyte activation...) “molecular mimicry”, expressed as a very marked phenomenon of antigen sharing between parasites and...
hosts. This “strategy” corresponds, in reality, to the selection of parasites best adapted to their environment. In this way, those having on their surface the largest number of antigens (Ag) mimicking host Ag would have less risk of being recognised as “foreigners” and of being rejected and therefore more chances of living a long-lasting cohabitation with the organism from which they obtain food as “professional opportunist”. Our opinion is precisely that, in order to obtain efficient protection against plasmodial (or even other protozoan or parasite) infection, at least part of the immune response generated against the parasite must simultaneously recognise host-parasite shared Ag, thus constituting an AI response (an immunological response directed against components of its own organism i.e. “self” or autoantigens – AAgs). As we shall see in the development of the paper, it is also possible that autoantibodies (AAbs – antibodies directed against self) are not necessarily parasite reactive but are rather specific of parasite ligants on erythrocyte and/or of parasite derived material (phospholipid?) endowed with properties of mitogenicity or tumour necrosis factor (TNF) induction. The general idea has been considered in the past by Jayawardena et al. (1979) – according to whom part of the malaria associated IgM response would be constituted by “protective AAbs” – and developed subsequently by Jarra (1983). According to the latter, the induction of protective immunity against intra-erythrocytic forms of Plasmodia would not be possible without the triggering of an immunological response to autologous red blood cell (RBC) components, which may simultaneously induce immunopathology. However, so far, no research effort has been made in order to verify this possibility.

In the present work we show that the relationship between autoimmunity and malaria is not an exceptional phenomenon. We discuss data showing that the immunological response against AAgs is in fact induced in mammals during the process of acquisition of anti-toxic and/or anti-parasite natural-immunity. We draw attention to the evidence now available that autoreactivity can indeed be acquired (or even aimed at) in the design of immuno-prophylatic procedure so that the protection of humans against malaria can be effective. A set of experiments, that could help to test this hypothesis, is finally proposed in conclusion.

AUTOIMMUNITY IN THE COURSE OF MALARIA INFECTION

Little data indicate that some of the clinical manifestations of malaria can result from an AI process (Sorensen et al. 1984, Wozencraft et al. 1990). On the other hand, numerous biological signs of autoimmunisation are apparent in the course of acute disease or among individuals chronically exposed to infection. These signs relate to AAgs such as double and single stranded DNA (Quakcy et al. 1979, Daniel-Ribeiro et al. 1984b, Zouali et al. 1986), erythrocyte (Facer et al. 1979, Facer 1980, Lefrançois et al. 1981, 1982), lymphocyte (De Souza & Playfair 1983), phospholipid (Bate et al. 1992a, b, Facer & Agiostratidou 1994, Bordmann et al. 1998), ribonucleoprotein (Greenwood et al. 1970a, Daniel-Ribeiro et al. 1983, 1991, Zouali et al. 1986), RNA (Kreier & Dilley 1969), and smooth muscle (Quacky et al. 1979, Daniel-Ribeiro et al. 1991) Ag and not to relate to organ-specific partially sequestered AAgs such as thyroglobulin (Daniel-Ribeiro et al. 1984a). This suggests that the formed AAb would result from specific activation of autoreactive B-lymphocytes and not from the activation of these cells within the framework of a generalised polyclonal B-cell activation (PBA) (Daniel-Ribeiro et al. 1984a, Daniel-Ribeiro 1988). We have proposed (Burger-Rolland et al. 1992) that the specificity of the process is the consequence of a “two signal” mechanism of cellular activation, depending both on the presence of immunogenic amounts of the corresponding AAgs (signal 1) and on parasite mitogens (Freeman & Parish 1978, Kataaha et al. 1984) able to replace the second signal usually delivered by T Cells that – in the case of AI responses – are under efficient and stringent control.

