Control of Malaria by Bio-Therapeutics and Drug Delivery Systems

Mohammed M Al-Qaraghuli1,2*, Mohammad A Obeid1,3, Omar Aldulaimi4,5 and Valerie A Ferro1

1Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, UK
2Department of Chemical and Process Engineering, University of Strathclyde, 78 Montrose Street, Glasgow, G1 1XJ, UK
3Department of Pharmacy, Yarmouk University, Irbid, Jordan
4College of Pharmacy, Al-Mustansiriyah University, Baghdad, Iraq
5Institute for Science and Technology in Medicine, Keele University, Staffordshire ST5 5BG, UK

Abstract

Malaria is a ubiquitous disease that can affect more than 40% of the world’s population who live with some risk of contracting this disease. The World Health Organization (WHO) has recently highlighted the high spread of this disease in Sub-Saharan Africa. Despite the considerable fall in mortality rate over the past decade, the development of resistance against main treatment strategies still exists. This problem has provoked scientific efforts to develop various treatment strategies including use of vaccines, drug delivery systems, and biotherapeutics approaches.

A vaccination strategy is being implemented to trigger direct clearance of the causative parasites from the human host. However, the complex life-cycle of Plasmodium parasites with continuous antigenic mutations has partly hindered this approach so far. The application of different types of drug delivery systems for the delivery of anti-malarial drugs is also being considered in order to improve the efficacy, pharmacokinetics, tolerability, and reduce toxicity of existing anti-malarial drugs. A third approach has emerged from the high success of antibodies to treat complex diseases like cancer and autoimmune diseases. Various antibody engineering methods and formats have been proposed to tackle the notable sophisticated lifecycle of malaria. Within the malaria research field, the characteristics of these diverse treatment strategies, individually, are broadly acknowledged. This review article considers the current status of these approaches and the future outlook.

Keywords: Immuno-conjugates; Antibodies; Drug delivery; Vaccines; Malaria

Introduction

Malaria is an infectious disease that is caused by the parasite Plasmodium. This transmissible disease affects around 200 million annually, killing about 650,000 people per year, especially children less than 5 years old living in sub-Saharan Africa [1]. The WHO 2015 Fact Sheet reported that over 15 years from 2000-2015, there was a global reduction in malaria incidence rates and mortality by 37% and 60%, respectively. However, the subsequent Fact Sheet in 2016 confirmed the emergence of parasite resistance to antimalarial medicines and mosquito resistance to insecticides, which could trigger a rise in global malaria mortality if ignored.

The five main parasite species in this respect are P. vivax, P. knowlesi, P. ovale, P. malariae, and P. falciparum; the latter represents the most lethal [2]. The parasite life cycle in humans typically begins by injection of sporozoites via the skin, which can then migrate to hepatocytes in less than one hour [3], where they replicate and generate merozoites. These merozoites complete the journey to erythrocyts of the patient (clinical stage), and then differentiate into gametocytes that eventually reach the parasite holder (the mosquito) through infected human blood [4].

Various reports have indicated the growth in malaria mortality rate, due to emergence and spread of multidrug-resistant P. falciparum against established antimalarial compounds [5,6]. Moreover, therapeutic failure of some anti-malarial medications has been attributed to their toxic side effects as well as their inconvenient dosing schedules. Therefore, there is an urgent requirement to identify new treatment strategies against malaria [7]. These approaches have been directed towards enhancing the characterisation of natural products, adaptation of effective vaccine and drug delivery strategies, and the development of specific biotherapeutic agents [8-13]. The main objective of this article is to review the anti-malarial role of bio-therapeutic formulations, and to evaluate their potential as effective treatments to malaria in the future.

Literature Review

Vaccines and immune-conjugates

Significant efforts have been dedicated over the past decades to develop vaccines that can protect humans against malaria parasites. Vaccine development has been directed to different infection stages including transmission blocking vaccines, pre-erythrocytic vaccines, and blood-stage vaccines; these have been reviewed comprehensively for both P. falciparum and P. Vivax [14-16]. Generally, vaccines have either been subunits of well-defined and conserved parasite antigens, or whole attenuated sporozoites. The most advanced malaria vaccine (RTS, S: Mosquitix TM) is currently in Phase III clinical trial, and contains the conserved central repeat and C-terminal regions of the P. falciparum circumsporozoite protein (CSP) that is expressed on sporozoites in early liver stages [17,18]. Despite this advancement, vaccine development against malaria has been dishearteningly hindered by the complex life cycle of the parasites, which results in several morphological changes and displays antigenic variations.

