Puzzling and ambivalent roles of malarial infections in cancer development and progression

ERIC FAURE*

Aix-Marseille Université, CNRS, Centrale Marseille, I2M, UMR-7373, 13453 Marseille, France

(*Received 15 July 2016; revised 6 August 2016; accepted 10 August 2016; first published online 13 September 2016*)

SUMMARY

Scientific evidence strongly suggests that parasites are directly or indirectly associated with carcinogenesis in humans. However, studies have also indicated that parasites or their products might confer resistance to tumour growth. *Plasmodium* protozoa, the causative agents of malaria, exemplify the ambivalent link between parasites and cancer. Positive relationships between malaria and virus-associated cancers are relatively well-documented; for example, malaria can reactivate the Epstein-Barr Virus, which is the known cause of endemic Burkitt lymphoma. Nevertheless, possible anti-tumour properties of malaria have also been reported and, interestingly, this disease has long been thought to be beneficial to patients suffering from cancers. Current knowledge of the potential pro- and anti-cancer roles of malaria suggests that, contrary to other eukaryotic parasites affecting humans, *Plasmodium*-related cancers are principally lymphoproliferative disorders and attributable to virus reactivation, whereas, similar to other eukaryotic parasites, the anti-tumour effects of malaria are primarily associated with carcinomas and certain sarcomas. Moreover, malarial infection significantly suppresses murine cancer growth by inducing both innate and specific adaptive anti-tumour responses. This review aims to present an update regarding the ambivalent association between malaria and cancer, and further studies may open future pathways to develop novel strategies for anti-cancer therapies.

Key words: Malaria, *Plasmodium*, parasitic infection, carcinogenesis, anti-carcinogenic effect, fever therapy, Burkitt lymphoma, Epstein-Barr virus, Kaposi sarcoma.

INTRODUCTION

More than 1400 parasite species, including viruses, bacteria, fungi, protozoa, helminths and nematodes, infect humans (Taylor *et al*. 2001), and worldwide, slightly more than 20% of the global cancer burden is attributable to infectious agents (viruses, bacteria and eukaryotic parasites) (de Martel *et al*. 2012). Moreover, two viruses (Epstein-Barr Virus (EBV) and Human herpesvirus 8, also known as Kaposi's sarcoma-associated herpes virus), which are cancer-causing agents, exhibit complex relationship with malaria (Thakker and Verma, 2016; Thorley-Lawson *et al*. 2016). Certain eukaryotic parasites may also play a critical role in human oncogenesis (e.g. Gupta *et al*. 2015; Reddy and Fried, 2015; Machicado and Marcos, 2016). Conversely, several reports indicate that pathogens, including eukaryotic parasites, may elicit anti-tumour immune responses that lead to protection against tumourigenesis (reviewed in Oikonomopoulou *et al*. 2013, 2014; Darani *et al*. 2016). To date, the factors influencing the bi-directional influence of infectious eukaryotic agents on carcinogenesis are not well understood.

Malaria parasites are among the very few infectious agents known to exert a possible bi-directional role on carcinogenesis (e.g. IARC, 2014; Deng *et al*. 2016). Malaria is likely the oldest documented disease affecting humans; some of the earliest medical writings from China and Assyria accurately describe malaria-like intermittent fevers (Neghina *et al*. 2010). Four species of *Plasmodium* (Protozoa: Apicomplexa) have long been recognized to infect humans: *Plasmodium falciparum* responsible of the most dangerous forms of malaria, *Plasmodium vivax* and *Plasmodium ovale* cause benign tertian malaria, *Plasmodium malariae* causes benign quartan disease (Igweh, 2012; Roucaute *et al*. 2014). Despite concerted efforts to reduce the deleterious impact of malaria, worldwide morbidity and mortality in 2015 were estimated at approximately 210 million and 0·44 million, respectively (WHO, 2015). Furthermore, in accordance with the old thinking, which assumed that malaria was beneficial to patients suffering from diseases, including cancers, the anti-tumourigenic potential of *Plasmodium* was recently investigated (e.g. Chen *et al*. 2011; Deng *et al*. 2016). Moreover, the mechanisms underlying the involvement of *P. falciparum* in oncogenesis are only just starting to be better understood (Thorley-Lawson *et al*. 2016). This paper reviews data concerning the bi-directional role of malaria in cancer and its relevance to cancer prevention and therapy.

PRO- AND ANTI-TUMOURIGENESIS ASSOCIATED WITH EUKARYOTIC PARASITE INFECTIONS

To the current knowledge, approximately half a dozen eukaryotic parasites are more or less directly

* Corresponding author: Aix-Marseille Université, CNRS, Centrale Marseille, I2M, UMR-7373, 13453 Marseille, France. E-mail: eric.faure@univ-amu.fr

Parasitology (2016), **143**, 1811–1823.
doi:10.1017/S0031182016001591

associated with human carcinogenesis, including Platyhelminths, Nematoda and Protozoa (e.g. Benamrouz *et al*. 2012; Oikonomopoulou *et al*. 2013; Gupta *et al*. 2015; Reddy and Fried, 2015); however, for certain parasites further evidence is required to elucidate cause-effect relationships (e.g. Machicado and Marcos, 2016). Non-eukaryotic pathogens can directly influence tumourigenesis, while eukaryotic parasites primarily appear to indirectly promote carcinogenesis (e.g. Oikonomopoulou *et al*. 2013; Machicado and Marcos, 2016). As noted by Machicado and Marcos (2016), the mechanisms of eukaryotic parasite-induced cancer included 'chronic inflammation, sustained proliferation, modulation of the host immune system, reprogramming of glucose metabolism and redox signalling, induction of genomic instability and destabilization of suppressor tumour proteins, stimulation of angiogenesis, resisting cell death and activation of invasion and metastasis'.

Conversely, several observations reported as early as the 1700s support a link between infection and cancer prevention or regression (reviewed in Oikonomopoulou *et al*. 2013; Darani *et al*. 2016). These observations were generally made in the context of bacterial diseases, but a few rare cases involved eukaryotic infections (reviewed in Hoption Cann *et al*. 2006; Kucerova and Cervinkova, 2016). Several recent epidemiological investigations demonstrated an inverse association between various acute infectious diseases, or even fever alone, and cancer risk (reviewed in Kienley, 2012). It is now known that hyperthermia can directly induce tumour cell necrosis and apoptosis (Kienley, 2012). Moreover, studies have revealed the complex modifying effects of fever and elevated temperature on the host response, cytokine levels, immune surveillance and anti-tumour activity (reviewed in Kienley, 2012). In addition, the suppression or regression of neoplastic growth through the application of infectious agents has been observed for bacterial pathogens but also for commensal bacteria (Hu *et al*. 2015) and there is evidence that certain microbial products (e.g. lipopolysaccharides) and vaccines exert anti-tumour effects (Oikonomopoulou *et al*. 2013). These examples show that fever-independent mechanisms may also play an anti-oncogenic role.

In the past two decades, adverse relationships between certain eukaryotic parasitic infections and human cancers have been reported by different research groups. For example, the anti-cancer activities of parasites belonging to several taxonomic groups (Euglenozoa, Protozoa, Nematoda, Amoebozoa and Platyhelminth) have been observed during *in vitro* investigations and/or in experimental animals (Alizadeh *et al*. 1994; Darani *et al*. 2009; Chookami *et al*. 2015; Sofronic-Milosavljevic *et al*. 2015; Ubillos *et al*. 2016; Wang and Gao, 2016). Moreover, parasites that exhibit anti-tumour potential might also be associated with the induction of carcinogenesis, such as the Platyhelminth *Echinococcus granulosus* and the Apicomplexa *Toxoplasma gondii* (Lun *et al*. 2015; Turhan *et al*. 2015; Machicado and Marcos, 2016), which exemplifies the ambivalent link between parasites and cancer. Throughout the course of parasitic infections, anti-tumour effects may be mediated by several mechanisms (e.g. reviewed in Oikonomopoulou *et al*. 2013, 2014). It is outside the scope of this study to perform an exhaustive review of these anti-tumour mechanisms; however, a brief summary is provided. The majority of these mechanisms imply interactions with the host immune system. Parasites may indeed influence the fine balance between immunosuppression and immunity against a tumour by modulating the availability and presentation of cross-reactive antigens, influencing the induction of pre-existing immunity and shaping the components of the tumour microenvironment (e.g. Daneshpour *et al*. 2016). Parasitic infections can also induce anti-inflammatory responses. As observed for helminths, this is often achieved with a balanced Th1/Th2 response or *via* the activation of immune regulatory pathways involving immune suppressive cells such as regulatory T (Treg) cells as well as immune regulatory cytokines (reviewed in Oikonomopoulou *et al*. 2013, 2014). Parasitic infections may also induce a high-level immune surveillance state and increase the antigenicity of nascent tumour cells. Moreover, infections can induce the inhibition of angiogenesis, which leads to a reduction in tumour growth as experimentally shown during *T. gondii* infection using a murine model (Kim *et al*. 2007). In addition, antigenic similarities exist between various tumours and certain parasites such as *E. granulosus*, and anti-tumour effects may be associated with these similarities (Chookami *et al*. 2015).

MALARIA, AN OLD PUTATIVE REMEDY AGAINST MENTAL AILMENTS AND INFECTIOUS DISEASES

The idea that intermittent fevers can have a curative effect dates back to classical antiquity (Faure, 2014), in the Hippocratic Corpus dated back to the 5th-4th centuries BC it was mentioned that quartan fevers cure convulsions and epilepsy (Adams, 1849, p. 751; Temkin, 1945, p. 46). The supposed beneficial influence of malaria against various types of mental diseases was noted by several physicians throughout the centuries that followed (Whitrow, 1990; Duffell, 2001). Furthermore, since the end of the 19th century, physicians have pointed to the supposed therapeutic value of malaria inoculation against infectious diseases. From the 1920s to the mid-1940s, a therapeutic strategy employing malarial inoculation for the treatment of patients with neuro-syphilis was used in both Europe and North America (Snounou and Pérignon, 2013). Few patients were definitively cured, and others

https://doi.org/10.1017/S0031182016001591 Published online by Cambridge University Press

demonstrated only partial remission. Therapeutic strategies involving malarial inoculation were also tested against other infectious diseases, although generally without convincing success (Snounou and Pérignon, 2013; Faure, 2014). It is now believed that the relative effectiveness of malaria against certain infectious bacterial diseases is attributable to the increase in body temperature, creating unfavourable conditions for parasites (Snounou and Pérignon, 2013). Currently, the use of malaria therapy has not been completely abandoned by all physicians. In the 1980s–1990s, *P. vivax* was injected into patients with late-stage Lyme disease (Heimlich, 1990; Anonymous, 1991*a*, *b*) and into HIV-infected individuals. However, these practices were risky, *P. vivax* can be associated with the development of severe diseases with complications (Wassmer *et al.* 2015) and their effectiveness was unproven (Chege *et al.* 2014).

