Why haven't we made an efficacious vaccine for malaria?

Michelle N. Wykes

Malaria, caused by *Plasmodium* spp., is annually responsible for approximately 780,000 deaths and more than 225 million clinical infections worldwide. In the past ten years, over 40 malaria vaccines designed to generate immunity against subunit components of liver or blood-stage parasites, or whole sporozoites, have undergone clinical trials. Many show excellent protection in pre-clinical and initial phase I and phase IIa trials, but none have progressed to the stage of a vaccine that protects in the field. Even the leading malaria vaccine candidate RTS,S was found in phase IIIb trials to provide only modest protection against both clinical and severe malaria in young infants. Which leads to the question: why haven't we been able to make an efficacious malaria vaccine?

Plasmodium spp. are efficient at establishing repeated, new and chronic clinical and sub-clinical infections, despite the best control efforts. It could be argued that malaria vaccine development is hindered by the complexity of the life cycle of the parasite and the vast repertoire of polymorphic proteins. However, given that so many vaccines have shown great promise in pre-clinical studies and then failed to completely protect in the field, suggests that perhaps we also need to consider whether the parasite has mechanisms to evade immunity. If the parasite does evade immune responses, then no vaccine will ever provide adequate protection.

Two longitudinal studies, undertaken in malaria-endemic Mali, allude to immune evasion. First, intensive *P. falciparum* (*Pf*) biweekly testing of 251 children and adults for seven months, found no evidence of acquired sterile immunity to *Pf* infections, despite years of exposure to intense malaria transmission [1]. Furthermore, a study tracking *Pf*-specific memory B cells over a year found that their numbers increased after acute malaria and then, after six months of decreased *Pf* exposure, contracted to a point slightly higher than pre-infection levels [2]. The loss of these memory B-cell responses could explain why protection, which for most vaccines trialled was based on antibodies, was not robust or long-lived.

Perhaps more telling are studies of $MSP1_{19,}$ which was a leading malaria vaccine candidate. In clinical trials undertaken in Kenya, the vaccine generated high titres of antibodies but did not protect against infection [3]. An evaluation of this vaccine, in an experimental mouse model, also found that vaccination generated excellent titres of protective antibodies and vaccine-specific memory B cells [4]. However, these responses were short-lived in mice exposed to malaria [4]. Further investigation revealed that malaria caused changes to dendritic cells, which decreased their capacity to support memory B-cell survival [5]. These laboratory-based studies thus suggest a possible reason for why memory B cells generated by vaccines or following the wet season are unable to protect against infection. There is ample further evidence that *Plasmodium* spp. might compromise dendritic cell functions [6] required to generate long-lasting immunity.

If the parasite escapes immunity by modulating immune responses, could we put immunity back on track by blocking immune signals or by using recombinant proteins to mimic signals absent during malaria? One study to show that this might be possible found that simultaneous blockade of programmed cell death 1 (PD-1) and lymphocyte-activation gene 3 (LAG-3) pathways reinstated immunity against malaria and accelerated clearance of the infection [7]. However, the cost and difficulty in administering such treatments are considered insurmountable. Whilst this is true for Africa, other parts of the world such as India and the armed forces of developed countries also face this disease, albeit on a smaller scale, and have economies better placed to adopt such treatments. If such a treatment were put in place for these countries or organizations, it could then move into Africa. Given that millions have died and that an exact figure cannot be placed on the financial cost of vaccine development or the cost to economies as a result of malaria, it is high time to think seriously of new treatments for this disease.

CONFLICT OF INTEREST

The author declares that she has no conflict of interest.

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Endless paces of degeneration—applying comparative genomics to study evolution's moulding of longevity

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Why can mice not live more than five years and dogs not more than 30, yet bats can live over 40 years and humans over a century? Differences in longevity between closely related species are one of the greatest mysteries in biology, and identifying the processes responsible could ultimately presage the development of therapies against a multitude of age-related diseases. The variation in mammalian longevity must have a genomic basis, with recent

genome sequencing efforts opening up exciting opportunities to decipher it; some promising results are beginning to emerge. Analysis of two bat genomes revealed that a high proportion of genes in the DNA damage checkpoint–DNA repair pathway, including *ATM*, *TP53*, *RAD50* and *KU80*, are under selection in bats [1]. This finding is exciting because these genes have been directly associated with ageing in model systems and, therefore, it points towards a potential role for averting DNA damage in longevity assurance mechanisms; a notion dating back several decades that remains contentious. In addition, the report of a systematic scan for proteins with accelerated evolution in mammalian lineages in which longevity increased over the course of their evolution, hinted that some repair systems, such as the ubiquitin–proteasome pathway and a few proteins related to DNA damage repair, might have been selected for in long-lived lineages [2]. However, much work remains to improve the signal-to-noise ratio of this and similar methods.

With decreasing costs of sequencing, the growing number of genomes of species with diverse lifespans is expected to facilitate studies in this area. As such, we can make an increasing number of comparisons such as those described above. Put simply, if we study long-lived species and find that they share genetic adaptations—for example in DNA damage response pathways—then we might assume that those adaptations are important to increase longevity. There are major intrinsic difficulties with this type of analysis, however, that one must keep in mind. Perhaps the best illustration is that despite the dramatic phenotypic divergence between humans and chimpanzees, only a relatively small number of genetic adaptations that are probably responsible for such divergence have thus far been identified [3]. One difficulty is that the genomic elements underlying species differences remain controversial. Possible processes include mutations in coding and non-coding sequences, gene family expansion and contraction, and copy number variation, all of which we think must be explored in the context of longevity adaptations. Whilst changes in regulatory regions might be important, standard methods are lacking for the detection of selection on functional non-coding sequences on a genome-wide scale and this, we think, is a limitation for progress in this area. Another limitation is that experimental validation of promising candidates is often extremely difficult to obtain.

Applying comparative genomics to study the evolution of longevity also has unique challenges. For one, the force of natural selection weakens with age, indicating that, although under low-hazard conditions selection favours genes and pathways conferring longevity, selective pressure for longevity is significantly less than for other traits. Furthermore, we think that the integration of additional data—for example gene expression and age-related phenotypic data—is crucial to link genotypes to phenotypes and identify physiological adaptations that are required for extended longevity. Unfortunately, such data and even the necessary samples to generate it are as yet only available for a subset of species. In our opinion, another crucial issue is the extent to which common mechanisms underlie the extension of longevity by evolution in different species. Just as rare variants contribute to missing human heritability, taxa-specific adaptations might contribute to longevity. It can be assumed that the environment—for example, diet—of each species will influence the physiological and biochemical pathways that must be optimized to fend off ageing and age-related diseases. However, the ageing process, despite progressing at different rates, is remarkably similar across most mammals studied [4], hinting that retarding ageing might involve adaptations in similar pathways. The degree of overlap between longevity assurance mechanisms is, in our view, a crucial determinant of how much we can expect to learn about species differences in ageing in the foreseeable future. If common pathways do indeed underlie longevity evolution in multiple species, even if involving different genetic elements in different taxa, then it is reasonable to expect that they can be identified by using comparative genomics as more genomes of short- and long-lived species are sequenced. We hope to live long enough to help unravel this age-old problem.

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