What motivated you to begin studying malaria and what is the overarching aim of your research?

After I obtained my PhD at Osaka University in Japan, I knew I wanted to continue studying and so I began to look for a postdoctoral opportunity. I hoped to find a position where I could put my molecular biology knowledge and training to good use, rather than working in a famous laboratory where I would simply be a ‘small cog in a large wheel’. The ideal opportunity presented itself when I received postdoctoral recruitment information from Professor Joseph Inselburg at Dartmouth College, USA. Now, almost 30 years down the line, I see myself as a biologist and parasitologist who strives to integrate, as much as possible, the fields of biochemistry, genetics, immunology, infectious diseases and epidemiology, in order to contribute to scientific advances in malaria research. My goal is to establish the serine repeat antigen (SERA) as a potential malaria vaccine.

Considering the existence of antimalarial drugs, can you explain why a malaria vaccine is necessary?

Vaccines are necessary for a number of reasons. Firstly, they would be able to combat the rising resistance to many antimalarials, especially when most available drugs in endemic areas are of low quality. Secondly, they are more cost-effective than chemoprophylaxis – plus adherence and compliance rates to vaccines are higher, especially in areas where access to medicines may be poor. Thirdly, they represent a viable alternative for intermittent visitor populations, such as aid or military workers. Finally, they would reduce mortality and morbidity in malaria endemic areas.

What characteristics of Plasmodium parasites make malaria difficult to control?

Malaria has a complex life cycle and Plasmodium parasites cause chronic infection in the human host. The pathogen has evolved several different mechanisms that confound the immune system: they replicate inside red blood cells and thus cannot be attacked by the immune system for much of their erythrocytic life cycle; they have developed antigenic diversity, either through the vast array of antigens expressed or through strain-specific antigen allelic polymorphism; they have the ability to induce immunomodulation, which in turn interferes with T cell and B cell presentation, recognition and activation, as well as generation of immunological memory; they have proteins that exhibit high polymorphism, with unusual patterns including tandem repeats; and finally, they have many proteins with redundant functions.

Will your research and development of a malarial vaccine have applications in other diseases caused by parasitic protozoa?

The identification of appropriate protective antigens alone is not the only difficulty in the development of vaccines against parasitic diseases. Efforts are further complicated by a lack of understanding in terms of the types of immune responses needed for protection; lack of animal models and rigorous assays for assessing vaccine candidates; and the lack of availability of immune-enhancing adjuvants. These make vaccine development studies expensive and time consuming. We anticipate that as we conduct more studies with BK-SE36 and malaria, we will generate more information regarding immune responses and malaria co-infections with other diseases; as well as valuable data on additional adjuvants compatible for human use that can effectively mobilise both cellular and humoral immune responses. These may help other parasitic protozoan diseases, but it is also very important to stress that, because of the uniqueness and complexity of each parasite infection, applicability may not always be straightforward.

Our collaborations have allowed us to conduct important epidemiological and immunological studies. The first courageous step to push SERA as a vaccine was made after we observed very good correlations between Ugandan high-titre individuals and absence of malaria symptoms. Collaborations have also allowed us to obtain a large, geographically diverse set of P. falciparum isolates that we have used to further characterise and understand the genetic diversity of SERAS. Most importantly, our collaborations have allowed us to build and strengthen our research results and answered the need for capacity building. The efficient use of biological samples, along with the exchange of skills and expertise to conduct both epidemiological work and in vitro analyses, have provided valuable opportunities with regard to bridging molecular data and clinical observations.

What is your role in malaria research? 

As a postdoctoral researcher, I contribute to projects conducted in my laboratory. My role is to conduct research under the direction of my principal investigator and to support the laboratory research with technical and/or administrative tasks. I also participate in meetings, seminars and courses to keep up with new developments in the field.

How do you collaborate with other academic groups in Uganda, Thailand, Indonesia and the Solomon Islands?

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How do your collaborations with other academic groups in Uganda, Thailand, Indonesia and the Solomon Islands assist your research into the molecular mechanisms underlying malaria?

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As one of the most serious infectious tropical diseases, malaria is an enormous burden on global public health. While the past decade has seen major advances in lifesaving prevention and treatment interventions, over 40 per cent of the world’s population live in malaria-endemic areas and it is a leading cause of death and disease in many sub-Saharan African countries. Worryingly, malaria control today is further threatened by growing incidences of drug-resistant parasites. Despite many years of intensive research into malaria, there is currently no commercially available vaccine. One of the main reasons for this is the complexity of the malaria parasite, *Plasmodium falciparum*, which has an incredible capacity to evade the host’s immune response, derived from its genetic complexity and antigenic variation. There is therefore an urgent need to build a fuller understanding of parasite biology in order to gain insights into potential vaccines. The disease can be controlled, and possibly eliminated, through the administration of an effective malaria vaccine, coupled with novel drug targeting strategies and other efforts.