POSSIBLE IMPLICATIONS OF MALARIA IN CARCINOGENESIS

The notion of a positive association between malaria and cancer has existed for more than three centuries (Durand-Fardel, 1868, p. 260; Deaderick, 1909). A possible empirical link had been established between malarial hepatomegaly, a type of morbidity frequently associated with this disease, and increased liver size during cancer. However, in two studies from Southeast Asia, no significant association was observed between malaria and primary hepatocellular carcinoma (Welsh *et al.* 1976; Lu *et al.* 1988). Nevertheless, there is evidence supporting a critical role for malarial infections in other types of cancer, as described below.

Burkitt lymphoma

The association between *P. falciparum* malaria and endemic Burkitt's lymphoma (eBL), which is a type of non-Hodgkin's lymphoma, was noted in Africa more than 50 years ago, when the co-occurrence of this cancer and highly malaria-endemic areas was first observed (reviewed in Thorley-Lawson *et al.* 2016). This cancer is aetiologically related to a member of the herpesvirus family (EBV) (National Toxicology Program, 2016). However, the precise mechanisms of *P. falciparum*'s involvement in lymphomagenesis are only just beginning to be better understood (Thorley-Lawson *et al.* 2016). Malaria-induced immunosuppression ('immunomodulation' may be more appropriate (Cunnington and Riley, 2010)) plays a deleterious role in EBV lymphomagenesis, permitting, *inter alia*, an increasing viral load in EBV-infected cells (IARC, 2014; Torgbor *et al.* 2014). More importantly, *P. falciparum* exerts several effects focused on germinal centre B cells, where eBL originates (Torgbor *et al.* 2014). Indirectly, *P. falciparum* induces the DNA-mutating and double-strand-breaking enzyme activation-induced cytidine deaminase, which is responsible for somatic hypermutation in B cells when they enter the germinal centre (Torgbor *et al.* 2014). This genomic instability protects the B cells, including those infected with EBV, from apoptosis (Torgbor *et al.* 2014). *In vitro* experiments employing a *Plasmodium chabaudi* mouse model of malaria have shown that chronic infection deregulates the expression of the cytidine deaminase gene, leading to DNA damage and translocations; ultimately, this might induce lymphomas in the absence of viral infection (Robbiani *et al.* 2015). In addition to eBL, EBV infection has been observed in other human malignancies, including lymphatic and haematological tumours such as Hodgkin's disease, T cell lymphoma and NK cell lymphoma and certain epithelial cancers, such as nasopharyngeal and gastric carcinomas (National Toxicology Program, 2016). In all cases, the nature of EBV infection in infected cancer cells is predominantly latent. The relationships between EBV, malaria and these types of cancer are not well understood.

Nasopharyngeal carcinoma (NPC)

NPC is found predominantly in Southeast Asia and tropical Africa; its aetiology is multifactorial and includes, among other factors, prior infection with EBV (Chu *et al.* 2008). Only two studies, carried out in Southeast Asia, suggest a possible association between malarial infection and the aetiology of NPC. The first study showed that patients with high titres of anti-malarial antibodies also had high titres of an EBV-associated antibody that is diagnostic for NPC (Yadav and Prasad, 1984); however, the tested dataset comprised only 22 patients with NPC. In the second study, a history of malarial infection was significantly associated with NPC in males only, and this NPC was related to high levels of anti-EBV antibodies (Chen *et al.* 1990). However, according to the working group of the IARC (2014), the reliability and specificity of recall for historically remote infections (i.e. a self-reported history of malaria) may be very uncertain, raising concern about exposure misclassification.

Kaposi sarcoma (KS)

Human herpesvirus 8 (HHV8) is the causal agent of all clinical forms of KS, even if infection with this virus alone is not sufficient to cause this cancer (Thakker and Verma, 2016). An immunodeficient state is one of the most important cofactors predisposing an HHV8-infected person to KS, as observed during HIV co-infection (Thakker and Verma, 2016). Non-HIV related KS named classical Kaposi sarcoma (cKS) is a rare indolent neoplasm that is more common among people of Mediterranean

https://doi.org/10.1017/S0031182016001591 Published online by Cambridge University Press

origin and Jews of Ashkenazi descent (Wahman *et al.* 1991). KS is a highly angiogenic and invasive tumour often involving diverse organ sites, including skin, visceral organs and oral cavity. Despite intensive studies, the histogenesis of KS (and cKS) tumour cells remains an enigma, it has been suggested that KS has an early stage of polyclonal reactive-inflammatory-angiogenic hyperplastic lesion, which progress to a monoclonal true sarcoma stage (Patrikidou *et al.* 2009).

Surprisingly, some studies (Geddes *et al.* 1995; Cottoni *et al.* 1997; see comments in IARC, 2014), although not all (Serraino *et al.* 2003; Cottoni *et al.* 2006), have suggested a positive link between malaria and Kaposi cancer in former malaria-endemic areas of Italy. These investigations examined people living (and/or born) in these regions before malaria eradication. In Italy, the campaign to eradicate malaria from the entire national territory was virtually ended in 1948; thus, if some of the conclusions are valid, the risk of cKS was increased 30 or more years after individuals had been exposed during their childhood. This would imply that either the viruses infecting individuals with malaria during their childhood had a greater chance to be reactivated several decades later or that malaria infection during childhood induced a state permitting virus reactivation after several decades. Moreover, the study of Geddes *et al.* (1995) suggests that *P. vivax* might be a more effective co-factor than *P. falciparum*.

Currently, HHV8 infection is highly prevalent in sub-Saharan African countries where malaria is endemic (reviewed in Nascimento, 2014); moreover, there is a co-incidence of aggressive forms of cKS in *P. falciparum* malaria-endemic regions (Conant and Kaleeba, 2013). Wakeham *et al.* (2011, 2013) showed that in Uganda, where malaria is highly endemic, positivity for malarial antibodies is strongly associated with HHV8 both in mothers and their children. In this country, these results have been recently confirmed (Nalwoga *et al.* 2015). Outside Africa, high HHV8 seroprevalence has been reported among populations of the Amazon region of Brazil, a malaria-endemic area. In this area, positivity for a history of malaria is highly associated with high HHV8 seropositivity among non-Amerindians but not among Amerindians; however, according to the authors, this association may have been underestimated in the latter population (Nascimento, 2014). In both African and Amazonian studies, *P. falciparum* is incriminated; however, in the majority of these studies, the lack of direct measurement of malaria and the timing of studies several years after malaria exposure complicate the interpretation of the results. In summary, further epidemiological and experimental laboratory studies are needed to underpin the role of malarial co-infections in the progression of HHV8 pathogenesis. Moreover, to date, experimental evidences demonstrating direct molecular mechanisms of interactions between HHV8 and *Plasmodium* are lacking. HHV8 infections have been linked with other malignancies, such as the lymphoproliferative disorders primary effusion lymphoma and plasmablastic variant of multicentric Castleman's disease (Starita *et al.* 2015; Thakker and Verma, 2016), and the putative correlation between malaria and these diseases should be investigated.

Cervical cancer

Odida *et al.* (2002) reported a geographical correlation in Uganda between malarial endemicity levels and the relative risk of high-grade cervical cancer malignancy (attributable to Human Papilloma Viruses (HPVs)). However, according to the working group of the IARC (2014), 'the completeness of the cancer and population data in this study were uncertain'. Moreover, malaria is not associated with reduced immune responses to the HPV-vaccines (Nakalembe *et al.* 2015) and there is even some evidence that participants with malaria exhibited increased vaccine responses compared with participants without malaria (Brown *et al.* 2014).

Cancers at other sites

Although the implications of viral infections are far from certain, as suggested in Uganda, a positive association between non-Burkitt and non-Hodgkin's lymphomas (NBNHL) and malarial endemicity has been observed; moreover, an elevated frequency of NBNHL demonstrating high-grade malignancy is present in highly malaria-endemic areas (Schmauz *et al.* 1990). In Los Angeles County (USA), an epidemiological case-control study of NBNHLs revealed an excess of patients reporting a history of malaria (Ross *et al.* 1982). In Northern Italy, a relationship between a history of malaria and risk of non-Hodgkin's lymphoma (NHL) but not Hodgkin's disease, was observed (Tavani *et al.* 2000), whereas another Italian study suggested an association between malaria at a young age and 'low grade' lymphatic malignancies, although past episodes of malaria weakly increased the risk of NHL (Vineis *et al.* 2000).

In the USA, a relationship was also observed between both malaria outbreaks and brain tumour incidence as well as all cancer mortality rates; however, the involvement of malaria is questionable and it was hypothesized that *Anopheles* could transmit unknown infectious agent (likely a virus) conferring predisposition to cancer (Lehrer, 2010*a*, *b*). Indeed, mosquito bites can introduce a complex cocktail of up to 60 infectious agents directly into the bloodstream, often resulting in contemporaneous immunosuppression and a multiplicity of co-infections (Benelli *et al.* 2016; Ward *et al.* 2016).

https://doi.org/10.1017/S0031182016001591 Published online by Cambridge University Press

Studies of carcinogenicity in experimental murine animals infected with Plasmodium spp.

