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Invited Review

Malaria research in Australia: looking through the lens of the past towards the future

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ABSTRACT

Malaria remains a global health priority, with substantial resources devoted to control and intervention since the causative parasite was first identified in 1880. Major advances have been made in discovery and translational research activities aimed at prevention, treatment and control. Laboratory-based, clinical, and field-based studies have complemented public health approaches. Australian scientists have played important roles, developing and applying innovative approaches, novel research tools and cutting-edge technologies in animal and human models of disease, as well as in disease-endemic settings. This article will provide an insight into 50 years of Australian efforts to discover mechanisms and targets of immunity and pathogenesis; develop new diagnostics, drugs, vaccines, and therapeutics; and assess new public health interventions and control measures in malaria-endemic settings.

1. Introduction

Malaria is among the oldest of diseases, first recorded almost 5000 years ago, and is one of the most widespread of all human parasitic diseases (Carter and Mendis, 2002). In the 20th Century alone, malaria was responsible for up to 5% of all deaths, claiming between 150 million and 300 million lives (Carter and Mendis, 2002). The disease has played a decisive role in driving human evolution, representing the strongest known force for evolutionary selection in the recent history of the human genome by selecting for host genetic mutations that provide a survival advantage against malaria (such as the sickle cell trait, thalassemia, and glucose-6-phosphatase deficiency) (Kwiatkowski, 2005).

2. Malaria: a historical perspective

At the start of the 21st Century, more than 80% of the world's population lived in malaria-endemic areas, across all five continents (Organization, 2020). In the middle of the 21st Century, in the 1950s, the annual global burden of disease was estimated to be approximately 250 million clinical cases and 2.5 million deaths. However, these numbers increased in the 1970s and 1980s due to the emergence of parasite resistance to the leading anti-malarial prophylaxis (chloroquine) and increasing vector resistance to insecticides, coupled with waning focus on malaria control efforts. The disease returned to some countries from which it had been considered to be eradicated, and the situation deteriorated in other countries where control efforts were previously making an impact (World Health Organization, 2020). As noted by Graham Brown, an Australian medical researcher internationally respected for his contributions towards combating malaria: "The excessive cost of malaria is not confined to illness and direct deaths from infection, but magnified by its contribution to all causes of illness and death and its huge economic impact on the countries in malaria-endemic regions." (Brown, 2011).

The past two decades have seen unprecedented success in the control of malaria, with 7.6 million malaria-related deaths and 1.5 billion clinical cases averted between 2000 and 2020, representing a 60% reduction in global malaria mortality during this period (World Malaria Report, 2020). Contributing to this was the challenge issued to the malaria community by Bill and Melinda Gates on 17th October 2007 to aim for the goal of eradication (Roberts and Enserink, 2007). During this historic event, Melinda Gates noted that "In the history of humanity, it's likely that no disease has ever caused more suffering, more sickness, and more death than malaria" (Gates, 2007). They proposed that the global community should capitalise on advances in science and medicine to chart a long-term course to eradicate the disease. The malaria community subsequently articulated the Malaria Eradication Research Agenda (malERA) initiative to identify knowledge gaps

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and new tools needed to eradicate malaria globally, following a consultative process spanning 2 years involving more than 250 scientists, program managers and policy makers from 36 countries. The crucial role of the academic and research community in the fight to eradicate malaria, and the need to develop innovative new tools, was recognised. The resultant comprehensive research and development agenda for malaria eradication was published in 2011 as a collection of 12 papers in the open-access journal *PLoS Medicine* (Panel, 2011), including an overview of the research agenda to underpin malaria eradication (Alonso et al., 2011), modelling (Modeling, 2011), basic science and enabling technologies (Technologies, 2011), vector control (Control, 2011), diagnostics (Diagnostics, 2011), and vaccines (Vaccines, 2011), as well as papers focused on other specific thematic areas. This research and development agenda for malaria elimination and eradication was updated in 2017 by a team of more than 180 experts and published as a series of seven articles in *PLOS Medicine*, including an updated research agenda for diagnostics, drugs, vaccines, and vector control in malaria elimination and eradication (Elimination, 2017). This malERA collection complements the World Health Organization (WHO) 'Global Technical Strategy for Malaria 2016-2030' (World Health Organization, 2015) and the Roll Back Malaria 'Action and Investment to defeat Malaria 2016-2030' (Roll Back Malaria Partnership, 2015), as well as the Lancet Commission on Malaria Eradication (Chen et al., 2018), to achieve the vision of the global malaria community of a world free of malaria. An additional tool in the arsenal is the WHO Vaccine Technology Roadmap that provides a strategic framework to guide malaria vaccine development efforts, towards a goal by 2030 of licenced vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* with at least 75% efficacy against clinical malaria that will be suitable for use in all malaria-endemic areas and will enable disease elimination (Moorthy et al., 2013). As noted by Michael Good, a leading Australian malaria vaccine researcher: "An effective vaccine could have dramatic effects in humanitarian and economic terms in developing countries, particularly in Africa" (Francombe, 2009).

