The end of malaria is within reach

Drs Nirbhay Kumar and Geetha Bansal are conducting investigations into malaria vaccine research. Here, they discuss what led to their specific project, ongoing inspirations and the impact their findings could have on malaria endemic countries around the world.

**What initially drew you both to malaria research, and what keeps you working to eliminate the effects of this serious illness?**

**NK:** Malaria is a public health issue of global significance where large numbers of people living in malaria endemic regions are innocent victims. One bite from an infected anopheline mosquito has the potential to start a complex infection. It is believed that effective vaccines will provide a long lasting and cost-effective strategy to control malaria, improve public health and elevate affected societies out of poverty. Societal needs and scientific challenges have drawn us to the field of malaria vaccines, especially those that will directly benefit the people who are residents of endemic regions.

**GB:** I am a very recent recruit into the malaria field; I started about three years ago. At the time, I was looking for a research laboratory where I could apply my knowledge and expertise in vaccine immunology. Disease transmission and immunopathogenesis were always particularly fascinating topics for me. I discovered that not much was known about the immune responses generated during the later stages of the malaria parasite in humans – stages that were critical to the transmission process. I was able to tie my interests with the interests of the Kumar lab, and together we have focused our efforts on creating immunity against the sexual stages of the parasite.

**You are sitting on a malaria transmission-blocking vaccine (TBV) candidate that is ready to scale up and be tested in humans. What are TBVs, and how do they work?**

**NK:** TBVs elicit immune responses comprised primarily of antibodies that target antigens uniquely expressed during the sexual stages of mosquito development.

**Malaria transmission-blocking vaccine (TBV) concept**

1. INFECTED PEOPLE
2. INFECTED MOSQUITOES
3. TRANSMIT MALARIA BY INFECTING MORE PEOPLE
4. INFECTED BUT TBV VACCINATED PEOPLE PRODUCE ANTIBODIES
5. ANTIBODIES BLOCK PARASITE DEVELOPMENT IN MOSQUITO
6. FEWER OR NO MOSQUITOES INFECTED
7. EFFECTIVE REDUCTION OF MALARIA TRANSMISSION

Through the creation of an effective TBV, vaccinated people – both infected and uninfected – will produce antibodies, which will then block the parasite’s development in the mosquito vector and as a result reduce the transmission and prevalence of malaria.
Presence of such antibodies aborts parasite growth and development in the mosquitoes. This translates into reduced malaria transmission potential, because the TBV-induced antibodies make these mosquitoes inconsequential to malaria transmission success.

What benefits do TBVs offer in comparison to current standard malaria treatments?

NK: A hungry, infected female anopheline mosquito landing on a person injects hundreds of infectious sporozoites (a product of mosquito stage parasite development) while feeding on blood. Sexual forms (also known as gametocytes) developing within erythrocytes in an infected person transmit the parasites back to blood hungry female mosquitoes. By blocking parasite development in the mosquitoes, a TBV aims to interfere with the transmission cycles.

Malaria exists if the transmission goes on. By reducing and/or stopping malaria transmission, a TBV will interrupt malaria transmission. There is currently no vaccine that targets the transmission cycle and the only vaccine advanced through phase III clinical trials has shown only marginal efficacy against clinical malaria.

Can you introduce your primary TBV candidates, CH-rPfs25 and CH-rPfs48/45?

NK: Pfs25 and Pfs48/45 are two of several proteins expressed in parasite stages during transmission. Pfs48/45 is expressed in the gametocytes developing within erythrocytes in an infected person. It is also a target of transmission reducing antibodies elicited during natural infection. Pfs25, on the other hand, is expressed only after parasites are ingested by the mosquitoes and male and female parasites have been united through the fertilisation process. Nonetheless, antibodies recognising specific sites on these molecules are effective blockers of parasite development in the mosquitoes.

Have you worked on other candidates to date?

GB: While focusing on these approaches, a recent research effort – led by the Bansal lab – has focused on natural immune attack against gametocytes themselves. These initial studies are expected to open a new area of investigation, leading to efforts to identify novel candidates for the same overall goal, such as transmission blocking immunity.

We are also working on generation of monoclonal antibody reagents that will be very useful in characterising the transmission blocking epitopes and the role of such proteins in the development of sexual stages. They may also play a part in the creation of detection and diagnosis assays for malaria.

Finally, how do you envisage your work will be received in the future?

NK&GB: We look forward to appreciation and recognition of our contributions. The latter for a scientist comes in the way of the development of partnerships that can facilitate translation of basic science discovery into a product for the good of society.

We seek industrial partnerships and collaborative interactions with experts who can work together for effective planning of vaccine trials for TBVs and develop models to predict vaccine efficacy and modifications to further vaccine trials.

The work done in the Kumar Lab for the last 30 years has culminated in an extremely well characterised vaccine candidate, and we are ready and willing – with support from funders and policy makers – to take this to clinical development and end the devastation of malaria.

MALARIA IS A tropical disease that can be spread by a single bite from an infected mosquito. It is estimated that some 3.2 billion people around the world are at risk of malaria and, tragically, there were approximately 438,000 malaria deaths in 2015. If the condition is diagnosed and treated promptly, there is an extremely high chance that patients will go on to make a full recovery. However, its prevalence and unprecedented levels of associated risks – in terms of the potential amount of people who can be affected by the condition – necessitates continued research to eliminate the disease entirely. As such, scientists around the world continue to investigate a means of realising a goal of malaria-free endemic regions and, ultimately, a malaria-free world.