A critical analysis of animal models of carcinogenesis associated with malarial infections can be found in the IARC report (2014), which commented almost all the following experiments. Indeed, the analysed experiments involved a certain degree of bias or were not statistically significant; therefore, they are only briefly summarized here. In mice, malarial (*Plasmodium berghei*) infection increased the rate of spontaneous lymphomagenesis (Jerusalem, 1968). However, in mice, on one hand, spontaneous leukaemias occurred, while on the other hand, malarial infection can activate both exogenous and endogenous retroviruses with frequently fatal consequences (Salaman *et al*. 1969; Wedderburn, 1974; Nickell *et al*. 1987). Another report mentioned that into mice, concurrent infection with *P. berghei* increased the incidence of malignant lymphoma during the first 6 months following the injection of an extract of spleen and thymus from mice with lymphoma induced by Moloney leukaemogenic virus (Wedderburn, 1970). Hargis and Malkiel (1979) had observed that sarcomas were induced in neonatal mice *via* the inoculation of simian virus 40 (SV40), and infection with *P. berghei* decreased the latency and increased the incidence and invasiveness of these tumours. Whereas, the more recent study suggested that *Plasmodium yoelii* infection of mice greatly facilitated the growth of a syngeneic virus-induced transplantable lymphoma (Wedderburn *et al*. 1981), this association was not statistically significant; however, once again there is a putative link between malaria and lymphoproliferative diseases. All of these experiments, even under criticism, suggest that it is not possible to exclude a putative link between malarial infection and cancerogenesis *via* virus-related cancer reactivation.

Molecular mechanisms potentially involved in malaria-induced carcinogenesis

To date, only the mechanisms underlying *P. falciparum*'s involvement in endemic Burkitt lymphomagenesis are relatively well understood (reviewed in Thorley-Lawson *et al*. 2016). In the other cases, it is hypothesized that malarial-induced cancers may be the indirect consequences of alterations in normal immune function induced by malaria (IARC, 2014). Indeed, there is strong evidence that malaria can lead to altered immune responses *via* the modulation of both humoral and cell-mediated immunity (Toure-Balde *et al*. 1996; Urban and Todryk, 2006; Weiss *et al*. 2010; Illingworth, *et al*. 2013; Pradhan and Ghosh, 2013; Riley *et al*. 2013). Therefore, *P. falciparum* malaria with subsequent transient immuno-dysfunctions can lead to opportunistic infections in previously immunocompetent patients (Wykes and Good, 2008). Similar effects have been observed during prolonged exposure to *P. vivax* infections in malaria-endemic areas, which are also known to induce immune system dysfunction (Goonewardene *et al*. 1990; reviewed in Longley *et al*. 2016). Transient malaria-induced immune disorders may contribute to the occurrence and severity of viral (and viral-linked cancers such as eBL), bacterial and eukaryotic infections (reviewed in Faure, 2014). Moreover, in mice, the immunodepressive effects of murine *Plasmodium* have also been demonstrated, including during virus co-infections and the immune response to vaccines (Salaman *et al*. 1969; Bomford and Wedderburn, 1973; Tarzaali *et al*. 1977). Both acute and chronic *Plasmodium* malarial mouse infections were accompanied by antigen-specific, as well as non-specific, immunosuppression (McBride *et al*. 1977). In addition, depression of the immunological response persisted for several weeks after recovery from clinical acute infection and during the entire duration of chronic infection (McBride *et al*. 1977). Thus, malaria exposure can facilitate the reactivation of virus-related cancers and perhaps also increase susceptibility to infection, which in turn may lead to increased transmission.

Plasmodium parasites may also be potent mutagens. *Plasmodium falciparum* and murine *P. chabaudi* malarial infections can indirectly induce chromosomal damages (Kusi, 2013; Robbiani *et al*. 2015). In addition, in response to *Plasmodium* infection, phagocytes produce superoxide and other reactive oxygen species (ROS), which can potentially increase the risk of oncogenesis (Eze *et al*. 1990). Moreover, as with other intracellular protists, *Plasmodium* spp. are known to induce apoptosis inhibition, an effect that may be a significant step in the progression to malignancy (Carmen and Sinai, 2007).

MALARIA MAY ALSO POSSESS ANTI-ONCOGENIC PROPERTIES

Empirical reasons justifying the use of malaria-therapy against human cancers

In the past, physicians believed that cancers were extremely rare in patients with infectious diseases principally due to bacterial infections but also, although rarely, to eukaryotic infections (reviewed in Hoption Cann *et al*. 2006; Kucerova and Cervinkova, 2016). Starting in the 17th century, European physicians were convinced of an inverse correlation between malaria and cancer; the first documented case involved the apparently complete remission of a breast cancer after a double attack of double tertian malaria, described in 1775 by the physician Trnka von Krzowitz (1775). After the 1850s, the belief that malaria could exert a protective role against cancer gained renewed interest because it was observed that as malaria progressively disappeared

https://doi.org/10.1017/S0031182016001591 Published online by Cambridge University Press

from areas of Europe that were highly malaria-endemic in the past, the number of cancers increased and it was widely believed that cancer was extremely rare in tropical Africa due to protective effects derived from malaria (Clemow 1903, pp. 71–72). However, at the beginning of the 20th century, an assumption of the beneficial effects of malaria on the incidence of malignant tumours was no longer tenable for several physicians (Setti, 1904; reviewed in von Hansemann, 1914). In addition, more recent studies have confirmed that cancers are not infrequent in Africa as it was previously believed (Parkin *et al*. 2008; Adloye and Grant, 2015).

However, despite the criticism of many physicians (reviewed in von Hansemann, 1914), analogous malaria-therapy strategies for the treatment of neurosyphilis were developed in Western countries in the second half of the 19th century in an attempt to combat various cancers. However, voluntary inoculations with *Plasmodium* to cure cancers were proposed or carried out by only a few physicians (e.g. Kruse, 1901; Loeffler, 1901; Davidson, 1902; Mori, 1902; Orta, 1902; Rovighi, 1902, 1905). This therapeutic strategy was abandoned at the beginning of the 20th century (Clemow 1903, pp. 71–72). However, clinical trials of malaria-therapy on generally terminal cancer patients continued to be sporadically performed as in Germany in the 1920s and from 1950s to 1970 (Braunstein, 1929*a*, *b*, 1931; Zabel, 1970). Moreover, studies examining the effectiveness of *P. vivax* malaria-therapy for the treatment of cancers were carried out at the very end of the 20th century in China (Xiaoping *et al*. 1999). However, *P. vivax* inoculations can be risky and their effectiveness against cancer has not been demonstrated.

Experiments suggesting that malarial infections and malarial proteins may possess anti-oncogenic properties

In mouse model, *P. yoelii* malarial infection slows the tumour growth of one specific type of experimental cancer (Wedderburn *et al*. 1981). In another study, to investigate the effects of malaria-therapy on the growth of murine sarcoma tumour cells, mice were infected with *P. yoelii* on the 2nd day after tumour cell inoculation (Liu *et al*. 2006). Seven days later, tumour diameters in mice in the experiment group were smaller than those of control mice inoculated only with tumour cells. However, the authors themselves concluded that the anti-cancer effects were weak (Liu *et al*. 2006). The results of these two studies are less conclusive than those summarized below.

In an epidemiological study, it has been concluded that there is a relationship between lung cancer mortality and malaria involving inverse growth and decline in certain countries (Zeng and Zhong, 2011) also Chen *et al*. (2011) have conducted various studies to determine if *P. yoelii* infection exerts therapeutic effects against cancer using the murine Lewis lung cancer (LLC) model. Both subcutaneous and intravenous malarial infection inhibited LLC growth and metastasis and prolonged the survival of tumour-bearing mice. Moreover, malarial infection exerted anti-tumour effects by inducing potent innate and adaptive anti-tumour immunity. Malarial infection significantly increased the secretion of IFN-γ and TNF-α, tumour-specific T cell proliferation, the activation of NK cell cytotoxicity activity and infiltration, and the cytolytic activity of $CD8^+$ T cells. Moreover, in infected mice angiogenesis was inhibited in tumours and the number of proliferative cells was decreased, whereas the levels of apoptotic cells were increased. Furthermore, malarial infection enhanced the immune response to an experimental lung cancer DNA vaccine, and the combination produced synergistic effects on both the inhibition of tumour growth and the prolongation of mouse survival. Moreover, tumour-bearing mice infected with malaria developed long-lasting tumour-specific immunity, and malaria-induced anti-cancer effects were stronger in mice with a relatively longer natural disease course (approximately 4 weeks) of *P. yoelii* infection compared with those with short courses of infection (2 weeks, following anti-malarial drug treatment or using *P. chabaudi*) (Chen *et al*. 2011). Interestingly, a recent experiment employing mice infected with genetically attenuated sporozoites of *P. yoelii*, which is a safer approach, confirmed malaria-induced anti-tumour effects involving the induction of both innate and adaptive immunity (Deng *et al*. 2016).

Furthermore, *in vitro* experiments have shown that plasmodial proteins can have direct or indirect anti-oncogenic effects.