*Corresponding authors: Mohammed M Al-Qaraghuli, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, UK, Tel: +44 (0)141 548 2176; E-mail: mohammed.al-qaraghuli@strath.ac.uk

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Immono-conjugation refers to the use of a delivery system to deliver a conjugated drug to facilitate its delivery into a target tissue. An example of this strategy is the delivery of Angiopep-2 conjugated paclitaxel through the use of the low-density lipoprotein receptor related protein (LRP) as a carrier. This contrasts with the concept of drug delivery systems that can be used with either conjugated or unconjugated drugs [19]. Immuno-conjugation strategies can be used as "Trojan-horses" for specific delivery of antimalarial drugs, to reduce the emergence of resistant strains, and curtail the adverse drug reactions and toxicity of these medicines. This approach is broadly implemented in various medical applications, especially to target cancer cells [19-22]. Generally, anti-malarial conjugates can be fermented to the infected host cells by parenteral routes through either passive or active targeting [23]. Passive targeting has been accomplished by conventional nano-carriers such as micelles, liposomes and polymersomes [24-27]. Whilst, active targeting can be achieved by functionalisation of the nano-carriers with specific biomolecules such as antibodies, proteins, or peptides [23].

Considering the peculiarities of erythrocytes, liposomal nanocarriers are premeditated as a promising approach for the targeted delivery of antimalarial drugs [28]. For instance, artesunate and lumefantrine were co-loaded into nanostructured lipid carriers, and their antiplasmodial effect was evaluated [29]. Similarly, curcuminoid-loaded liposomes in combination with arteether has prevented the recrudescence of malaria in mice [30]. An advancement to liposomal research was actualised through the introduction of staring molecules based on polymersomes for blocking invasion, and causing augmented drug delivery systems for the delivery of anti-malarial agents are summarised such as collagen and chitosan [46-48]. The most commonly used emulsions, poly (lactide-co-glycolide) (PLGA), and natural polymers like starch or cellulose acetate butyrate [24-27].

Table 1: Outline of the anti-malarial drug delivery systems.

<table>
<thead>
<tr>
<th>Anti-malarial drugs</th>
<th>Delivery system used</th>
<th>Purpose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artesunate</td>
<td>Liposomes</td>
<td>Improve patient compliance for multiple administrations</td>
<td>[50]</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Dendrimers</td>
<td>Reduce chloroquine toxicity</td>
<td>[53]</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Liposomes</td>
<td>Reduce primaquine toxicity</td>
<td>[56]</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Chylomicron emulsion</td>
<td>Target primaquine to hepatocytes</td>
<td>[10]</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Polysisohexylcyanacrylate (PHCA) nanoparticles</td>
<td>Reduce primaquine toxicity</td>
<td>[57]</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Oral lipid nanoemulsion</td>
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<td>[58]</td>
</tr>
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<td>Chloroquine</td>
<td>PEGylated poly-L-lysine-based dendrimers</td>
<td>To induce controlled and sustained delivery</td>
<td>[142]</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>PEGylated neutral and cationic liposomes</td>
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<td>Chloroquine</td>
<td>Amidated pectin hydrogel beads</td>
<td>Delay the release of oral chloroquine to distal parts of the gastrointestinal tract</td>
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<tr>
<td>Chloroquine</td>
<td>Poly (amidoadamines) drug conjugates</td>
<td>Selectively deliver chloroquine to Plasmodium-infected red blood cells</td>
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<td>Monensin</td>
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<td>Improving the anti-malarial activity of monensin</td>
<td>[147]</td>
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Table 1: Outline of the anti-malarial drug delivery systems.

Liposomes are the most extensively studied system for the delivery of different therapeutic agents. As lipid based nanoparticles, they are formed by the self-assembly of their lipid components into bilayer structures encapsulating an aqueous moiety. This results in a versatile structure in which hydrophilic drugs can be encapsulated in the inner aqueous core while hydrophobic agents will be embedded in the lipid bilayer structure [49]. Several research groups have investigated the use of liposomal formulations for the delivery of different antimalarial
agents in order to improve their pharmacokinetics or therapeutic index. Gabriels et al. developed a formulation that can improve patient compliance towards artesunate, which is an anti-malarial agent that requires frequent administration due to its rapid elimination, through the use of liposomes [50]. They developed a slow release preparation by encapsulating artesunate into liposomes containing egg phosphatidylcholine/cholesterol in a molar ratio of 4.3 [50].