It seems also that the specificity of produced AAb differs according to the degree of anti-toxic or anti-parasite immunity. In this way, anti-nuclear Ab (ANA) are often observed in immune animals and among individuals chronically exposed to infection (Poels et al. 1980, Daniel-Ribeiro et al. 1983), while smooth muscle Ab (SMA) are detected in the course of the acute infection (Quakcy et al. 1979, Poels et al. 1980, Ben-Slama 1982, Daniel-Ribeiro et al. 1991). Since it has been clearly shown in man, at least as far as ANA and anti-SMA are concerned, that the production of AAb during malaria does not depend on racial factors (Voller et al. 1972, Daniel-Ribeiro et al. 1991), these observations suggest the existence of a correlation between autoreactivity and immune-protection or degree of exposure to malaria.

In the same way, the existence and the pattern of AI response seem to be related to the clinical form of the disease and/or to the virulence of the Plasmo-
induced by the injection of cross-reacting rat RBC also those directed against autologous erythrocytes can suppress not only anti-lymphocyte responses but cells from mice infected with the non-lethal strain, reactivity with other AI responses. In fact, spleen cells from mice infected with the non-lethal strain, can suppress not only anti-lymphocyte responses but also those directed against autologous erythrocytes induced by the injection of cross-reacting rat RBC in normal mice (Playfair et al. 1985).

**DOES AUTOIMMUNITY PROTECT AGAINST MALARIA?**

Jaywardena et al. (1979) first proposed that part of the malaria associated IgM response could be constituted by “protective AAb” directed to RBC modified determinants or against crypto-Ag exposed at the erythrocyte membrane, as a consequence of the parasitisation. While admitting not knowing precisely how AAb could act at the level of RBC to limit parasite growth, these authors assumed that alterations of the erythrocyte membrane induced by AAb could contribute to the control of the primary infection.

This possibility has practically not been studied so far, but the hypothesis was taken-up again by Jarra (1983). According to him anti-erythrocyte autoreactivity could be an essential component of protective immunity against Plasmodium blood stages, even though it could also cause immunopathology.

The AI response against RBC in the course of malaria infection has indeed been demonstrated on several occasions in humans (Facer et al. 1979, Facer 1980, Lefrançois et al. 1981, 1982). Zouali et al. (1982) showed that Africans living in malaria hyper-endemic areas as well as Europeans presenting an acute episode of the disease, had high titres of Ab directed to T-erythrocyte crypto-Ag that are only exposed after enzymatic treatment of RBC. In the same way, it has been shown that experimental P. berghei infection is accompanied by an important B-cell response against bromelin-treated mouse RBC (Rosenberg 1978).

Jarra (1983) also admitted that the intra-erythrocytic development of Plasmodium could induce cellular membrane alterations (expression of neo-Ag and exposition of crypto-Ag) leading to the rupture of immune tolerance to AAg or modified AAg. This author used serological and immunocytochemical studies to show that sera from P. berghei infected or immune mice had Ab to iso-Ag determinants of the parasitised RBC. Ag specifically associated with paratisized erythrocyte was revealed – in absorption studies – to be closely associated with erythrocyte Ag at the surface membrane.

One alternative, and not conventional, manner of explaining anti-erythrocyte autoimmunity has been proposed by Sayles and Wasson (1992); according to these authors anti-RBC AAb could be anti-idiotypic Ab reacting with anti-plasmodial Ab specific for parasite ligands of erythrocyte receptors.

However, the RBC specific AI response during malaria infection has always been proposed to explain the anaemia, that in spite of the intra-erythrocytic parasitism, is not related to the importance of the parasitaemia and can arise even in the absence of any circulating parasite. The originality of Jayawardena and collaborators and of Jarra has thus been to propose a protective role for these AAb. Literature effectively provides a certain number of arguments supporting this hypothesis and suggests that it should not be restricted to the anti-erythrocyte AAb.