The circumsporozoite protein (CSP) of *P. yoelii*, a key component of the sporozoite stage of malaria parasites, can significantly suppress the growth of human colon cancer cells in a dose-dependent manner and induce their apoptosis (Ding *et al*. 2012). CSP appears to have a pleiotropic role as follows: this protein induces the complete blockage of protein synthesis machinery, which can kill cells; moreover, macrophages appear to be particularly sensitive to the presence of this protein in the cytosol, thus providing a mechanism of immune evasion for *Plasmodium* (Frevert *et al*. 1998). The inhibitory role of CSP on the proliferation of cancer cells may be dependent on outcompeting NF-κB nuclear translocation through its nuclear localization signal (NLS) motif (Ding *et al*. 2012) (Fig. 1). However, other mechanisms cannot be excluded, as CSP can also modulate non-NF-κB target genes (Singh *et al*. 2007). Moreover, peptides of *Plasmodium* spp. containing both the CD36 binding region and the NLS motif inhibit *in vitro* protein synthesis by binding to the ribosome

https://doi.org/10.1017/S0031182016001591 Published online by Cambridge University Press

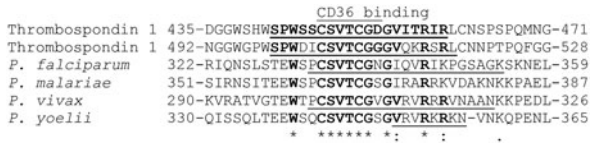

Fig. 1. Alignement between two regions of the human Thrombospondin 1 type 1 repeats and parts of various plasmodial circumsporozoite proteins. The thrombospondin 1 peptides, which inhibit both FGF-2 or VEGF-induced angiogenesis (Iruela-Arispe *et al*. 1999), the NLS domain of *P. yoelii* (Ding *et al*. 2012) and peptides of *P. vivax* and *P. falciparum* analogous from those which inhibit *in vitro* the translation (Frevert *et al*. 1998) have been underlined. A line has been drawn above the amino acids the CD36 binding sequence (reviewed in Lawler, 2002). Human thrombospondin 1 (accession number (acc. n°): AAI36471), *P. falciparum* (acc. n°: AAW78182), *P. vivax* (acc. n°: BAO10674), *P. malariae* (acc. n°: CAA05617) and *P. yoelii* (acc. n°: CDZ10959). Identical amino acids are indicated by asterisks, and partly conserved amino acids are indicated by dots (two-dot regions show a higher degree of similarity). FGF, fibroblast growth factor; NLS, nuclear localization signal; VEGF, vascular endothelial growth factor.

(Frevert *et al*. 1998) (Fig. 1). The NLS region of CSP contains basic (lysine and arginine) amino acids, and another region of the CSP of *P. falciparum* that is particularly rich in arginine also inhibits protein translation (Frevert *et al*. 1998). Native *Plasmodium* CSP and recombinant CSP constructs introduced into the cytoplasm also lead to the inhibition of protein synthesis in mammalian cells. Using this strategy, the parasites can manipulate hepatocyte protein synthesis to meet the requirements of a rapidly developing schizont and destroy macrophages, representing an additional immune evasion mechanism of *Plasmodium* (Frevert *et al*. 1998). Interestingly, a certain region of CSP exhibits strong sequence similarity with the three repeat sequences of the thrombosopondin-1 (TSP-1) type 1 region (Fig. 1). This extracellular matrix glycoprotein can play an anti-angiogenic role with potent anti-tumour effects (Lawler and Detmar, 2004). Synthetic peptides derived from this protein inhibit angiogenesis (Tolsma *et al*. 1993) induced by basic fibroblast growth factor (FGF-2) or vascular endothelial growth factor (VEGF) (Iruela-Arispe *et al*. 1999). More importantly, suppression of tumour growth by TSP-1 has been associated with its ability to inhibit neovascularization (Weinstat-Saslow *et al*. 1994). In a more recent study using epithelial ovarian cancer cells, peptides with only one repeat demonstrated lower pro-apoptotic and anti-proliferation effects than those containing three repeats (Russell *et al*. 2015). In addition, peptides containing the CD36 binding region (CSVTCG (see Fig. 1) or CSTSCG) mediate tumour cell metastasis (Tsuzynski *et al*. 1992); however, it is known that TSP-1 exerts pleiotropic effects, and reversed responses may also be observed depending on the cancer cell type (Pinessi *et al*. 2015).

More recently, Salanti *et al*. (2015) have showed that *P. falciparum*-infected erythrocytes express the plasmodial protein Variant Surface Antigen 2-CSA (VAR2CSA), which binds a distinct type of chondroitin sulphate A (CSA) exclusively synthesized in the placenta and in several types of malignant cells. This observation allowed the investigators to develop a promising strategy to specifically target cancer cells and block tumour growth *in vivo*. This might indirectly provide a new molecular explanation for the putative anti-oncogenic effects of malaria. Indeed, antibodies against VAR2CSA were detected in exposed multigravid women but also in men and children exposed either to *P. falciparum* or *P. vivax* (Gnidehou *et al*. 2014). In addition, the majority of naturally acquired responses target certain a part of VAR2CSA that does not mediate binding to CSA (Barfod *et al*. 2007). Thus, if infected erythrocytes bind to malignant cells and if antibodies recognize VAR2CSA (or other malarial proteins) without blocking CSA adhesion, this may induce the destruction of both the infected erythrocyte and the linked cancerous cell.

DISCUSSION

Pro-carcinogenesis role of malarial infection

Several studies have provided evidence that certain eukaryotic parasites can promote oncogenesis and influence metastasis to distant tissues *via* various mechanisms (reviewed in Oikonomopoulou *et al*. 2013, 2014; Gupta *et al*. 2015; Tripathi *et al*. 2015; Turhan *et al*. 2015; Machicado and Marcos, 2016). Moreover, studies have shown that plasmodial infections may induce DNA damage and apoptosis inhibition, which led to the emergence and the progression of cancer, respectively (Carmen and Sinai, 2007; Kusi, 2013; Torgbor *et al*. 2014; Robbiani *et al*. 2015). However, the association between malaria and cancer induction can largely be explained by the well-established ability of *Plasmodium* infections to induce immune dysfunction (Toure-Balde *et al*. 1996; Urban and Todryk, 2006; Weiss *et al*. 2010; Illingworth *et al*. 2013) and by the positive relationship between malaria and certain virus-associated cancers. *Plasmodium* spp. exposure may facilitate the reactivation of virus-associated cancers, viral transmission and related diseases *via* several mechanisms, including malaria-induced immunomodulation (e.g. Thorley-Lawson *et al*. 2016; Thakker and Verma, 2016). Most studies have focused on endemic Burkitt lymphoma and to a lesser extent on classical KS, both caused by gamma herpes viruses. Currently, only the positive relationship between malaria and EBV is relatively well understood (e.g. Thorley-Lawson *et al*. 2016). To date almost all of

https://doi.org/10.1017/S0031182016001591 Published online by Cambridge University Press

Table 1. Details about experimental studies suggesting that *Plasmodium* spp. or some of their products might play a pro- or an anti-tumour role

Species	Experimental model	Virus implication[a]	Type of cell and/or organ	Types of cancer	References
Pro-tumour role					
P. falciparum	*in vitro*	EBV	B lymphocytes	Lymphoma	Reviewed in Thorley-Lawson *et al.* (2016)
P. berghei	Mouse	Possibly	All lymphomas involved the thymus	Lymphoma R-MuLV-type leukaemia	Jerusalem (1968)
P. berghei	Mouse	MLV	Injection of an extract of spleen and thymus from mice with lymphoma induced by MLV	Lymphoma	Wedderburn (1970)
P. berghei	Mouse[b]	SV40	Tumours of the liver and/or spleen	Sarcoma	Hargis and Malkiel (1979)
P. chabaudi	Mouse	–	Abnormal lymphoid tissue architecture and/or dissemination to multiple organs	Lymphoma	Robbiani *et al.* (2015)
P. yoelii	Mouse	Viruses-induced lymphoma	Injection of syngeneic virus-induced transplantable lymphoma	Lymphoma	Wedderburn *et al.* (1981)
Anti-tumour role					
P. yoelii	Mouse	–	Methylcholanthrene-induced fibrosarcoma	Sarcoma	Wedderburn *et al.* (1981)
P. yoelii	Mouse	–	S180 tumour cells	Sarcoma	Liu *et al.* (2006)
P. yoelii P. chabaudi	Mouse	–	Lewis lung cancer	Carcinoma	Chen *et al.* (2011)
Genetically attenuated *P. yoelii*	Mouse	–	Lewis lung cancer	Carcinoma	Deng *et al.* (2016)
Circumsporozoite protein of *P. yoelii*	*in vitro*	–	SW480 human colon cancer cell line	Carcinoma	Ding *et al.* (2012)
Recombinant VAR2CSA protein of *P. falciparum*	*in vitro*	–	Numerous malignant tumours from human patients	Carcinoma sarcoma	Salanti *et al.* (2015)

EBV, Epstein-Barr Virus; MLV, Moloney leukaemogenic virus; R-MuLV, Rauscher murine leukaemia virus.
[a] Mentioned only if it is relevant.
[b] Neonatal.

the studies focused deliberately on *P. falciparum*, in the future, it will be interesting to determine if other human *Plasmodium* species also play a role in tumourigenesis.

Anti-carcinogenesis role of malarial infection

As previously mentioned, the idea of an antagonistic relationship between malaria and cancer dates back several centuries (e.g. Trnka von Krzowitz, 1775). Several studies have shown that temperature elevation, which can occur with infection, can induce numerous anti-tumour effects (reviewed in Kienley, 2012). The history of anti-oncological malaria-therapy started with the supposition that cancer could be cured by concomitant malarial fevers (Freitas *et al*. 2014). Even if malarial temperature elevation exerts both direct and indirect anti-oncogenic effects, most of the anti-tumourigenic actions of malaria would not be dependent on temperature elevation (e.g. Deng *et al*. 2016). The anti-tumour effects of malarial infections imply the induction of both a potent anti-tumour innate immune response and adaptive anti-tumour immunity (Chen *et al*. 2011; Deng *et al*. 2016). Moreover, in mice infected with malaria, angiogenesis was inhibited in tumours (Chen *et al*. 2011).

Additionally, *Plasmodium* spp. produces proteins that also demonstrate certain anti-oncogenic effects. The potential anti-tumourigenic ability of the CSP is limited, but derived peptides possess interesting anti-angiogenesis properties (Ding *et al*. 2012). Moreover, infected erythrocytes potentially bind to several types of malignant cells *via* the plasmodial protein VAR2CSA (Salanti *et al*. 2015) and potentially facilitate their destruction. The putative anti-tumourigenic properties of other malarial proteins should be explored; moreover, the use of proteins is a safer approach than the inoculation of wild type *Plasmodium*.