Chloroquine (CQ) is an effective anti-malarial drug against all five species of parasites. The activity of CQ is thought to take place in the parasite’s acidic digestive vacuole (DV) against the intraerythrocytic stage of the human malaria parasite [51]. However, inside the acidic DV, CQ becomes protonated and less membrane-permeable leading to its accumulation in the DV with subsequent efflux out of the DV, away from its primary site of accumulation and action, and reduction in the anti-malarial activity of CQ [52]. In order to reduce the efflux of CQ from DV, chitosan-tripolyphosphate (CS-TPP) nanoparticles (NPs) were conjugated to CQ and examined in Swiss mice infected with attenuated of P. berghei [11]. These NPs were demonstrated to act as an effective formulation, eliminating parasites, while protecting lymphocytes, serum and red blood cells against P. berghei infection at a dose of 250 mg/kg body weight for 15 days treatment. Another approach was adopted using galactose coated polylysine dendrimers loaded with CQ, and haemolytic toxicity was drastically reduced by at least 50% through a sustained drug release behaviour compared to free CQ both in vitro and in vivo [53].

Primaquine (PQ) is another anti-malarial drug which exerts a broad-spectrum activity against various stages of parasitic malaria. PQ targets latent liver stage of malaria infection caused by different plasmodia such as P. vivax and P. ovale [54]. Moreover, PQ is also prescribed for terminal prophylaxis to prevent infection by P. falciparum and P. vivax. However, PQ can cause severe tissue toxicity including haematological and gastrointestinal related side effects [55]. PQ targeting of the liver, would possibly help to reduce therapeutic dose and subsequently its dose related toxic effects. Encapsulation of PQ in different delivery systems such as liposomes was initially designed, and shown to significantly increase the LD50 and LD90 in mice, as a result of changing the distribution pattern of PQ after encapsulation [56]. In an attempt to target PQ to hepatocytes, Dierling et al. encapsulated PQ into chylomicron emulsion, with an average particle size of 180 nm, which led to significantly enhanced accumulation of PQ in the liver compared to free PQ [10]. Whilst the in vitro anti-leishmanial activity of PQ-loaded polysaccharide-cholesterol (PiHCA) NPs showed a 21-fold increase in ED50 compared with free PQ [57]. Moreover, when PQ was incorporated into an oral inert lipid nanoemulsion, PQ exhibited improved oral bioavailability, and was taken up preferentially by the liver with a drug concentration 45% higher than the free PQ. This resulted in a 25% lower dose required to achieve effective antimalarial activity against P. berghei infection in Swiss albino mice compared to free oral doses of PQ [58]. Other systems investigated for PQ delivery include dendrimeric NPs [59], poly (lactide) NPs [60], and the use of gum arabic microspheres [61].

**Anti-malarial antibodies**

Alternatively, the active targeting of malaria parasites can be achieved using antibodies, which has high proven efficacy against cancer and several other autoimmune diseases [62-65]. The antimalarial drug CQ showed improved efficacy when delivered inside immunoliposomes targeted with the pRBC-specific monoclonal antibody BM1234 [28]. Likewise, CQ-loaded MAbs F10-liposomes were able to clear not only CQ-susceptible, but also CQ-resistant parasites in mice [66]. Antibodies are glycoproteins belonging to the immunoglobulin (Ig) superfamily, and have been widely used in different biomedical applications. The antibody molecule is structurally composed of two heavy and two light polypeptide chains, linked together by disulphide bonds [67]. One light chain type (λ or κ) can be linked to one heavy chain (μ, δ, 1- 4, a1-2, or ε) to create any of the nine antibody subclasses in humans (IgM, IgD, IgG1-4, IgA1-2, or IgE) [68-72]. Functionally, an antibody consists of three fragments: a fragment crystallisable region (Fc) that represents the stem of the “Y” shaped molecule, and two fragment antigen binding (Fab) regions (Figures 1A-1D). While the Fab fragments are responsible for antigen binding, the Fc fragment interacts with other elements of the immune system including Fc-receptors (FcRs), pattern recognition receptors (PRR), and components of the complement cascade, to promote removal of the antigen from tissues [73,74]. Within the Fab region, each of the variable heavy (VH) or light (VL) chains consist of three complementarity determining regions (CDRs), which are accountable for antigen recognition [75].