The extensive RBC modification and destruction, artificially generated by treatment of mice with phenylhydrazine is in fact followed by an increase in immunity against *P. chabaudi* infection. On the other hand, the induction of anti-erythrocytic AAb in mice by the injection of cross-reacting rat RBC, failed to augment immunity against malaria (Jarra 1983).

A very interesting work (Hogh et al. 1994) concerned the immune response developed against band 3 neo-Ag of *P. falciparum*-infected erythrocyte. Ab against these Ag block the cytoadherence of infected RBC. At present it is not known whether reactivity to these Ag simply reflects the exposure to the malaria parasite or is correlated with protective immunity. However, children and adults living in an area of intense malaria transmission showed a much higher reactivity with the band 3 peptides than those from non-immune individuals. High reactivity to the loop 3 peptides was correlated with lower mean parasite density in children in the 5- to 9-year-old age group. Inversely, higher than average reactivities against loop 3 and 7 peptides were positively correlated with high hematocrit values, indicating that these Ab are not involved in haemolysis (through autoimmunity) and, on the contrary, suggesting that they can be involved in protection.

Besides anti-erythrocyte Ab, the AAb observed during the course of malaria are those that classi-
cally accompany non-organ specific AI diseases, such as systemic lupus erythematosus (SLE). In addition to ANA (quoted above) the presence of anti-phospholipid (PL) Ab, responsible for false positive Wasserman reactions and also known as anti-cardiolipin (CL) Ab, have also been reported in malaria. A potential role for anti-PL AAb in the anti-malaria protective (anti-toxic as well as anti-parasite) immunity can be better understood if the following observations are taken into account: (i) parasite phospholipids may induce the expression of inflammatory cytokine such as TNF (Bate et al. 1992a), (ii) anti-PL AAb may modulate the synthesis of TNF in mice (Bate et al. 1992b), (iii) immunisation of mice with phospholipids, such as phosphatidylethanolamine, induces partial protection against the infection by *P. chabaudi* (Bordmann et al. 1998), and (iv) Gambian children with cerebral malaria presented significantly less IgM anti-phosphatidylinositol Ab than those with non severe malaria (Facer & Agiostratidou 1994). In another study however, Soni et al. (1993) could not find any correlation between levels of anti-CL Ab, parasitaemia, severity of disease or cerebral manifestations and splenomegaly even though these Ab were observed at frequencies and titres significantly higher among malarious than among control individuals.

It is obvious that, if it is claimed that an AI response can act on parasites, the existence of cross-reactions between AAg and parasite Ag should be detected. A close relationship between these Ag has already been demonstrated even with the aid of parasite specific monoclonal Ab (Daniel-Ribeiro et al. 1984c). Work presently being undertaken in our laboratory showing that sera from AI patients as well as mouse monoclonal AAb react with different *P. falciparum* isolates represent additional evidence to the existence of Ag sharing by host and parasite. Such cross-reactions could also be at the origin of false positive reactions of diagnostic (dipstick) tests which use Ag considered parasite specific, such as the histidine rich protein-2Ag of *P. falciparum* (Laferi et al. 1997).

Work done at the Pasteur Institute (Ternynck et al. 1991) shows that mice experimentally infected with *P. chabaudi* develop, simultaneously to a marked degree of PBA, intense immunological activity against actin, myoglobin, myosin, spectrin and tubulin AAg as well as against trinitrophenylated (TNP)-ovalbumin. The response, detected at the level of RBC membrane Ag (such as spectrin and band 3 Ag) as well as of Ag studied on fibroblast preparations (such as tubulin, actin and the 70 Kd heat shock protein) persisted for several weeks after parasite clearance before returning to pre-infection values. Following a challenge with parasitised erythrocytes, and curiously after injection of normal RBC to animals that had already cleared the parasitaemia, a similar increase of AAb was consistently observed. The polyreactivity of these “natural” AAb must be emphasised: after absorption and elution from infected mouse RBC or affinity-purification on a mouse tubulin immunoadsorbent, they react with all Ag of the panel including parasite extracts.