Despite this reinvigorated and coordinated global fight against malaria with substantial funding dedicated to malaria control and elimination (estimated at US$ 3.0 billion in 2019) (Haakenstad et al., 2019; RBM Partnership to End Malaria., 2019), malaria remains a formidable challenge. In 2019, almost half a million people (409,000) people died of malaria, two-thirds (67%) were children under 5 years of age; and 229 million malaria cases in 87 malaria-endemic countries were documented (World Health Organization, 2020). Concerningly, control of malaria appears to have plateaued at these high levels over recent years, challenged by rapid development of drug resistance in the parasite (Dondorp et al., 2009; Noedl et al., 2009) and insecticide resistance in the vector (Mnzava et al., 2015), and will likely be further adversely impacted by the SARS-CoV2 (COVID-19) pandemic (Dyer, 2020; Yanow and Good, 2020).

As noted by the Director-General of the WHO, Dr. Tedros Adhanom Ghebreyesus, "Eradicating malaria has been one of the ultimate public health goals for a century. It is also proving to be one of the greatest challenges" (Ghebreyesus, 2019). When considered in the perspective of the COVID-19 pandemic that has provided a global wake-up call into the devastating effects that a single pathogen can have, Dr Pedro Alonso, Director of the WHO Global Malaria Programme, shared the view held by many: "This unprecedented investment into COVID-19 pandemic has revealed the extraordinary power of science . . . The investment and benefits from science, coupled with global solidarity and a focus on equity . . . should also be extended to other diseases, such as malaria, that currently threaten the lives of millions of people around the world." (Alonso, 2021).

The recent announcement on 6th October 2021 that the WHO is recommending widespread use of the RTS,S/AS01 (Mosquirix™) malaria vaccine candidate in children living in regions with moderate to high *P. falciparum* malaria transmission, as defined by WHO, is a historic step in the right direction (World Health Organization, 2021). But it is not enough (Maxmen, 2021). Under development since 1987 at a cost of more than US$750 million, efficacy is low and short-lived: 35.2% in the target group of children and further waning over time (RTS,S. Clinical Trial Partnership, 2015). At an estimated cost of US$325 million per year to administer across 10 African countries, other effective control measures will be impacted (Maxmen, 2021). Decisions from the global health community regarding broader rollout, and from malaria-impacted countries on whether to adopt it as part of national malaria control strategies are now needed (World Health Organization, 2021).

There is a view amongst some of the malaria community that effective control and global eradication will not be achievable using currently available tools, and that new and innovative tools and strategies are needed; and especially those that involve a change in thinking and partnership with the vulnerable communities. To address this need, at the 1st Malaria World Congress convened in 2018 in Melbourne, delegates from 66 countries representing the spectrum of people involved in the fight against malaria, compiled a Statement of Action (Global Civil Society for Malaria Elimination Declaration) after concluding that there is little likelihood of achieving the current ambitious elimination targets without a radical change in thinking and action (CS4ME, 2018). The following priority areas for urgent action were identified. (1) Think creatively outside existing solutions and promote scientific and social innovation at every level to achieve global targets. (2) Engage vulnerable communities and civil society as equal partners. (3) Listen, then act collaboratively. (4) Hold ourselves to account. Facilitate cross-sector conversations and relationships to build and align political, scientific, technical, community and operational leadership. (5) Commit to mobilising increased and sustained financing for malaria control and elimination. In the closing address, Congress co-founder Brendan Crabb (Director of the Burnet Institute, Australia) emphasized that the status quo is not OK in the fight against malaria. "There are huge challenges to deliver . . . so we should take away that the status quo is not OK. . . so many lives, so much suffering depends on us acting, and acting vigorously. . . The Statement of Action tries to capture that it is not the specifics as much as the culture that's going to drive our response (Parish, 2018). Culture and defining the values that we as a community have is what will give us the motivation to finish the job. . . Not just engaging but putting the vulnerable communities that are the least listened to at the head of the table, to innovate, and to collaborate . . ." (GCS4ME, 2018).

On the 50th anniversary of the International Journal for Parasitology, which is hosted in Australia, it is timely to consider malaria from an Australian perspective; including the contributions by Australian institutions and Australian researchers in developing tools to understand, prevent and eradicate malaria.