Antibodies are prominent immune modulators that bridge innate and acquired immunity, and therefore, can be effective against micro-organisms, if they do not mediate a direct biological effect within the infection process [76]. This perception has sustained their candidacy to combat malaria by, for instance, curtailing the damage associated with any inappropriate host inflammatory responses [77]. The role of antibodies in malaria protection can also be attributed to inhibition of merozoite invasion of erythrocytes [78], antibody-mediated phagocytosis through FcR and complement pathways [79], and antibody-dependent cellular inhibition [80,81]. Both autoantibodies and antibody immune complexes can drive B-cell responses, through the PRR toll-like receptor-9, and support their potential in malaria [82]. Several years of repeated infections are, however, required to develop protective responses to malaria [83], in defiance of the critical importance of humoral immunity in the development of acquired immunity to malaria [84,85]. Variation of surface antigens and antigenic diversity facilitates the development of recurrent infections over the years, as new infections seem to exploit gaps in the repertoire of variant-specific antibodies [84,86]. P. falciparum expressed antigens on erythrocyte surfaces, for instance, appear to be highly polymorphic and undergo clonal antigenic diversity, and antibodies against these antigens typically inaugurate a high degree of strain specificity [87,88].
Previous studies have acknowledged the fact that upon exposure to a new malaria infection, parasite-specific antibody levels rise noticeably within 1-2 weeks [89,90]. The boosted antibodies then reduce quickly after the infection is controlled, and accordingly signify that protective memory for a specific antibody response is either not provoked or is being debilitated [91]. Passive transfer of IgG from immune African adults to African children was observed to be highly effective against malaria parasites [80,92]. Furthermore, transfer of serum from partially immune individuals to non-immune persons induces significant antimalarial activity [92,93]. This anti-malarial response was verified to be associated with malaria specific antibodies [94,95]. Nevertheless, serum therapy is notoriously correlated with high difficulty of finding a sufficient number of donors, possibility of transferring other infectious diseases, and the impracticality of dealing with human blood products. In addition, sera normally consist of polyclonal antibodies, which might contain numerous nonspecific antibodies [96,97]. Consequently, serum treatment is associated with several limitations, and adoption of a bespoke antibody engineering approach is essential to match the sophisticated life cycle of this parasite and the scale of this ubiquitous disease.

Amongst the four IgG subclasses, anti-malarial protective antibodies are restricted to a panel of IgG1 and IgG3 subclasses [81]. The IgG2 subclass can compete with IgG1 and IgG3, and interfere with their protection effectiveness [98], although others have suggested IgG2 antibodies participate in protection if individuals possess a rare mutated allele encoding an Fc gamma receptor-type IIa (FcyRIIA) that can bind IgG2, IgG3, and IgG1 subclasses [99]. On the other hand, IgG4 antibodies are considered as completely non-protective [98,100-102]. Subsequently, the IgG3 subclass is epitomised as the prevailing isotype of antibody responses incarnated with protection against malaria [101-103]. The propagated antibodies were primarily of the IgG2a and IgG3 subclasses [104,105]. In addition, immunisation with an antigen preparation derived from P. falciparum merozoite surface protein (MSP)-1 has induced a shift to IgG2b [106], even though most protein antigens in a murine model are expected to induce IgG1 antibodies. Interestingly, mouse IgG2b is to a certain degree the equivalent of human IgG3 [107], and has a shorter half-life than other mouse IgG subclasses [108]. Consequently, a human vaccine aimed at eliciting antibody protection against blood-stage P. falciparum would preferentially generate IgG1 and/or IgG3 antibody responses against the selected candidate antigens, and downregulate a concomitant IgG4 and IgG2 antibody response. Therefore, an anti-malarial vaccine should ideally be administered in combination with an adjuvant that stimulates the production of cytokines, such as interleukin (IL)-10 and/or transforming growth factor (TGF)-β [109,110], in target cells to switch Ig responses to IgG1 and IgG3.

Along with IgG class, other Ig classes were explored to envisage whether infection with Plasmodium parasites can be preferentially inhibited. The therapeutic inappropriateness of IgE antibodies to treat malaria was commonly suggested, due to their observed role in malaria pathogenesis [111,112]. Nevertheless, a reduced risk of subsequent malaria infection was also linked to the existence of high levels of parasite-specific IgE antibodies [113]. Pentameric IgM antibodies were additionally implemented as an adjuvant for malaria vaccine development, through their ability to stimulate the development of acquired T-cell immunity [114]. Whilst the ability to steer IgA antibodies to target FcRn have shown remarkable potential in eliminating serum pathogens [115]. Re-appraisal of the role of IgA in malaria infections is necessary, since Plasmodium-specific IgA antibodies were detected at high levels in human's breast milk [116,117] and serum [118].