Types of cancer in which eukaryotic parasites potentially exert pro- and anti-oncogenic roles

The human cancers for which eukaryotic parasite involvement has been implicated are principally carcinomas and certain sarcomas localized in the target tissues or organs of the parasites (e.g. Oikonomopoulou *et al*. 2013; Benamrouz *et al*. 2014; Turhan *et al*. 2015; Machicado and Marcos, 2016). Similarly, the anti-cancer activities of eukaryotic parasites are principally concerned with carcinomas (e.g. Hibbs *et al*. 1971; Pyo *et al*. 2014; Vasilev *et al*. 2015; Ubillos *et al*. 2016; Wang and Gao, 2016); however, some anti-sarcoma activities have also been observed (Alizadeh *et al*. 1994; Darani *et al*. 2009). Regarding other types of cancers, positive parasite-induced effects against cancers of the haematopoietic and lymphoid tissues are only mentioned for two species, according to a relatively old study (Hibbs *et al*. 1971). Based on current knowledge, the anti-tumour effects observed are attributable to modifications to the host immune response, and thus their characteristics and locations within the host can be highly diverse. It must also be emphasized that, similarly to *Plasmodium*, *T. gondii* and *E. granulosus*, which exhibits certain anti-tumours effects, may also promote tumour development (Chookami *et al*. 2015; Turhan *et al*. 2015; Daneshpour *et al*. 2016; Jung *et al*. 2016).

Details regarding the studies suggesting the pro- or anti-cancer implications of *Plasmodium* spp. have been summarized in Table 1. We incorporated all data known to us, even if the design or the statistical significance of the studies has been criticized (IARC, 2014). Two important features are evident from this analysis. On one hand, anti-carcinoma and anti-sarcoma activities have been observed for certain eukaryotic parasites, whereas *Plasmodium* spp. appears to be involved, either directly or indirectly, in the induction of lymphomas and leukaemias. However, even if certain data suggest that *Plasmodium* spp. alone are oncogenic agents (e.g. Thorley-Lawson *et al*. 2016), the majority of studies primarily suggest an indirect pro-tumourigenic role *via* virus involvement. A single experimental study suggested that malaria could play a role in the induction of sarcomas; neonatal mice infected with both *P. berghei* and the virus SV40 developed sarcomas of the liver and/or spleen (Hargis and Malkiel, 1979). However, in this study, no adult mice developed sarcomas. Furthermore, when a parasite plays a favourable role in cancer development *via* virus involvement, the type and location of the cancer depend on the specificity of the virus species.

CONCLUSIONS AND FUTURE PERSPECTIVES

To date, there is a great deal of scientific evidence indicating that eukaryotic parasites can act as carcinogens or create a pre-cancerous environment for tumour development, but eukaryotic parasites, sometimes the same ones, can also exhibit notable anti-tumour properties. Malarial parasites potentially exert pro- and anti-oncogenic roles; however, despite the growing body of evidence that malarial infections or the application of parasite-derived proteins can result in potent anti-tumour activities, it must be noted that malaria remains a life-threatening disease. Moreover, several virus-associated cancers are common both in highly malaria-endemic areas, such as tropical Africa, and in a variety of disorders associated with immune system impairment (Purtilo *et al*. 1984), and it is well known that malarial infection induces immune dysfunction. To date, anti-carcinogenic mechanisms involving parasites remain relatively poorly understood. Studies have noted the importance of the immune response in both pro- and anti-tumour processes and, in

https://doi.org/10.1017/S0031182016001591 Published online by Cambridge University Press

particular, the role of Th1-mediated immunity during infection with apicomplexan parasites (*Plasmodium* spp. and *T. gondii*), among others (e.g. Kim *et al.* 2007; Chen *et al.* 2011; Deng *et al.* 2016). As therapeutic measures to inhibit tumours may be induced by Th1-dominant immunity (Nishimura *et al.* 2000), studies employing Apicomplexa could open interesting pathways to combat cancers. Moreover, the relatively simpler genomes of eukaryotic single-cell parasites may open future pathways for new therapeutic approaches to treat cancers and also to better understand mechanisms of tumour induction.

ACKNOWLEDGEMENTS

The author thanks the referee for his review, which significantly improved the manuscript.

FINANCIAL SUPPORT

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

REFERENCES

Adams, F. (1849). *The Genuine Works of Hippocrates*. Sydenham Society, London, UK.

Adloye, D. and Grant, L. (2015). A review of cancers in Africa. In *Chronic Non-Communicable Diseases in Low and Middle-income Countries* (ed. de Graft Aikins, A. and Agyemang, C.), pp. 14–29. CABI, Boston, USA.

Alizadeh, H., Pidherney, M. S., McCulley, J. P. and Niederkorn, J. Y. (1994). Apoptosis as a mechanism of cytolysis of tumour cells by a pathogenic free-living amoeba. *Infection and Immunity* **62**, 1298–1303.

Anonymous. (1991*a*). From the centers for disease control. Imported malaria associated with malariotherapy of Lyme disease – New Jersey. *Journal of the American Medical Association* **265**, 317–318.

Anonymous. (1991*b*). From the centers for disease control. Self-induced malaria associated with malariotherapy for Lyme disease – Texas. *Journal of the American Medical Association* **266**, 2199.

Barfod, L., Bernasconi, N. L., Dahlback, M., Jarrossay, D., Andersen, P. H., Salanti, A., Ofori, M. F., Turner, L., Resende, M., Nielsen, M. A., Theander, T. G., Sallusto, F., Lanzavecchia, A. and Hviid, L. (2007). Human pregnancy-associated malaria-specific B cells target polymorphic, conformational epitopes in VAR2CSA. *Molecular Microbiology* **63**, 335–347.

Benamrouz, S., Guyot, K., Gazzola, S., Mouray, A., Chassat, T., Delaire, B., Chabé, M., Gosset, P., Viscogliosi, E., Dei-Cas, E., Creusy, C., Conseil, V. and Certad, G. (2012). *Cryptosporidium parvum* infection in SCID mice infected with only one oocyst: qPCR assessment of parasite replication in tissues and development of digestive cancer. *PLoS ONE* **7**, e51232.

Benamrouz, S., Conseil, V., Chabé, M., Praet, M., Audebert, C., Blervaque, R., Guyot, K., Gazzola, S., Mouray, A., Chassat, T., Delaire, B., Goetinck, N., Gantois, N., Osman, M., Slomianny, C., Dehennaut, V., Lefebvre, T., Viscogliosi, E., Cuvelier, C., Dei-Cas, E., Creusy, C. and Certad, G. (2014). *Cryptosporidium parvum*-induced ileo-caecal adenocarcinoma and Wnt signaling in a mouse model. *Disease Models & Mechanisms* **6**, 693–700.

Benelli, G., Lo Iacono, A., Canale, A. and Mehlhorn, H. (2016). Mosquito vectors and the spread of cancer: an overlooked connection? *Parasitology Research* **115**, 2131–2137.

Bomford, R. and Wedderburn, N. (1973). Depression of immune response to Moloney leukaemia virus by malarial infection. *Nature* **242**, 471–473.

Braunstein, A. (1929*a*). Krebs und Malaria I. Mitteilung. *Zeitschrift für Krebsforschung* **29**, 330–333.

Braunstein, A. (1929*b*). Experimentelle und klinische grundlagen fuer malariabehandlung des krebses. *Zeitschrift für Krebsforschung* **29**, 468–490.

Braunstein, A. (1931). Über durch malaria bei krebskranken hervorgerufene reaktionen und ihre beziehungen zum reticuloendothelialen System (RES.). *Zeitschrift für Krebsforschung* **34**, 230–233.

Brown, J., Baisley, K., Kavishe, B., Changalucha, J., Andreasen, A., Mayaud, P., Gumodoka, B., Kapiga, S., Hayes, R. and Watson-Jones, D. (2014). Impact of malaria and helminth infections on immunogenicity of the human papillomavirus-16/18 AS04-adjuvanted vaccine in Tanzania. *Vaccine* **32**, 611–617.

Carmen, J. C. and Sinai, A. P. (2007). Suicide prevention: disruption of apoptotic pathways by protozoan parasites. *Molecular Microbiology* **64**, 904–916.

Chege, D., Higgins, S. J., McDonald, C. R., Shahabi, K., Huibner, S., Kain, T., Kain, D., Kim, C. J., Leung, N., Amin, M., Geddes, K., Serghides, L., Philpott, D. J., Kimani, J., Gray-Owen, S., Kain, K. C. and Kaul, R. (2014). Murine *Plasmodium chabaudi* malaria increases mucosal immune activation and the expression of putative HIV susceptibility markers in the gut and genital mucosae. *Journal of Acquired Immune Deficiency Syndromes* **65**, 517–525.

Chen, C. J., Liang, K. Y., Chang, Y. S., Wang, Y. F., Hsieh, T., Hsu, M. M., Chen, J. Y. and Liu, M. Y. (1990). Multiple risk factors of nasopharyngeal carcinoma: Epstein-Barr virus, malarial infection, cigarette smoking and familial tendency. *Anticancer Research* **10**, 547–553.

Chen, L., He, Z., Qin, L., Li, Q., Shi, X., Zhao, S., Zhong, N., and Chen, X. (2011). Antitumour effect of malaria parasite infection in a murine Lewis lung cancer model through induction of innate and adaptive immunity. *PLoS ONE* **6**, e24407.

Chookami, M. B., Sharafi, S. M., Sefiddashti, R. R., Jafari, R., Bahadoran, M., Pestechian, N. and Darani, Y. H. (2015). Effect of two hydatid cyst antigens on the growth of melanoma cancer in C57/black mice. *Journal of Parasitic Diseases* **39**, 1–4.

Chu, E. A., Wu, J. M., Tunkel, D. E. and Ishman, S. L. (2008). Nasopharyngeal carcinoma: the role of the Epstein-Barr virus. *Medscape Journal of Medicine* **10**, 165.

Clemow, F. G. (1903). *Medical Geography*. Cambridge University Press, Cambridge, UK.

Conant, K. L. and Kaleeba, J. A. R. (2013). Dangerous liaisons: molecular basis for a syndemic relationship between Kaposi's sarcoma and *P. falciparum* malaria. *Frontiers in Microbiology* **12**, 35.

Cottoni, F., Masala, M. V., Budroni, M., Rosella, M., Satta, R., Locatelli, F., Montesu, M. A. and De Marco, R. (1997). The role of occupation and a past history of malaria in the etiology of classic Kaposi's sarcoma: a case-control study in north-east Sardinia. *British Journal of Cancer* **76**, 1518–1520.