3. Malaria from an Australian perspective

Historically, malaria was endemic in northern Australia but was eradicated following implementation of control measures and changes to water supply practices. Australia was certified as malaria-free by the WHO in 1981 (World Health Organization, 1983). The last epidemic of malaria in Australia was at the Roper River Mission in the Northern Territory in 1962 (Whelan, 1991). There have, however, been four documented episodes of malaria acquired in mainland Australia in the past 30 years, all in Far North Queensland. All were caused by *Plasmodium vivax*, and three

involved single cases, while the fourth was an outbreak in Cairns in 2002 that included 10 locally acquired cases (Brookes et al., 1997; Walker, 1998; Hanna et al., 2004).

The country remains vulnerable to malaria transmission, however, as the vectors have not been eradicated and hundreds of imported cases of malaria (acquired outside Australia) are recorded in Australia each year, and local transmission from imported cases still occurs (introduced cases). The region of northern Australia above 19° S latitude is a receptive zone for malaria transmission (Ford, 1950), and some of Australia's nearest neighbours still have very high malaria transmission rates, including Papua New Guinea and other countries of the south-west Pacific or south-east Asia. The impact of climate change on malaria transmission is growing concern, with modelling showing that current climatic conditions in northern Australia are suitable for the survival of both parasite and vector and that global warming will extend the range of vectors and expand the potential threat (Bryan et al., 1996; Caminade et al., 2014).

Australia has played a critical part in fundamental research into malaria. With a critical shortage of quinine in Australia during the Pacific campaign of World War II, Colonel Neil Hamilton Fairley persuaded the Australian army to establish the Land Headquarters Medical Research Unit (directed by Fairley) in 1943 at Cairns, Queensland, to investigate malarial pathogenesis and chemoprophylaxis using human 'guinea pigs'. Several hundred volunteers were infected with *Plasmodium* spp. parasites during 1943–1945, establishing the fundamentals of anti-malaria chemoprophylaxis by demonstrating that malaria in experimentally-infected non-immune individuals could be eliminated by routine use of drugs, and fast-tracking research into new anti-malarial drugs (Fairley, 1957). This formed the basis of the Australian army policy for regular enforced administration of anti-malarial drugs to troops, resulting in a dramatic drop in the malaria rate and influencing the ultimate success of military campaigns. As Ford noted, '(Fairley's) great enterprise, in a few years, had brought greater advances to the knowledge of malarial prophylaxis than had occurred in the past fifty years, or was to occur in the subsequent twenty. Its value to the world was inestimable' (Ford, 1969).

While in Cairns, Fairley also contributed to the existence of the tissue phase of the *Plasmodium* parasite life cycle, by his observation of exoerythrocytic schizogony when the blood of volunteers infected with *P. vivax* or *P. falciparum* sporozoites by mosquito bite was infectious to other volunteers for approximately 30 min but then non-infectious until 6–9 days later (Fairley, 1945, 1947). Subsequent demonstrations of a pre-erythrocytic cycle in the parenchyma cells of the liver of a *P. vivax*-infected human volunteer (Shortt et al., 1948) and the presence of the parasite in the liver of a *P. falciparum*-infected human volunteer (Shortt et al., 1949) elucidated the critical liver-stage of the parasite life cycle, now considered an optimal target for vaccine and drug interventions (Hoffman and Doolan, 2000).

4. The past 50 years (1971–2021)

4.1. Key Australian institutions involved in the fight against malaria

The overarching goal of malaria research in Australia has been to better understand, diagnose, treat and prevent malaria, in order to improve health outcomes and eliminate the disease (particularly in the Asia-Pacific region). The significant contributions made by Australian researchers are reflected in bibliometric analysis of global malaria vaccine research which identified the USA, UK and Australia as the top ranked of 40 countries for quantity, quality and citations, together contributing more than half of the total publication output (from 117, 44, and 17 institutions, respectively) (Garg et al., 2009). The Queensland Institute of Medical Research (QIMR) was ranked fourth of 399 institutions for most prolific and impact of output, and the Walter and Eliza Hall Institute of Medical Research (WEHI) was 18th.

Australia's first institute dedicated only to medical research was the Australian Institute of Tropical Medicine (AITM), founded in 1910 in Townsville, Queensland, to address health concerns for people and communities in northern Australia, under the directorship of Dr Anton Breinl (Douglas, 1977a, b, c). AITM closed in 1930, when the functions of the research institute were transferred to Sydney (School of Public Health and Tropical Medicine), but the building still exists and is listed on the Queensland Heritage Register. The Institute was re-established in the same building in 1987 by James Cook University (JCU), following a recommendation from the Kerr White Report into research, public health and tropical health with a series of name changes including The Tropical Health Surveillance Unit and the Anton Breinl Centre for Tropical Health and Medicine. It was incorporated into the JCU Department of Public Health and Tropical Medicine and then the JCU Division of Tropical Health and Medicine. In 2009, JCU broadened its tropical health research with the founding of the Queensland Tropical Health Alliance (QTHA, a Queensland Government initiative, which morphed into Australian Institute of Tropical Health and Medicine (AITHM) in 2013 with nodes in Townsville, Cairns, Thursday Island, and Mackay (Australian Institute of Tropical Medicine, 2021).