Different antibody formats can be accouted to neutralise Plasmodium parasites, ranging from a full monoclonal antibody (mAb) to smaller fragments including Fab, a single chain antibody (scFv), or even a single domain antibody (sdAb) (Figures 1 and 2). Whole mAbs are time-honoured bio-therapeutic molecules, through their ability to maximise the benefits of activating the cellular response by Fc regions [119]. In the murine malaria model, the recruitment of effector cells by Fc is vital, as the passive transfer of specific antibodies to malarial MSP1 could not impede death in FcR-deficient and immunodeficient models [81,120]. However, the utilisation of mAbs in malaria might be inappropriate per se, especially if these antibodies interact with the incongruously inhibitory FcRs [115]. Moreover, high concentrations of antimalarial mAbs are requisite to compete for FcRs binding with infection induced low-affinity polyclonal antibodies [121]. These low-affinity antibodies were developed against short highly repetitive amino acid sequences, cross-reactive with several malarial antigens, and might be generated from a process of immune evasion [122].

In order to develop a "magic bullet" that would specifically neutralise and eradicate invading microbes, like malaria parasites, various antibody engineering approaches and formats have been investigated. This includes bispecific antibodies (BsAbs) that were developed to recognise both P. yoelii MSP1 and human FcyRI [9]. Another bispecific scFv combination, linked by a flexible peptide linker (Gly4-Ser)3, has been developed to target P. falciparum blood-stage malaria parasites, by linking CD3 antigen of human T-cells and MSP1 [123]. Even a trispecific antibody has been developed in the malaria field, as previously involved in cancer treatment development, to link two potential targets of malaria (merozoite surface protein 1

Figure 2: Binding site topography and CDRs orientation. CDRs orientation of Fab (PDB ID: 2J5L), VH (PDB ID: 4GFT), and VNA (PDB ID: 1VES) domains were examined as top (T) and side (S) views. The CDR regions were colour coded for CDR1: red, CDR2: green, CDR3: blue, HV2 (1VES VNAR): yellow, and HV4 (1VES VNA): magenta, CDR1L (2J5L) cyan, CDR1L2 (2J5L) orange, CDR3L (2J5L) violet. The PDB entries of these crystal structures are depicted at the lower corner of each picture. Structures were viewed by PyMOL 1.3 (academic version).
Table 2: Summary of the crystal structures retrieved from the PDB PIRH5. *P. falciparum* reticulocyte binding protein homologue 5; *Pvs25*: *P. vivax* P25 protein; AMA-1: *Malarial Apical Membrane Antigen-1*; PIEBA-175: *P. falciparum* EBA-175; MSP1: *Merozoite surface protein 1*; MyoA- MTIP: myosin A- myosin tail interaction protein; Fab: fragment antigen-binding; VNAR: single variable new antigen receptor domain antibody fragments; VH: variable domain of heavy chain antibodies.

<table>
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<tr>
<th>S. No.</th>
<th>PDB entry</th>
<th>Resolution (Å)</th>
<th>Species</th>
<th>Format</th>
<th>Target</th>
<th>Reference</th>
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</table>

**Discussion**

Malaria is a highly infectious disease that has diminished the lives of millions around the globe. Treatment strategies to date are based on either natural/synthetic small molecules, or macromolecules such as vaccines and antibodies. Most treatment approaches have been hindered by the complex life-cycle of the parasite that has continuously caused the emergence of drug-resistant species. Despite this unprecedented difficulty, several promising drug delivery approaches, vaccines, and antibody formats have been developed to tackle this fatal disease. Future research should be directed to find new antimalarial candidates with either new mechanisms of action, resistance modifying actions or target novel metabolic pathways that are essential for parasite survival and applying new tools for designing these drugs. In addition, more novel combinations of small molecules or micro-macro complexes should be implemented as combination strategies or antibody-small molecule drug conjugates to synergise the treatment effect.

**Conclusion**

In order to achieve this objective, additional funding is required to support the drug discovery process academically, and to attract pharmaceutical companies to invest within this highly pandemic, but not very commercially-attractive field.

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