It must also be stressed that malaria, like certain types of AI diseases such as SLE, is a disease associated with a marked PBA phenomenon and that, for this reason, a given phenomenon may be more easily demonstrated if investigated at the level of responses seemingly secondary to the network of immunological interactions potentiated by the PBA effect. One example could be the cross-reactions between idiotypic, plasmodial and heterologous Ag, already demonstrated (Daniel-Ribeiro et al. 1992).

**CAN ANTI-PARASITE ANTIBODIES PRESENT AN AUTOANTIBODY ACTIVITY WITHOUT BEING HARMFUL TO THE ORGANISM?**

A fundamental question that needs to be clarified, concerns the possibility of induction of an efficient protective response (as an anti-parasite heterologous response) but inoffensive to the organism (as an AI response). Indeed, when Jarra (1983) considered that, in order to be effective, the immune response against the parasite would need to include an AI response, he admitted that this could even be at the risk of inducing an immunopathology. Studies published so far, lead us to believe that this is not necessarily the case.

Although this is still a matter of discussion (Dighiero 1997) it may be considered that two types of AAb (or of cellular AI responses) exist. One type corresponds to the AAb which accompany the AI diseases (let us call them pathogenic AAb). Examples are anti-DNA Ab or ANA associated with SLE, anti-erythrocyte AAb of the AI haemolytic anaemias, rheumatoid factors of rheumatoid arthritis (RA), anti-thyroid and anti-thyroglobulin AAb associated with AI thyroiditis; to cite only a few (Bach 1993). The second type comprises the so-called “natural AAb” described by the team of Avrameas at the Pasteur Institute of Paris (Guilbert et al. 1982, Dighiero et al. 1982). These AAb, present in all normal individuals, are characterised by such a degree of polyreactivity that they can be completely absorbed, regardless of their basic reactivity, by successive affinity purification on immunoadsorbent with only three Ag: DNA, TNP and actin (Dighiero, pers. commun.).

Dighiero (1997) considers that although “self-reactive”, the natural AAb (as well as the patho-
The most important argument in favour of the idea that the AAb may not be associated with any immunopathology is based on the work done by Avrameas and Dighiero’s group (Dighiero et al. 1982, 1983). These authors were able to study 612 monoclonal proteins from patients with multiple myeloma or Waldenstron macroglobulinaemia and demonstrated that 36 of them presented a natural AAb activity (actin for 32 of them, DNA, thyroglobulin) without evidence of any clinical manifestation of AI disease.

Thus, the detection of these natural AAb at high frequencies and levels among malaria infected mice (Ternynck et al. 1991) could indicate the attempt of the infected organism to mobilise the relevant immune response for its defence. This could also explain – at any rate, in part – the severity of the experimental infection of the CBA/N mice, incapable of developing AAb against bromelin treated mouse RBC (Jayawardena at al. 1979). These mice are deficient in CD5+ B cells – believed to be the source of virtually all natural AAb (Sidman et al. 1986).

It is also important to draw attention to the fact that the AAb formed in the course of several infectious and parasitic diseases, and those encountered in AI diseases often recognise the same AAg, but have neither the same fine specificity nor the same biological properties, even though they often share idiotypes in common and even similar structures.

In this respect, reference should be made to the work done by Lloyd et al. (1994) comparing monoclonal AAb obtained from AI mice with those produced by splenocytes of P. berghei infected animals. While presenting public idotype of the same family as those usually encountered in anti-DNA AAb associated with SLE and other AI diseases, the latter presented specificities different from those of the first group and reacted also with parasite infected erythrocytes.