The WEHI in Melbourne, the second oldest medical research institute in Australia (created in 1912), has been a leading institution for malaria research since the formation of the Applied Immunobiology laboratory in 1974, under the direction of Graham Mitchell (Mitchell, 1990). Notably, Neil Hamilton Fairley was appointed first assistant director of WEHI, in 1920, before leaving for Bombay and then London to work on tropical medicine (Ford, 1969). WEHI is closely associated with the University of Melbourne and the Royal Melbourne Hospital, and was the birthplace of malaria vaccine development in Australia. Another prominent malaria research institute in Melbourne is the Macfarlane Burnet Institute for Medical Research and Public Health (Burnet Institute) which combines medical research in the laboratory and the field with public health action to address major health issues affecting disadvantaged communities.

The QIMR in Brisbane (now the QIMR Berghofer Medical Research Institute) was founded in 1945 by Edward Derrick as an institute dedicated to research into infectious disease of northern Australia. The research focus established by Derrick and the subsequent director, Ian Mackerras, continued well into the 21st Century, when it expanded to include cancer, chronic disorders and mental health. Celebrating its 75th anniversary last year, it is closely affiliated with the adjacent Royal Brisbane and Women's Hospital.

Another very active malaria research institute located in the tropics of northern Australia is the Menzies School of Health Research (referred to hereafter as Menzies), in Darwin (Northern Territory) located on the campus of the Royal Darwin Hospital, which opened in 1984 under the directorship of John Mathews. Menzies has retained and expanded its primary focus, and is a leading institution for research dedicated to improving the health and wellbeing of Indigenous Australians as well as tropical health research. Researchers located at a number of other institutes throughout Australia have also made key contributions to malaria research, including (but not limited to) Monash University, LaTrobe University and Deakin University in Melbourne, as well the Australian National University (ANU, Canberra), University of Adelaide, University of Sydney, University of New South Wales, University of Technology Sydney, Griffith University (Brisbane and Gold Coast), and the Australian Army Malaria Institute (Brisbane).

An important collaborating partner for the past 50 years has been the Papua New Guinea Institute of Medical Research (PNGIMR, founded in 1968), with a malaria research programme established in 1977 supported by the WHO Special Programme for Research and Training in Tropical Diseases. Under the stewardship of Michael Alpers who remained as Director for 23 years, PNGIMR complemented Australian-based laboratory studies by providing malaria-endemic field sites for a diverse portfolio of basic and applied research including prophylactic and chemotherapeutic interventions, malaria control measures, and epidemiology (Alpers et al., 1983). The PNGIMR remains an engaged and valuable partner, together with other institutions in malaria-endemic countries of the Asia-Pacific region, Africa, and South America; as well as in the United States of America, United Kingdom, and Europe. Close partnerships with researchers, communities, health workers and control programs in malaria-endemic countries ensure that the research is targeted and relevant, and develops capacity in personnel as well as infrastructure. Collaboration with industry partners ensures that the basic research discoveries can be translated to develop novel and effective diagnostics, drugs, vaccines, therapeutics, and other control measures, and drive policy. Extensive networks of national and international multidisciplinary teams underpin these efforts.

4.2. Research disciplines and resources

Malaria research in Australia spans a very broad range of discovery (basic) and translational (applied) research activities aimed at prevention, treatment and control. Laboratory-based, clinical, and field-based studies complement public health approaches, exploiting expertise in epidemiology, entomology, parasite biology, cell biology, molecular biology, imaging, immunology, pathophysiology, molecular genetics, modelling, biochemistry, medicinal chemistry, protein chemistry, structural biology, genomics, proteomics, transcriptomics, metabolomics, systems biology, bioinformatics, biostatistics, vaccine engineering, product development, and clinical testing.

Of the five species of *Plasmodium* parasites that infect humans (*P. falciparum*, *P. vivax*, *Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium knowlesi*), most of the work by Australian researchers has focused on the two leading causative agents impacting global health: *P. falciparum* and *P. vivax*, which is particularly burdensome in the Asia-Pacific region (Vivax Working Group, 2015; Battle et al., 2019); and more recently *P. knowlesi*, the zoonotic malaria parasite first identified in Malaysia (Cox-Singh, 2012).