The disease itself is caused by four species of Plasmodium, commonly known as the malaria parasite. These parasites live inside many species of anopheline mosquitoes and so much of the work into curbing incidence of malaria has focused on targeting the mosquito vector and treating the infection. “The problem with this strategy is that mosquitoes continue to evolve resistance to insecticides and parasites themselves are able to evolve resistance mechanisms to antimalarial drugs,” notes Dr Nirbhay Kumar, a malaria expert based at Tulane University’s School of Public Health and Tropical Medicine.

ELIMINATION IS BETTER THAN TREATMENT A far more effective strategy for eliminating malaria would be to find a means of preventing transmission in the first place. To achieve this goal, it is important to understand the precise ways in which malaria is transmitted. During infection, parasites invade red blood cells, multiply and manifest clinical symptoms, including death. However, in order to transmit the disease successfully, these previously asexual parasites must transform into male and female sexual stages (gametocytes); these gametocytes continue the transmission cycle when ingested by blood sucking female anopheline mosquitoes. Furthermore, additional extensive development of gametocytes in the mosquitoes leads to a rapid proliferation of the parasites, thereby significantly increasing the chances of successful transmission of malaria.

Knowing this, alongside Dr Geetha Bansal, Kumar has adopted an approach that targets the formation and survival of gametocytes within the infected human host, and the development of parasites inside the mosquitoes. Kumar and Bansal have been
Through a process of persistence and patience, Kumar and Bansal have shown reproducible potent functional immunogenicity of Pfs25 vaccine formulations working on developing a malaria transmission-blocking vaccine (TBV) candidate. “Through our research we have developed methodology to produce and evaluate TBV candidates,” explains Kumar. “We have focused our efforts on two specific candidates – Pfs48/45 protein expressed within gametocytes and Pfs25 expressed during mosquito stage development of the parasites.”

While both Pfs48/45 and Pfs25 are valid targets of TBV, the team is particularly excited by the potent immunogenicity outcomes that have been revealed by their vaccine trials in preclinical animal studies. The reason for this is based on their unique patented process of producing the vaccine candidate. “This is what makes our vaccine so unique,” enthuses Kumar. “It is also what makes it better than other similar protein out there whose immunogenicity is not as potent.”

**TWO PROTEINS, ONE GOAL**

The dedication Kumar has towards eliminating malaria is evidenced by his grit – he has been working at achieving this goal since 1982. Although there has been a significant increase in the attention TBVs have attracted in recent years, Kumar has long held the belief that Pfs25, and possibly Pfs48/45 proteins, hold the key to the development of successful TBVs.

In the last few years, Kumar has joined forces with Bansal, who brings her expertise in vaccine immunology to his considerable experience in tackling malaria. Their studies thus far have revealed much about both Pfs25 and Pfs48/45 proteins, understanding that has boosted the chances of combating malaria. “Pfs25 is seen only in mosquito stages and therefore the parasite escapes immune pressure,” explains Bansal. “On the other hand, Pfs48/45 is seen during sexual development in humans and can therefore trigger immune responses. Thus, it acts as a natural booster dose that can enhance antibody development in humans.”

Incredibly, through a process of persistence and patience, Kumar and Bansal have shown reproducible potent functional immunogenicity of Pfs25 vaccine formulations. In fact, their Pfs25 vaccine formulations are ready for further clinical development – they are now looking to start clinical trials in humans.

**ACHIEVING ENHANCED IMMUNOGENICITY**

Alongside these activities, the team has also pursued an approach that relies on a DNA vaccine platform: “These are easy to produce,” Bansal explains. Excitingly, their research has established that this approach is a clear alternative for creating a successful vaccine. A DNA vaccine platform may also offer a convenient strategy for combining multiple vaccines into a ‘cocktail’ aimed at targeting multiple life cycle stages of malaria on one hand and vaccines targeting multiple species of malaria parasites on the other.

Developing vaccines, as one might expect, is an extremely difficult process. While the team has made great leaps in the area of TBVs, Kumar and Bansal have also considered the methods best suited to deliver the vaccine. Effective vaccines require both a formulation with molecules known as immunomodulators and an appropriate means of delivering them. Kumar and Bansal have therefore been collaborating with a company to evaluate the impact of in vivo electroporation to increase the level of immune responses. “Our studies have revealed 10-100-fold enhanced immunogenicity of DNA vaccines. Our current efforts seek to develop other technologies that can produce similar results but without the need for applying electroporation,” enthuse Kumar and Bansal.

**AN HONOURABLE THREE DECADES**

Despite the burden malaria places upon societies across the globe, it does not receive the same level of support as other infectious diseases, such as HIV and tuberculosis. Indeed, funding has proved a huge obstacle in Kumar’s attempts to combat malaria, although his enthusiasm is far from diminished. “Working in US academic institutions with other academic commitments such as teaching, as well as trying to seek research funds, takes away a lot of time from creative thinking and dedicated uninterrupted effort to eliminate malaria,” explains Kumar. "Despite these obstacles, my laboratory has maintained steady progress, and I genuinely believe that breaking the malaria transmission cycle with TBVs will play a critical role in elimination efforts.”

Kumar’s experience, his extremely successful collaborations with Bansal and their impressive results serve to demonstrate the important role that research funders and policy makers could play to improve quality of life for millions of people. Partnerships to help them to clinically develop their TBV vaccine candidates for humans. The chance to eradicate malaria completely is within reach – it simply requires collaborative partnership between funders and vaccine developers.