Cottoni, F., Masala, M. V., Pattaro, C., Pirodda, C., Montesu, M. A., Satta, R., Cerimele, D. and de Marco, R. (2006). Classic Kaposi sarcoma in northern Sardinia: a prospective epidemiologic overview (1977–2003) correlated with malaria prevalence (1934). *Journal of the American Academy of Dermatology* **55**, 990–995.

Cunnington, A. J. and Riley, E. M. (2010). Suppression of vaccine responses by malaria: insignificant or overlooked? *Expert Review of Vaccines* **9**, 409–429.

Daneshpour, S., Bahadoran, M., Hejazi, S. H., Eskandarian, A. A., Mahmoudzadeh, M. and Darani, H. Y. (2016). Common antigens between hydatid cyst and cancers. *Advanced Biomedical Research* **5**, 9.

Darani, H. Y., Shirzad, H., Mansoori, F., Zabardast, N. and Mahmoodzadeh, M. (2009). Effects of *Toxoplasma gondii* and *Toxocara canis* antigens on WEHI-164 fibrosarcoma growth in a mouse model. *Korean Journal of Parasitology* **47**, 175–177.

Darani, H. Y., Yousefi, M., Safari, M. and Jafari, R. (2016). Parasites and immunotherapy: with or against? *Journal of Parasitic Diseases* **40**, 217–226.

Davidson, S. S. (1902). Carcinoma and malaria. *British Medical Journal* **1**, 77.

de Martel, C., Ferlay, J., Franceschi, S., Franceschi, S., Vignat, J., Bray, F., Forman, D. and Plummer, M. (2012). Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncology* **13**, 607–615.

Deaderick, W. H. (1909). *A Practical Study of Malaria*. Saunders & Co, London, UK.

Deng, X.-F., Zheng, H., Zhou, D., Liu, Q.-X., Ding, Y., Xu, W.-Y., Chen, Q., Hou, B., Min, J.-X. and Dai, J.-G. (2016). Antitumour effect of intravenous immunization with malaria genetically attenuated sporozoites through induction of innate and adaptive immunity. *International Journal of Clinical and Experimental Pathology* **9**, 978–986. http://www.ijcep.com/files/ijcep0019160.pdf.

Ding, Y., Huang, X., Liu, T., Fu, Y., Tan, Z., Zheng, H., Zhou, T., Dai, J. and Xu, W. (2012). The Plasmodium circumsporozoite protein, a novel NF-kappaB inhibitor, suppresses the growth of SW480. *Pathology Oncology Research* **18**, 895–902.

Duffell, E. (2001). Curative power of fever. *Lancet* **358**, 1276.

Durand-Fardel, M. (1868). *Traité Pratique des Maladies Chroniques*. Baillière, Paris, France.

Eze, M. O., Hunting, D. J. and Ogan, A. U. (1990). Reactive oxygen production against malaria – a potential cancer risk factor. *Medical Hypotheses* **32**, 121–123.

Faure, E. (2014). Malarial pathocoenosis: beneficial and deleterious interactions between malaria and other human diseases. *Frontiers in Physiology* **5**, 441.

Freitas, D. R., Santos, J. B. and Castro, C. N. (2014). Healing with malaria: a brief historical review of malariotherapy for neurosyphilis, mental disorders and other infectious diseases. *Revista da Socieda de Brasileira de Medicina Tropical* **47**, 260–261.

Frevert, U., Galinski, M. R., Hügel, F. U., Allon, N., Schreier, H., Smulevitch, S., Shakibaei, M. and Clavijo, P. (1998). Malaria circumsporozoite protein inhibits protein synthesis in mammalian cells. *EMBO Journal* **17**, 3816–3826.

Geddes, M., Franceschi, S., Balzi, D., Arniani, S., Gafà, L. and Zanetti, R. (1995). Birthplace and classic Kaposi's sarcoma in Italy. Associazione Italiana Registri Tumouri. *Journal of the National Cancer Institute* **87**, 1015–1017.

Gnidehou, S., Doritchamou, J., Arango, E. M., Cabrera, A., Arroyo, M. I., Kain, K. C., Ndam, N. T., Maestre, A. and Yanow, S. K. (2014). Functional antibodies against VAR2CSA in nonpregnant populations from Colombia exposed to *Plasmodium falciparum* and *Plasmodium vivax*. *Infection and Immunity* **82**, 2565–2673.

Goonewardene, R., Carter, R., Gamage, C. P., Del Giudice, G., David, P. H., Howie, S. and Mendis, K. N. (1990). Human T cell proliferative responses to *Plasmodium vivax* antigens: evidence of immunosuppression following prolonged exposure to endemic malaria. *European Journal of Immunology* **20**, 1387–1391.

Gupta, R., Nowakowski, M. and Haseeb, M. A. (2015). Human protozoal infections and their potential for causing neoplasms. In *Infection and Cancer: Bi-Directorial Interactions* (ed. Shurin, M. R., Thanavala, Y. and Ismail, N.), pp. 75–92. Springer, New-York, USA.

Hargis, B. J. and Malkiel, S. (1979). Sarcomas induced by injection of simian virus 40 into neonatal CFW mice. *Journal of the National Cancer Institute* **63**, 965–968.

Heimlich, H. J. (1990). Should we try malariotherapy for Lyme disease? *New England Journal of Medicine* **322**, 1234–1235.

Hibbs, J. B., Jr., Lambert, L. H., Jr. and Remington, J. S. (1971). Resistance to murine tumours conferred by chronic infection with intracellular protozoa, *Toxoplasma gondii* and *Besnoitia jellisoni*. *Journal of Infectious Diseases* **124**, 587–592.

Hoption Cann, S. A., van Netten, J. P., and van Netten, C. (2006). Acute infections as a means of cancer prevention: opposing effects to chronic infections? *Cancer Detection and Prevention* **30**, 83–93.

Hu, J., Wang, C., Ye, L., Yang, W., Huang, H., Meng, F., Shi, S. and Ding, Z. (2015). Anti-tumour immune effect of oral administration of *Lactobacillus plantarum* to CT26 tumour-bearing mice. *Journal of Biosciences* **40**, 269–279.

IARC (International Agency for Research on Cancer), author. (2014). Malaria and some polyomaviruses (SV40, BK, JC and Merkel Cell Viruses). *IARC Monograph on the Evaluation of Carcinogenic Risks to Humans* **104**, 9–350.

Igweh, J. C. (2012). Biology of malaria parasites. In *Malaria Parasites* (ed. Okwa, O. O.), pp. 17–36. InTech, Rijeka, Croatia.

Illingworth, J., Butler, N. S. and Roetynck, S., Mwacharo, J., Pierce, S. K., Bejon, P., Crompton, P. D., Marsh, K. and Ndungu, F. M. (2013). Chronic exposure to *Plasmodium falciparum* is associated with phenotypic evidence of B and T cell exhaustion. *Journal of Immunology* **190**, 1038–1047.

Iruela-Arispe, M. L., Lombardo, M., Krutzsch, H. C., Lawler, J. and Roberts, D. D. (1999). Inhibition of angiogenesis by thrombospondin-1 is mediated by 2 independent regions within the type 1 repeats. *Circulation* **100**, 1423–1431.

Jerusalem, C. (1968). Relationship between malaria infection (*Plasmodium berghei*) and malignant lymphoma in mice. *Zeitschrift fur Tropenmedizin und Parasitologie* **19**, 94–108.

Jung, B. K., Song, H., Kim, M. J., Cho, J., Shin, E. H. and Chai, J. Y. (2016). High *Toxoplasma gondii* seropositivity among brain tumour patients in Korea. *Korean Journal of Parasitology* **54**, 201–204.

Kienley, G. S. (2012). Fever in cancer treatment: Coley's therapy and epidemiologic observations. *Global Advances in Health and Medicine* **1**, 92–100.

Kim, J. O., Jung, S. S., Kim, S. Y., Kim, T. Y., Shin, D. W., Lee, J. H. and Lee, Y. H. (2007). Inhibition of Lewis lung carcinoma growth by *Toxoplasma gondii* through induction of Th1 immune responses and inhibition of angiogenesis. *Journal of Korean Medical Science* **22**(Suppl.), S38–S46.

Kruse, W. (1901). Krebs und malaria. *Munchener Medizinische Wochenschrift* **48**, 1920–1923.

Kucerova, P. and Cervinkova, M. (2016). Spontaneous regression of tumour and the role of microbial infection – possibilities for cancer treatment. *Anti-Cancer Drugs* **27**, 269–277.

Kusi, S. (2013). *Detecting and quantifying* Plasmodium falciparum *in blood and tonsils: towards an understanding of malaria-related oncogenesis*. Thesis of Biological Sciences, Kwame Nkrumah University of Science and Technology, Ghana.

Lawler, J. (2002). Thrombospondin-1 as an endogenous inhibitor of angiogenesis and tumour growth. *Journal of Cellular and Molecular Medicine* **6**, 1–12.

Lawler, J., and Detmar, M. (2004). Tumour progression: the effects of thrombospondin-1 and -2. *International Journal of Biochemistry & Cell Biology* **36**, 1038–1045.

Lehrer, S. (2010*a*). Anopheles mosquito transmission of brain tumour. *Medical Hypotheses* **74**, 167–168.

Lehrer, S. (2010*b*). Association between malaria incidence and all cancer mortality in fifty US States and the district of Columbia. *Anticancer Research* **30**, 1371–1373.

Liu, Y.-J., Zhu, X.-T., Ma, S. H. and Li, J. (2006). Effect of malariotherapy on the growth of S180 tumour cells. *Chinese Journal of Zoonoses* [in Chinese] **10**, 1001–1003.

Loeffler, F. (1901). Einer neue Behandlungsmethode des Karzinoms. *Deutsche Medizinische Wochenschrift* **27**, 725–726.

Longley, R. J., Sattabongkot, J. and Mueller, I. (2016). Insights into the naturally acquired immune response to *Plasmodium vivax* malaria. *Parasitology* **143**, 154–170.