Models and facilities that have facilitated the discovery, development and evaluation of novel diagnostics, drugs, vaccine candidates, and other control measures include:

- state-of-the-art insectories (at WEHI, QIMR and JCU-AITHM) in which *Anopheles* mosquitoes can be infected with *P. falciparum*, *P. vivax*, *P. berghei* or *P. yoelii* parasites, to enable studies on all aspects of vector biology and disease transmission, as well as providing parasites for challenge studies in rodents or humans;
- wild-type, transgenic and genetically modified *Plasmodium* spp. parasites (including rodent: *Plasmodium yoelii, Plasmodium berghei, Plasmodium chabaudi,* and *Plasmodium vinkeii*; human: *P. falciparum* and *P. vivax*; zoonotic: *P. knowlesi*);
- wild-type, genetically modified, immunocompromised, and humanised mice;
- Quarantine Approved Premises, for work with quarantine-restricted materials (including imported rodent malaria parasites or exotic materials);
- human models, including controlled human malaria infection (CHMI) models (especially the induced blood stage malaria (IBSM) model (Pombo et al., 2002; Collins et al., 2018; Cooper et al., 2019); and
- clinical trial capability for Phase 1 and 2a clinical trials in malaria-naïve human volunteers, and phase 2b, interventional studies, randomised controlled trials and longitudinal cohort studies in malaria-exposed human volunteers in disease-endemic settings.

4.3. Research areas

The majority of malaria work in Australia prior to the mid-1970s comprised entomological, epidemiological, and public health population-based studies. Over the past 50 years, the breadth of research has expanded to include parasite biology, immunology, pathogenesis, vaccines, drugs, diagnostics and vector control, much of it recognised internationally. Key questions being addressed in these focal areas (compiled from websites of prominent Australian malaria research groups) are described below.

4.3.1. Parasite biology

- understand the biology of the malaria parasite at all life stages, especially gametocytes and *P. vivax* hypnozoites, to inform molecular targets for new treatments
- decipher host–parasite interactions, to inform how malaria parasites and human hosts interact and what allows the parasite to enter into host cells
- define the mechanisms by which parasite proteins recognise and bind to human proteins
- understand the mechanisms by which parasites are able to survive within their host
- identify and characterize parasite proteins, especially those that are important in invasion of mammalian host cells or transmission to the mosquito vector
- dissect the role of parasite proteins in immunity, pathogenesis and transmission
- define the molecular basis of gametocyte development and parasite transmission
- identify parasite metabolic pathways
- define parasite dynamics within the human host, and genetic diversity
- develop human parasite challenge models, to study host-pathogen interactions and immune responses, and test new drugs and therapeutics
- comparative studies of *P. falciparum*, *P. vivax* and *P. knowlesi*

4.3.2. Pathogenesis

- improve understanding of the pathogenesis of malaria
- identify and characterize mechanisms of pathogenesis
- define the pathophysiological responses to infection, and how these responses relate to clinical disease
- understand how the malaria parasite causes disease, to discover potential drug targets

4.3.3. Immunology

- identify and characterize mechanisms of immunity to malaria in humans, and in animal models of disease, to inform the development of effective malaria vaccines
- understand the acquisition and maintenance of immunological memory
- understand natural acquisition of clinical immunity to malaria

- understand the induction and longevity of vaccine-induced immunity
- interrogate parasite evasion of host immunity
- investigate immune regulation, and modulation of host immune responses by chronic parasite exposure
- define the association between immune responses and protection against infection or disease
- identify immunological correlates of protection

4.3.4. Vaccine development

- identify and characterize novel parasite proteins as potential vaccine targets, for pre-erythrocytic (sporozoite/liver stage), blood-stage, sexual stage, or multiple lifecycle stages
- identify cross-species malaria vaccine candidates
- characterise the antigenic diversity of potential vaccine candidates, and capacity for immune escape
- advance the preclinical development and clinical evaluation (Phase 1 and 2a in malaria-naïve, and 2b in malaria-endemic settings) of leading vaccine candidates
- explore vaccine platforms capable of inducing protective immune responses against vaccine candidates
- develop and evaluate subunit vaccines (recombinant protein, viral vector, synthetic peptide, virus-like particles, nanoparticles) expressing vaccine candidates
- develop and evaluate genetically-attenuated and chemically-attenuated whole parasite vaccines, based on the concept that organisms attenuated by radiation, chemical, or genetic manipulation are unable to replicate inside a host but can present hundreds or thousands of parasite antigens which would be targets of immunity
- develop a rationally designed genome-based vaccine, which exploits the wealth of information in the parasite genome to discover the subset of antigens likely to be good vaccine candidates, using biologically and functionally relevant selection criteria