In the same way it has been observed that anti-PL AAb present different profiles of epitopic specificities in syphilis, malaria, and a subset of thrombotic lupic patients, although presenting comparable anti-CL activity (Colaço & Male 1985). Similarly, Hunt et al. (1992) reported that purified anti-CL AAb from AI patients reacted with a plasma protein binding to β2 glycoprotein I in contrast with those isolated from patients with malaria, infectious mononucleosis, tuberculosis, hepatitis A or syphilis that did not require the presence of this ligand to react with CL. The AAb from the first group, and not those from infected patients, were associated with thrombotic complications.

**PROTECTION OFFERED BY MALARIA AGAINST THE DEVELOPMENT OF AUTOIMMUNE DISEASES**

A last set of arguments showing that the AI response in malaria is not necessarily harmful, is based on epidemiological observations. Taking into account simply the existence of a protection of autoimmunity against malaria and a *fortiori* if this effect were indissociable from the induction of an AI pathology, an increase in the frequency of AI diseases (including SLE, prototype of AI disease) in malaria hyperendemic areas, should logically be observed. But this is not the case.

More than 30 years ago Greenwood (1968) observed, on the contrary, that the lists of admission to a Nigerian hospital presented few cases of AI diseases. Only 104 out of 98,454 admissions were classified as AI diseases, including 2 SLE and 42 RA, considerably less (respectively 4 and 6 times) than the figures expected for European populations. Greenwood (1968) proposed that parasitic diseases – especially malaria – could prevent the development of AI diseases. In contrast with the relatively low frequency in West Africans, SLE is more common in the American black population – originating particularly from West Africa – than in white American individuals (Lee & Siegel 1976, Symmons 1995). Following Greenwood’s initial epidemiological observation, an original work by Greenwood et al. (1970b) showed that experimental malarial infection was able to prevent the spontaneous development of the SLE like AI disease frequently present in NZBxNZW F1 hybrid mice.

For a long time, this interesting and striking information was neglected until recent progress in the knowledge of immunological mechanisms involved in the malaria pathogenesis and of factors predisposing to SLE, showed that a possible link between these diseases could involve TNF (Jacob & McDevitt 1988, Butcher & Clark 1990, Butcher 1991, Adebajo 1992, Jacob 1992). Individuals presenting class-II HLA Ag (DR2, DQW1) which predispose to the development of SLE and of which monocytes are low *in vitro* producers of TNF, develop lupic nephritis in contrast with those who also have a genetic predisposition (DR3) but produce a high level of TNF. In addition, the low TNF producer individuals predisposed to nephritis are...
protected from this condition by repeated TNF injections. Butcher (1991) postulated that the absence of malaria leads to a decreased TNF production, increasing the risk of SLE development (this would be the reason for the greater frequency in the American black population).

However, TNF is certainly not the sole way whereby malaria would prevent or retard SLE development. Studying also the experimental model of NZBxNZW mice, Hentati et al. (1994) were able to observe a 6-month delay in the occurrence of SLE in \( P. \) \textit{chabaudi} infected mice. The injection of polyclonal IgG or IgM or of cryoglobulin from infected mice had the same property, although less marked. Compared to normal Ig, the polyclonal Ig had an increased quantity of natural AAb bearing the D23 idiotypes characteristic of natural polyreactive AAb with anti-Fc and anti-Fab activities. The level of anti-DNA AAb, particularly those of the IgG1 isotype, in the mice surviving the development of the AI diseases was diminished. The authors concluded that malarial infection induces the synthesis of IgG and IgM natural AAb endowed with immunoregulating properties able to restore at least temporarily the natural AAb network which is deficient in B/W mice and thus to prevent the development of AI disease. In other words, they could be meaning to suggest that AI diseases are not caused by an excess of “bad” AAb but rather by a lack of the “good” ones.

Malaria associated autoimmunity can also be prevented by the injection of cryoglobulin (obtained from infected mice) prior to \( P. \) \textit{berghei} experimental infection. The animals thus treated developed lower levels of circulating immune-complexes and of AAb against nuclear and cytoplasmatic Ag and did not produce cryoglobulin. This is a long-lasting effect, since the administration of cryoglobulin has an identical effect 10 days or 9 months before injection, suggesting that the malaria could be actively immunised against the production of AAb (Fawcett et al. 1989).