Lu, S. N., Lin, T. M., Chen, C. J., Chen, J. S., Liaw, Y. F., Chang, W. Y. and Hsu, S. T. (1988). A case-control study of primary hepatocellular carcinoma in Taiwan. *Cancer* **62**, 2051–2055.

Lun, Z. R., Lai, D. H., Wen, Y. Z., Zheng, L. L., Shen, J. L., Yang, T. B., Zhou, W. L., Qu, L. H., Hide, G. and Ayala, F. J. (2015). Cancer in the parasitic protozoans *Trypanosoma brucei* and *Toxoplasma gondii*. *Proceedings of the National Academy of Sciences of the United States of America* **112**, 8835–8842.

Machicado, C. and Marcos, L. A. (2016). Carcinogenesis associated with parasites other than *Schistosoma*, *Opisthorchis* and *Clonorchis*: a systematic review. *International Journal of Cancer* **138**, 2915–2921.

McBride, J. S., Micklem, H. S. and Ure, J. M. (1977). Immunosuppression in murine malaria. I. Response to type III pneumococcal polysaccharide. *Immunology* **32**, 635–644.

Mori, A. (1902). Carcinosi e malaria. *La Clinica Moderna* (*Pisa*) **8**, 158–162.

Nakalembe, M., Banura, C., Namujju, P. B. and Mirembe, F. M. (2015). Immunogenicity to the bivalent HPV-16/18 vaccine among adolescent African students exposed to helminths and malaria. *Journal of Infection in Developing Countries* **9**, 197–205.

Nalwoga, A., Cose, S., Wakeham, K., Miley, W., Ndibazza, J., Drakeley, C., Elliott, A., Whitby, D. and Newton, R. (2015). Association between malaria exposure and Kaposi's sarcoma-associated herpes virus seropositivity in Uganda. *Tropical Medicine & International Health* **20**, 665–672.

Nascimento, M. C. (2014). Malaria may influence the transmission of Kaposi sarcoma associated herpesvirus in endemic areas. *Journal of Acquired Immune Deficiency Syndromes* **67**, e41–e43.

National Toxicology Program. (2016). Report on carcinogens monograph on Epstein-Barr virus. *Report on Carcinogens Monograph*. https://ntp.niehs.nih.gov/ntp/about_ntp/monopeerrvw/2015/december/ebv_revised_draft_monograph20160513.pdf.

Neghina, R., Neghina, A. M., Marincu, I. and Iacobiciu, I. (2010). Malaria, a journey in time: in search of the lost Myths and forgotten stories. *American Journal of the Medical Sciences* **340**, 492–498.

Nickell, S. P., Freeman, R. R. and Cole, G. A. (1987). Depression of virus-specific cytotoxic T-cell responses during murine malaria. *Parasite Immunology* **9**, 161–174.

Nishimura, T., Nakui, M., Sato, M., Iwakabe, K., Kitamura, H., Sekimoto, M., Ohta, A., Koda, T. and Nishimura, S. (2000). The critical role of Th1-dominant immunity in tumour immunology. *Cancer Chemotherapy and Pharmacology* **46**(Suppl.), S52–S61.

Odida, M., Schmauz, R. and Lwanga, S. K. (2002). Grade of malignancy of cervical cancer in regions of Uganda with varying malarial endemicity. *International Journal of Cancer* **99**, 737–741.

Oikonomopoulou, K., Brinc, D., Kyriacou, K. and Diamandis, E. P. (2013). Infection and cancer: revaluation of the hygiene hypothesis. *Clinical Cancer Research* **19**, 2834–2841.

Oikonomopoulou, K., Brinc, D., Hadjisavvas, A., Christofi, G., Kyriacou, K. and Diamandis, E. P. (2014). The bifacial role of helminths in cancer: involvement of immune and non-immune mechanisms. *Critical Reviews in Clinical Laboratory Sciences* **51**, 138–148.

https://doi.org/10.1017/S0031182016001591 Published online by Cambridge University Press

Orta, F. (1902). Carcinoma e malaria. *Studio clinic e sperimentale Milano* **23**, 1340–1342.

Parkin, D. M., Sitas, F., Chirenje, M., Stein, L., Abratt, R. and Wabinga, H. (2008). Part I: cancer in Indigenous Africans – burden, distribution, and trends. *Lancet Oncology* **9**, 683–692.

Patrikidou, A., Vahtsevanos, K., Charalambidou, M., Valeri, R. M., Xirou, P. and Antoniades, K. (2009). Non-AIDS Kaposi's sarcoma in the head and neck area. *Head & Neck* **31**, 260–268.

Pinessi, D., Ostano, P., Borsotti, P., Bello, E., Guffanti, F., Bizzaro, F., Frapolli, R., Bani, M. R., Chiorino, G., Taraboletti, G. and Resovi, A. (2015). Expression of thrombospondin-1 by tumour cells in patient-derived ovarian carcinoma xenografts. *Connective Tissue Research* **56**, 355–363.

Pradhan, V. and Ghosh, K. (2013). Immunological disturbances associated with malarial infection. *Journal of Parasitic Diseases* **37**, 11–15.

Purtilo, D. T., Manolov, G., Manolova, Y., Harada, S. and Lipscomb, H. (1984). Squamous cell carcinoma, Kaposi's sarcoma and Burkitt's lymphoma are consequences of impaired immune surveillance of ubiquitous viruses in acquired immune deficiency syndrome, allograft recipients and tropical African patients. *IARC Scientific Publications* **63**, 749–770.

Pyo, K. H., Jung, B. K., Xin, C. F., Lee, Y. W., Chai, J. Y. and Shin, E. H. (2014). Prominent IL-12 production and tumour reduction in athymic nude mice after *Toxoplasma gondii* lysate antigen treatment. *Korean Journal of Parasitology* **52**, 605–612.

Reddy, A., and Fried, B. (2015). An update on helminths in human carcinogenesis. In *Infection and Cancer: Bi-Directorial Interactions* (ed. Shurin, M. R., Thanavala, Y. and Ismail, N.), pp. 93–108. Springer, New-York, USA.

Riley, E. M., Hviid, L. and Theander, T. G. (2013). Malaria. In *Parasitic Infections and the Immune System* (ed. Kierszenbaum, F.), pp. 119–143. Academic Press, San Diego, California, USA.

Robbiani, D. F., Deroubaix, S., Feldhahn, N., Oliveira, T. Y., Callen, E., Wang, Q., Jankovic, M., Silva, I. T., Rommel, P. C., Bosque, D., Eisenreich, T., Nussenzweig, A. and Nussenzweig, M. C. (2015). Plasmodium infection promotes genomic instability and AID-dependent B cell lymphoma. *Cell* **162**, 727–737.

Ross, R., Dworsky, R., Nichols, P., Paganini-Hill, A., Wright, W., Koss, M., Lukes, R. and Henderson, B. (1982). Asbestos exposure and lymphomas of the gastrointestinal tract and oral cavity. *Lancet* **2**, 1118–1120.

Roucaute, E., Pichard, G., Faure, E. and Royer-Carenzi, M. (2014). Analysis of the causes of spawning of large-scale, severe malarial epidemics and their rapid total extinction in western Provence, historically a highly endemic region of France (1745–1850). *Malaria Journal* **13**, 72.

Rovighi, A. (1902). Cancro e malaria. *Gazzetta degli ospedali e delle cliniche* **23**, 1175–1176.

Rovighi, A. (1905). Ueber krebs und malaria. *Zeitschrift für Krebsforschung* **3**, 604.

Russell, S., Duquette, M., Liu, J., Drapkin, R., Lawler, J. and Petrik, J. (2015). Combined therapy with thrombospondin-1 type I repeats (3TSR) and chemotherapy induces regression and significantly improves survival in a preclinical model of advanced stage epithelial ovarian cancer. *FASEB Journal* **29**, 576–588.

Salaman, M. H., Wedderburn, N. and Bruce-Chwatt, L. J. (1969). The immunodepressive effect of a murine plasmodium and its interaction with murine oncogenic viruses. *Journal of General Microbiology* **3**, 383–391.

Salanti, A., Clausen, T. M., Agerbæk, M. Ø., Al Nakouzi, N., Dahlbäck, M., Oo, H. Z., Lee, S., Gustavsson, T., Rich, J. R., Hedberg, B. J., Mao, Y., Barington, L., Pereira, M. A., LoBello, J., Endo, M., Fazli, L., Soden, J., Wang, C. K., Sander, A. F., Dagil, R., Thrane, S., Holst, P. J., Meng, L., Favero, F., Weiss, G. J., Nielsen, M. A., Freeth, J., Nielsen, T. O., Zaia, J., Tran, N. L., Trent, J., Babcook, J. S., Theander, T. G., Sorensen, P. H. and Daugaard, M. (2015). Targeting human cancer by a glycosaminoglycan binding malaria protein. *Cancer Cell* **28**, 500–514.

Schmauz, R., Mugerwa, J. W. and Wright, D. H. (1990). The distribution of non-Burkitt, non-Hodgkin's lymphomas in Uganda in relation to malarial endemicity. *International Journal of Cancer* **45**, 650–653.

Serraino, D., Corona, R. M., Giuliani, M., Farchi, F., Sarmati, L. and Uccella, I., Andreoni, M. and Rezza, G. (2003). Infection with human herpesvirus type 8 and kaposi's sarcoma in a central Italian area formerly endemic for malaria. *Infection* **31**, 47–50.

Setti, G. (1904). Cancro e chinino. Del preteso antagonismo fra carcinosi e malaria. In *La Nuova Rivista Clinico-terapeutica* (ed. de Renzi, E.), pp. 319–321. Jovene, Napoli, Italy.

Singh, A. P., Buscaglia, C. A., Wang, Q., Levay, A., Nussenzweig, D. R., Walker, J. R., Winzeler, E. A., Fujii, H., Fontoura, B. M. and Nussenzweig, V. (2007). Plasmodium circumsporozoite protein promotes the development of the liver stages of the parasite. *Cell* **131**, 492–504.

Snounou, G. and Pérignon, J.-L. (2013). Malariotherapy-insanity at the service of malariology. *Advances in Parasitology* **81**, 223–255.