4.3.5. Drug development

- understand how *Plasmodium* spp. parasites become resistant to drugs
- develop novel antimalarial drugs targeted at emerging drug resistance
- develop novel antimalarial drugs targeted at *P. vivax* hypnozoites (hidden reservoir)
- develop novel antimalarial drugs that block parasite transmission from infected humans to *Anopheles* mosquitoes
- test in vitro drug sensitivity and drug resistance
- investigate the effectiveness of novel antimalarial drug candidates in clinical studies, in malaria-naive humans using controlled human malaria infection models, or in humans exposed to natural parasite challenge in the field
- conduct intervention trials of antimalarial drug combinations and intermittent preventative therapy in disease-endemic settings

4.3.6. Diagnostics

- develop novel diagnostic tests, including for *P. vivax* hypnozoites and for the subpatent *P. falciparum* reservoir
- develop serological markers of recent exposure
- develop rapid low-cost point-of-care diagnostics for mass screening and population-based surveillance, to improve treatment and enable malaria eradication
- create new tools and strategies for improved malaria treatment and enhanced disease surveillance

4.3.7. Entomology and vector control

- improve vector surveillance and vector control programs to eliminate disease transmission
- develop and evaluate novel surveillance tools
- investigate the impact of insecticide-treated bed nets on regional and global malaria burden
- evaluate new insecticidal approaches to mosquito control
- understand mosquito-parasite interactions and parasite uptake by mosquitoes, and identify novel strategies to interrupt this process
- evaluate vectorial capacity (the ability of mosquitoes to transmit disease)
- develop and assess new transmission-blocking interventions targeting the mosquito vector
- translate basic applied research into policy guidance

4.3.8. Epidemiology

- investigate disease transmission patterns to understand the sources and spread of infections; and the emergence and spread of antimicrobial drug resistance, to inform malaria control and elimination
- undertake parasite genomic surveillance to inform the evolution of antimalarial drug resistance
- establish surveillance and response systems to improve efficiency of malaria control
- develop tools to identify and target areas of high malaria transmission risk
- define the burden of *P. vivax* infection, and morbidity/mortality attributable to relapses from hypnozoites
- elucidate how *P. vivax* relapse contributes to the burden of vivax infection, morbidity and transmission
- develop tools and strategies for the control and elimination of *P. vivax*
- measure the impact of intensified malaria control on the epidemiology and transmission of malaria

4.4. Research outcomes

4.4.1. Awards for scientific contributions

A number of seminal discoveries in the malaria field have been made by Australian researchers. A comprehensive and balanced description of these contributions is beyond the scope of this review, but some snippets are provided below as an indication of the breadth and power of Australian science. Some of these researchers have been awarded the Bancroft-Mackerras Medal for Excellence by the Australian Society for Parasitology for outstanding contributions to the science of parasitology: Graham Mitchell (1984), Kiaran Kirk (2008), Brendan Crabb (2009), Leann Tilley (2010), Malcolm McConville (2012), Una Ryan (2014), and Denise Doolan (2016). This Medal commemorates the contribution of the Bancroft-Mackerras dynasty to the development of the discipline of parasitology in Australia from the 1860s to 1960s. Some have been honoured as Fellows of the Australian Society for Parasitology, the highest honour the Society can award: Josephine Bancroft (1966), Ian Mackerras (1976), Graham Mitchell (1993), Alan Cowman (2011), David Kemp (2013), Geoff McFadden (2014), Leann Tilley (2018), Alex Maier (2018), Denise Doolan (2019), Kevin Saliba (2019), and Katherine Andrews (2020).

Australian malaria researchers have also been recognised by the Australian Academy of Science as among the Nation's most distinguished scientists, by election as Fellows of the Australian Academy of Science (AAS) for their ground-breaking research and contributions that have had clear impact including: Alan Cowman

(2001), Geoff McFadden (2005), Michael Alpers (2012) and Brendan Crabb (2021). Others have been honoured as Fellows of the Australian Academy of Health and Medical Sciences (AAHMS) including: Simon Foote (2014), Graham Brown (2015), Michael Good (2015), Brendan Crabb (2015), Ross Coppel (2015), Nick Anstey (2015), Kiaran Kirk (2017), James Beeson (2017), James McCarthy (2018), Alan Cowman (2020), Tim Davis (2020), and Ric Price (2021).

Research teams have also received The Eureka Prize for Infectious Diseases Research - awarded for outstanding infectious diseases research that benefits, or has the potential to benefit, human health, including: Alan Cowman and his WEHI team in 2011 for their extended research into the malaria parasite; the Bio21 team of Leann Tilley and James McCaw in 2016 for their work on resistance to artemisinin, the most commonly used frontline malaria treatment; and WEHI-Burnett researchers Wai Hong Tham, Ivo Mueller, Leanne Robinson, Rhea Longley and Michael White in 2019 for their work to develop new diagnostics and vaccine candidates for *P. vivax*.