**PROPOSED EXPERIMENTS**

To contribute to further knowledge of the interactions between AI phenomena and anti-parasite immune protection, certain experiments should be envisaged. We hereby propose some which could help to demonstrate a protective effect of autoimmunity against malaria.

- To characterise the existence of cross-reactions between parasite and host antigens by studying the reactivity of monoclonal AAb (or Ab produced during the acute phase of AI diseases) against parasite Ag (or corresponding synthetic peptides), and the reactivity of parasite specific Ab against AAg.

This could be achieved by immunoblotting technique (Towbin & Gordon 1984) using parasite total extracts (and normal erythrocyte control extracts) or by ELISA with the aid of different synthetic peptides corresponding to parasite Ag, specially those suspected of being involved in immunoprotection. It might be important to include in the study the overall Igs produced in the course of malaria as well as of AI diseases – and not solely those with an AAb or an anti-parasite evidenced activity – since this strategy could allow the evaluation of other Ab (anti-idiotypic for instance) mobilised in response to the aggressor phenomenon.

- To study the effect of IgG showing AAb activity (and/or obtained from patients with active or inactive SLE or RA) alone or in the presence of human monocytes (MØ) on the \textit{in vitro} growth of \( P. \) \textit{falciparum} (Trager & Jensen 1976).

It has been effectively demonstrated that the serum from adult individuals living in malarial endemic areas for sufficiently long periods to acquire clinical immunity (premunition), can inhibit the \textit{in vitro} \( P. \) \textit{falciparum} growth (Wilson & Philips 1976). In addition, Bouharoun-Taoun and Druilhe (1992) have demonstrated that IgG from immune individuals presented various degrees of capacity to inhibit the \textit{in vitro} proliferation of \( P. \) \textit{falciparum} in the presence of normal monocytes and, that this activity, so called Ab dependent cell inhibition (ADCI), was in the IgG1 and IgG3 fractions of the immune sera.

- To study the evolution of \( P. \) \textit{yoelii} experimental malaria in mice spontaneously developing a SLE like AI disease (NZB, F1 NZBxNZW, NRL/1, BxSB).

If the AI response can effectively act against \textit{Plasmodia}, it can be assumed that spontaneously AI mice could control the development of parasitaemia more effectively than normal animals (with similar genetic background) or even than young animals of the same strain (before the age of AI disease development).

- To study, in a model of experimental malaria induced (serum transferable) immune-protection (\( P. \) \textit{yoelii}-CBA mice – Jayawardena et al. 1978, \( P. \) \textit{chabaudi}-C3H mice – Lima et al. 1991), the effect of prior absorption of serum by AAg, on the transferred protection.

Absorption on tissue AAg or by immunopurification using immunoadsorbants coated with Ag recognized by natural AAb (actin, thyroglobulin, DNA) must be provided. A neutralizing effect on protection observed after absorption would imply an autoreactivity of anti-parasite protective Ab and constitute strong evidence of the existence of the proposed mechanism.
Traditionally, immunology accepts as a paradigm that the immunisation of individuals, for the purpose of vaccination, must not result in the induction of an AI response. The questioning of this notion and, inversely, the demonstration of a beneficial role of autoimmunity in the process of acquiring protective anti-parasitic immunity could justify the elaboration of new strategies for the immunoprophylactic approach of parasitic disease control in the future. Some of the experiments described above are being undertaken in our laboratory and can bring more light to this approach of the immune protection against malaria.

ACKNOWLEDGEMENTS

To Graziela Zanini and Marjolein Snippe for help in the editorial work, to Mrs Stella Albaret for reviewing the English text, and to Dr LF Souza Passos for his valuable comments and criticism.

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