Dr Toshihiro Horii – Head of the Department of Molecular Protozoology and Director of the Research Centre for Infectious Disease Control and International Research Centre for Infectious Diseases at the Research Institute for Microbial Diseases, Osaka University – has spent the past three decades studying malaria. With more than 150 research papers published in peer-reviewed journals, Horii’s research is currently focused on the development of malaria vaccines and drugs. The researchers in his laboratory are using molecular and cell biology approaches to study the mechanisms by which members of the *Plasmodium* genus adapt to a new host. The hope is that their research insights will help to inform the development of a malaria vaccine and antimalarial drugs.

**Investigating Immunity**

For the past 13 years, Horii has focused on developing a serine repeat antigen (SERA) malaria vaccine. In a landmark achievement in the early 1990s, his team pioneered a technique enabling them to prepare recombinant SERA proteins from *Escherichia coli* using artificial synthetic genes. Excitingly, through mouse models and preclinical trials using squirrel monkeys and chimpanzees, the researchers subsequently demonstrated that animals develop antibodies following vaccination with these recombinant SERA proteins and, in turn, that the antibodies inhibit the growth of malaria parasites.

Following the success of their initial laboratory experiments, the researchers embarked on a research study with Professor Thomas Egwang, Director General and CEO of Med Biotech Laboratories in Uganda. In 1997, they sent Egwang recombinant SERA proteins in order to ascertain whether these antibodies existed in inhabitants of malaria endemic areas in Africa. Encouragingly, it was found that naturally acquired immunity against malaria correlates with the development of anti-SERA IgG3 antibodies. These highly promising results motivated Horii to push harder for a SERA vaccine, paving the way for human clinical trials.

**Clinical Investigations**

Horii and his collaborators have recently completed phase I clinical trials for their novel BK-SE36 SERA malaria vaccine candidate. After conducting a phase 1a trial in malaria-naive Japanese adults, they carried out a phase 1b trial in a malaria-endemic area of northern Uganda; made possible by their long-term collaboration with Egwang. The phase 1b trial was randomised, single-blinded and placebo-controlled. It was done in two stages, with the

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**Scientists from Osaka University, Japan, are investigating the immunogenic and protective effects of a promising vaccine candidate for malaria.**

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**The Horii Laboratory**
first involving adults aged 21-40 and the second including individuals aged 6-20. A computer sequence randomised healthy subjects for two subcutaneous injections at 21-day intervals. The safety was monitored throughout the trial and antibody responses were measured 21 days after each vaccination.

Although the trial was not designed to measure efficacy, the researchers completed a follow-up study to gather preliminary information about the potential efficacy of BK-SE36: “In malaria-endemic areas, it is common for the population to carry asymptomatic infections,” explains Horii. “Thus evaluation was carried out using a risk ratio, as well as conducting statistical tests that allow inclusion of various covariates and assessment of risk to subsequent malaria episodes between the vaccinated individuals and the control group.” Encouragingly, in the one-year follow-up study, those who had been vaccinated with BK-SE36 were found to have a 72 per cent protective efficacy against high parasitaemia and fever – and they also experienced fewer multiple malaria episodes.

PARASITE EVOLUTION

Another area of research in Horii’s laboratory is the evolution of malaria parasites. The scientists have conducted population genetics analyses that have assisted with and informed their vaccine development studies. For example, while multigene families often evade the host immune response by presenting a variety of antigenic molecules to the host immune system, the SERA multigene family does not display this typical antigenic variation; some family members are expressed at the same time. “Other SERA gene family members also appear to work at different parasite stages,” continues Horii. “Studies on the evolutionary history of 134 SERA genes from 18 Plasmodium species allowed us to speculate that SERA genes may have acquired multiple functions relevant to the parasite expansion of the host range.” In addition, other population genetics research conducted in Africa, Southeast Asia, Oceania and South America has shown that the antigen gene PFSERAS does not display substantial polymorphism. Crucially, these evolutionary studies help the researchers identify the strength of vaccine candidates.

FUTURE DIRECTIONS

Horii and his team have made steady progress in their development of the BK-SE36 malaria vaccine, with their preliminary results showing promise for its safety and efficacy. Looking ahead, the researchers are eager to continue refining and testing their candidate, in the hope that it will eventually be used among children and adults in endemic areas as well as travellers from non-endemic areas. With this objective in mind, they are currently exploring the possibility of reformulating the BK-SE36 vaccine with a humanised CpG adjuvant to find out whether this will improve immunogenicity in subjects over 10 years old. Additionally, in view of the protective response observed in the phase 1b follow-up study, the researchers are planning to implement further BK-SE36 clinical trials in children aged 0-5 years. The ultimate goal is that their research efforts will contribute to the increased control and potential elimination of one of the world’s most deadly diseases.