4.4.2. Some key discoveries in brief

A particular strength of Australian research has been key insights into the parasite biology, in particular parasite invasion of the host erythrocyte, led by researchers at WEHI and the Burnet Institute (Cowman and Crabb, 2006). For example, Alan Cowman and team identified plasmepsin V protein as critical in parasite invasion of host cells, providing important insights into potential therapeutic targets to inform the development of novel antimalarial drugs (Boddey et al., 2010; Marapana et al., 2018). In-depth parasite biology studies at WEHI have now expanded to sporozoite invasion of host hepatocytes (Justin Boddey; Yang et al., 2017) and structural biology approaches (Wai-Hong Tham; Gruszczyk et al., 2018a, 2018b).

Geoff McFadden has provided innovative insights into the biology and evolution of *Plasmodium* spp., showing that it is related to algae and contains an organelle known as the "apicoplast", providing the foundation for the identification of new drug targets in the plastid of malaria parasites and increasing the number of strategies for the development of anti-malarial drugs (Ralph et al., 2004).

More recently, Stephen Kho and colleagues at Menzies have identified a hidden lifecycle stage of the *Plasmodium* parasite in the human spleen, which contributes to chronic anaemia and chronic infections and therefore will impact the malaria elimination agenda (Kho et al., 2021).

Researchers at Menzies (including Nick Anstey and Ric Price) have also been instrumental in studies of the non-falciparum malaria parasites, establishing *P. vivax* to be a major cause of severe and fatal malaria and conducting multi-country clinical trials to prevent *P. vivax* relapse using primaquine (Price et al., 2007). They also showed that *P. knowlesi* malaria is more likely to cause severe disease than *P. falciparum* and are leading research into this zoonotic parasite, establishing that the threat from *P. knowlesi* is increasing as other *Plasmodium* spp. are controlled (Anstey et al., 2021).

Australian scientists have made significant contributions to malaria vaccine development, including from the early days of subunit vaccine development when a team at WEHI (Graham Brown, Robin Anders, David Kemp, Ross Coppel, Alan Cowman and Robert Saint) developed an approach to clone proteins from the *Plasmodium* spp. parasite, publishing simultaneously with scientists from New York University (Ellis et al., 1983; Kemp et al., 1983). Those studies enabled the identification and characterization of numerous proteins as candidates for subunit malaria vaccines, some of which progressed to clinical testing. A combination of some of these antigens (fragments of MSP1, MSP2, RESA), called Combination B, was one of the first multi-antigen malaria vaccine candidates, developed by the Australian Malaria Vaccine Joint Venture in collaboration with the Swiss Tropical Institute, CSL, and Hoffmann-La Roche (Genton et al., 2003).

Important contributions have been also made towards the development of a whole parasite vaccine. The first genetically-attenuated antimalarial vaccine, tested in human clinical trials in 2013, was produced by Alan Cowman's team at WEHI in collaboration with international researchers including Stefan Kappe at the Seattle Biomedical Research Institute (USA; Mikolajczak et al., 2014; VanBuskirk et al., 2009). More recently, Michael Good and Danielle Stanisic at Griffith University have been developing a chemically attenuated whole parasite vaccine that targets the blood-stage of the malaria parasite, called PlasProtecT®, that elicits cross-species protective immune response in rodent models and was immunogenic in first-in-human clinical studies (Stanisic et al., 2021).

Australia has been also recognised internationally for efforts directed to drug discovery. Leann Tilley's team at the Bio21 Institute, University of Melbourne, has generated innovative insights into the cell biology of the parasite to inform drug development, including using cutting-edge imaging to probe biological structures and processes (Bridgford et al., 2018). Also at Bio21, Malcolm McConville's team has pioneered the development of metabolomic approaches for dissecting the metabolism of *Plasmodium* parasites and host cells in vitro and in vivo; these metabolic pathways are potential drug targets and also enable high content phenotypic screens for screening drug libraries (Creek et al., 2016). At ANU, Kiaran Kirk and colleagues have provided insights into the mechanisms of action and of resistance to antimalarial drugs (Martin et al., 2009). Vicky Avery at Griffith University's Eskitis Institute (now Griffith Institute of Drug Discovery, GRIDD) had a long partnership with AstraZeneca and other partners for high throughput screening for drug discovery (Duffy and Avery, 2012). Kathy Andrews is leading other GRIDD efforts on developing new drug leads. Over the past decade, a major contribution has been the application of the blood-stage controlled human malaria infection model, termed induced blood stage malaria (IBSM), for screening new drugs by assessing drug effectiveness against live malaria parasites inside human volunteers, by James McCarthy at QIMR Berghofer Medical Research Institute working with the Medicines for Malaria Venture (McCarthy et al., 2011; Cooper et al., 2019).