Sofronic-Milosavljevic, L., Ilic, N., Pinelli, E. and Gruden-Movsesijan, A. (2015). Secretory products of *Trichinella spiralis* muscle larvae and immunomodulation: implication for autoimmune diseases, allergies, and malignancies. *Journal of Immunology Research* **1**, 523875.

Starita, N., Annunziata, C., Waddell, K. M., Buonaguro, L., Buonaguro, F. M. and Tornesello, M. L. (2015). Identification of Human Herpesvirus 8 sequences in conjunctiva intraepithelial neoplasia and squamous cell carcinoma of Ugandan patients. *BioMed Research International* **1**, 801353.

Tarzaali, A., Viens, P. and Quevillon, M. (1977). Inhibition of the immune response to whooping cough and tetanus vaccines by malaria infection, and the effect of pertussis adjuvant. *American Society of Tropical Medicine and Hygiene* **26**, 520–524.

Tavani, A., La Vecchia, C., Franceschi, S., Serraino, D. and Carbone, A. (2000). Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. *European Journal of Cancer Prevention* **9**, 59–64.

Taylor, L. H., Latham, S. M. and Woolhouse, M. E. J. (2001). Risk factors for human disease emergence. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **356**, 983–989.

Temkin, O. (1945). *The Falling Sickness: A History of Epilepsy from the Greeks to the Beginnings of Modern Neurology*. Johns Hopkins Press, Baltimore, USA.

Thakker, S. and Verma, S. C. (2016). Co-infections and pathogenesis of KSHV-associated malignancies. *Frontiers in Microbiology* **7**, 151.

Thorley-Lawson, D., Deitsch, K. W., Duca, K. A. and Torgbor, C. (2016). The link between *Plasmodium falciparum* malaria and endemic Burkitt's lymphoma-new insight into a 50-year-old Enigma. *PLOS Pathogens* **12**, e1005331.

Tolsma, S. S., Volpert, O. V., Good, D. J., Frazier, W. A., Polverini, P. J. and Bouck, N. (1993). Peptides derived from two separate domains of the matrix protein thrombospondin-1 have anti-angiogenic activity. *Journal of Cell Biology* **122**, 497–511.

Torgbor, C., Awuah, P., Deitsch, K., Kalantari, P. and Duca, K. A. and Thorley-Lawson, D. A. (2014). A multifactorial role for *P. falciparum* malaria in endemic Burkitt's lymphoma pathogenesis. *PLOS Pathogens* **10**, e1004170.

Toure-Balde, A., Sarthou, J. L., Aribot, G., Michel, P., Trape, J. F., Rogier, C. and Roussilhon, C. (1996). *Plasmodium falciparum* induces apoptosis in human mononuclear cells. *Infection and Immunity* **64**, 744–750.

Tripathi, R., Jaiswal, N., Sharma, B. and Malhotra, S. K. (2015). Helminth infections mediated DNA damage: Mechanisms and consequences. *Single Cell Biology* **4**, 117.

Trnka von Krzowitz, W. (1775). *Historia Febrium Intermittentium, Omnis Aevi Observata et Inventa Illustriora Medica ad has Febres Pertinentia Complectens*. Ehelen, Vienna, Autria.

Tsuzynski, G. P., Rothman, V. L., Deutch, A. H., Hamilton, B. K. and Eyal, J. (1992). Biological activities of peptides and peptide analogues derived from common sequences present in thrombospondin, properdin, and malaria proteins. *Journal of Cell Biology* **116**, 209–217.

Turhan, N., Esendagli, G., Ozkayar, O., Tunali, G., Sokmensuer, C. and Abbasoglu, O. (2015). Co-existence of *Echinococcus granulosus* infection and cancer metastasis in the liver correlates with reduced Th1 immune responses. *Parasite Immunology* **37**, 16–22.

Ubillos, L., Freire, T., Berriel, E., Chiribao, M. L., Chiale, C., Festari, M. F., Medeiros, A., Mazal, D., Rondán, M., Bollati-Fogolín, M., Rabinovich, G. A., Robello, C. and Osinaga, E. (2016). *Trypanosoma cruzi* extracts elicit protective immune response against chemically induced colon and mammary cancers. *International Journal of Cancer* **138**, 1719–1731.

Urban, B. C. and Todryk, S. (2006). Malaria pigment paralyzes dendritic cells. *Journal of Biology* **5**, 4.

Vasilev, S., Ilic, N., Gruden-Movsesijan, A., Vasilijic, S., Bosic, M. and Sofronic-Milosavljevic, L. (2015). Necrosis and apoptosis in *Trichinella spiralis*-mediated tumour reduction. *Central-European Journal of Immunology* **40**, 42–53.

Vineis, P., Crosignani, P., Sacerdote, C., Fontana, A., Masala, G., Miligi, L., Nanni, O., Ramazzotti, V., Rodella, S., Stagnaro, E., Tumino, R., Viganò, C., Vindigni, C. and Costantini, A. S. (2000). Haematopoietic cancer and medical history: a multicentre case control study. *Journal of Epidemiology and Community Health* **54**, 431–436.

von Hansemann, D. (1914). Über das Vorkommen von Geschwülsten in den Tropen. *Z Krebsforsch Zeitschrift für Krebsforschung* **14**, 39–45.

Wahman, A., Melnick, S. L. and Rhame, F. S. (1991). The epidemiology of classic, African and immunosuppressed Kaposi's sarcoma. *Epidemiologic Reviews* **13**, 178–199.

Wakeham, K., Webb, E. L., Sebina, I., Muhangi, L., Miley, W., Johnson, W. T., Ndibazza, J., Elliott, A. M., Whitby, D. and Newton, R. (2011). Parasite infection is associated with Kaposi's sarcoma associated herpesvirus (KSHV) in Ugandan women. *Infectious Agents and Cancer* **6**, 15.

Wakeham, K., Webb, E. L., Sebina, I., Nalwoga, A., Muhangi, L., Miley, W., Johnston, W. T., Ndibazza, J., Whitby, D., Newton, R. and Elliott, A. M. (2013). Risk factors for seropositivity to Kaposi sarcoma-associated herpesvirus among children in Uganda. *Journal of Acquired Immune Deficiency Syndromes* **63**, 228–233.

Wang, G. and Gao, M. (2016). Influence of *Toxoplasma gondii* on in vitro proliferation and apoptosis of hepatoma carcinoma H7402 cell. *Asian Pacific Journal of Tropical Medicine* **9**, 63–66.

Ward, M., Ward, A. and Johansson, O. (2016). Does the mosquito have more of a role in certain cancers than is currently appreciated? – The mosquito cocktail hypothesis. *Medical Hypotheses* **86**, 85–91.

Wassmer, S. C., Taylor, T. E., Rathod, P. K., Mishra, S. K., Mohanty, S., Arevalo-Herrera, M., Duraisingh, M. T. and Smith, J. D. (2015). Investigating the pathogenesis of severe malaria: a multidisciplinary and cross-geographical approach. *American Society of Tropical Medicine and Hygiene* **93**(Suppl.), S42–S56.

Wedderburn, N. (1970). Effect of concurrent malarial infection on development of virus-induced lymphoma in Balb-c mice. *Lancet* **296**, 1114–1116.

Wedderburn, N. (1974). Immunodepression produced by malarial infection in mice. In *Parasites in the Immunized Host: Mechanisms of Survival*. (ed. Porter, R. and Knight, J.), pp. 123–135. Ciba Foundation Symposium n°25 (new series), Elsevier, Amsterdam, The Netherlands.

Wedderburn, N., Campa, M., Tosta, C. E. and Henderson, D. C. (1981). The effect of malaria on the growth of two syngeneic transplantable murine tumours. *Annals of Tropical Medicine and Parasitology* **75**, 597–605.

Weinstat-Saslow, D. L., Zabrenetzky, V. S., VanHoutte, K., Frazier, W. A., Roberts, D. D. and Steeg, P. S. (1994). Transfection of thrombospondin 1 complementary DNA into a human breast carcinoma cell line reduces primary tumour growth, metastatic potential, and angiogenesis. *Cancer Research* **54**, 6504–6511.

Weiss, G. E., Traore, B. and Kayentao, K., Ongoiba, A., Doumbo, S., Doumtabe, D., Kone, Y., Dia, S., Guindo, A., Traore, A., Huang, C. Y., Miura, K., Mircetic, M., Li, S., Baughman, A., Narum, D. L., Miller, L. H., Doumbo, O. K., Pierce, S. K. and Crompton, P. D. (2010). The *Plasmodium falciparum*-specific human memory B cell compartment expands gradually with repeated malaria infections. *PLoS Pathogens* **6**, e1000912.

Welsh, J. D., Brown, J. D., Arnold, K., Mathews, H. M. and Prince, A. M. (1976). Hepatitis BS antigen, malaria titers, and primary liver cancer in South Vietnam. *Gastroenterology* **70**, 392–326.

Whitrow, M. (1990). Wagner-Jauregg and fever therapy. *Medical History* **34**, 294–310.

WHO (World Health Organization). (2015). *World Malaria Report 2015*. World Health Organization, Geneva, Switzerland. http://www.who.int/malaria/media/world-malaria-report-2015/en/.

Wykes, M. N. and Good, M. F. (2008). What really happens to dendritic cells during malaria? *Nature Reviews. Microbiology* **6**, 864–870.

Xiaoping, C., Heimlich, H. J. and Binquan, X. (1999). Preliminary report of malariotherapy for advanced tumours. [in Chinese] *Zhejiang Cancer Journal* **3**, 15.

Yadav, M. and Prasad, U. (1984). Malaria antibody levels in patients with nasopharyngeal carcinoma. *Southeast Asian Journal of Tropical Medicine and Public Health* **15**, 234–237.

Zabel, W. (1970). Die Malariatherapie beim karzinom und die technik der malariablutkonservierung. In *Die Zusätzliche Therapie der Geschwulsterkrankungen* (ed. Zabel, W.), pp. 99–116. Haug, Heidelberg, Germany.

Zeng, G. and Zhong, N. (2011). Translational medicine: what is in a name from the perspective of Chinese clinicians? *Science China Life Sciences* **54**, 1077–1080.