QIMR researchers Allan Saul and Qin Cheng pioneered molecular detection of *Plasmodium* using controlled human malaria infection studies, providing important fundamental information into molecular diagnostics (Cheng et al., 1997) which has been instrumental in advancing vaccine and drug development. Karen Day and Alyssa Barry have led important studies on the genetic epidemiology of malaria, describing the diversity of malaria parasites globally to further our understanding of the parasite, improve disease surveillance and control and informing drug and vaccine development (MalariaGEN Plasmodium falciparum Community Project., 2016).

Australia has also made important contributions to the understanding of host-parasite immunity, including the role of T cells in pre-erythrocytic stage immunity (Michael Good and Denise Doolan at QIMR; Good and Doolan, 2010), T cells and other host factors in immune regulation (Magdalena Plebanski at Monash University (Plebanski et al., 1999) and Christian Engwerda at QIMR (Engwerda et al., 2014), antibody-mediated immunity (James Beeson and Michelle Boyle at WEHI-Burnet; (Boyle et al., 2015; Reiling et al., 2019), and most recently tissue resident memory T cells (Bill Heath (Fernandez-Ruiz et al., 2016).

George Grau at the University of Sydney is internationally known for his work on malaria pathogenesis and severe malaria, particularly of cerebral malaria (Wassmer and Grau, 2017). Stephen Rogerson has provided important insights into the pathogenesis and immunity of malaria in the humans, with an interest in the

treatment and prevention of malaria in pregnancy and young children (Ataide et al., 2014). This work extends the long-term contributions made by Graham Brown, bridging clinical work through population and public health, and basic science in the field of malaria (Brown, 2011). Brendan Crabb and researchers at the Burnet Institute have expanded Australia's reputation in this area, working with international partners in malaria-endemic regions of the Asia-Pacific Australia in "real-world applications"

The above represents only a very small part of the overall contribution that Australian scientists have made to the fight against malaria, and the importance of other contributions not noted here should be acknowledged.

5. The next 50 years

The past decade has seen tremendous advances in science, including conceptual and technological advances. A major advance has been a paradigm switch in thinking away from a reductionist (gene-by-gene or protein-by-protein) to a holistic (whole organism) viewpoint. This acknowledges that effective interventions against complex pathogens need to take into account the underlying complexity considered as a whole. It also acknowledges that host-pathogen immunity is composed of complex, dynamic interactions of cellular and molecular components and networks that cannot be represented by any individual component in isolation (Loiseau et al., 2020). Systems-based approaches which measure a large number of parameters on a global scale have proved to be powerful in deconstructing the big picture of the whole organism into smaller segments that can be understood and assessed, and that can capture the underlying phenotypic and functional complexity. Coupled with this has been a paradigm switch from "empirical" to "knowledge-based" design of effective interventions against disease.

Critical to this change in thinking has been recognition of the importance of inter-disciplinary and cross-disciplinary research, to integrate expertise and methods from different disciplines to work together towards a common goal. Important in progressing the cross-disciplinary development of interventions against malaria has been the recognition of the power of inter-institutional and international collaboration. An important (but not the only) collaboration in this regard was the OzeMalR Australia-Europe Malaria Research Cooperation, with a strategic goal to strengthen collaborative links between European and Australian laboratories with the objective to exploit synergies and foster innovative approaches in the field of malaria research.

Another important conceptional advance has been the recognition of the importance of human samples and human models to study a human disease. Historically, rodent models of disease have played a key role in basic and applied research to inform our understanding of protective and pathological immune mechanisms, potential vaccine antigens, and vaccine platforms. However, animal models do not necessary reflect the true situation in humans. Thus, there has been an increasing recognition of the importance of clinical research in humans; and models of CHMI have been developed (Pombo et al., 2002; Collins et al., 2018; Cooper et al., 2019). These facilitate improved understanding of parasite biology, host-parasite interactions, and immune mechanisms, and facilitate the development of novel drugs, vaccines and host-directed therapeutics.

Rapid technological advances and sophisticated cutting-edge technologies, especially in systems-based disciplines, complement these conceptual advances, enabling an unprecedented comprehensive high-resolution and high-throughput examination of thousands of genes, transcripts, and proteins to provide a multi-dimensional, holistic view. Accompanying this has been extraordinary advances in computational sciences, bioinformatics and analytical tools to interrogate the large metric datasets.

The rapidly expanding resolution, dimensionality and diversity of biological datasets, fuelled by technological and conceptual advances, suggest that innovations in the development of diagnostics, drugs, vaccines, therapeutics, control measures, and other interventions against malaria will escalate during next half century. It remains to be seen whether we can harness the tools of modern science to eliminate the global public health burden during the next 50 years, but the transformative advances made during the past 50 years suggest that this will be possible.

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