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Malaria parasite genetics: doing something useful

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ABSTRACT

Genetics has informed almost every aspect of the study of malaria parasites, and remains a key component of much of the research that aims to reduce the burden of the disease they cause. We describe the history of genetic studies of malaria parasites and give an overview of the utility of the discipline to malariology.

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1. The beginning

Observe the ciliate protozoa *Paramecium aurelia* in a drop of pond water through a microscope, and you'll see it slide, glide and dance. Add a drop of serum from a rabbit immunized against that particular strain, and the movement ceases as the cilia stop beating. Apply the same sera to a different strain of *P. aurelia*, however, and the ciliates will carry on swimming happily. The reason? Strain-specific antigen variation; and investigating the genetics of the inheritance of the antigens was the task undertaken by Geoffrey Beale at Edinburgh University's Institute of Animal Genetics during the 1950s.

Beale was the UK's most eminent protozoan geneticist, and his work on the genetics of *P. aurelia* [1] was groundbreaking. It led to his appointment as a Royal Society Professor, and enabled him to set up his own Protozoan Genetics Unit in the mid 1960s. It was at this time, specifically in 1966, that he was approached by Professor P.C.C Garnham, of the London School of Hygiene and Tropical Medicine, and tasked with "doing something useful". What Garnham had in mind, of course, was the application of genetic studies to malaria parasites.

Classical genetic studies require the ability to perform crosses, and with malaria parasites, crossing occurs in the mosquito. Shortly after the insect has engorged herself on malaria parasite infected blood, male and female gametes fuse to produce an ookinete, which traverses the mid-gut epithelium, encysts on the mid-gut epithelium wall, and undergoes multiple rounds of nuclear fission followed by cell division into multiple daughter cells (multiple fission, or schizogony), producing thousands of sporozoites – the forms infective to the next host – which, about two weeks following the initial blood meal, migrate to the salivary glands where they lie ready and waiting to infect a new host (Fig. 1).

The most obvious laboratory-friendly models of malaria were the rodent malaria parasites, discovered and subsequently isolated in central Africa, and first introduced into laboratory mice in 1948 [2]. From that date until the mid-1960s no one had managed to transmit them through mosquitoes, making genetic crosses impossible. In 1965 came the big breakthrough; Jerome Vanderberg and Meir Yoeli of New York University became the first people to transmit a rodent malaria parasite to mosquitoes, when they successfully infected *Anopheles quadrimaculatus* with *Plasmodium berghei* [3].

The breakthrough came following the observation by Yoeli that the forest galleries of Katanga, where the parasites had first been isolated, were rather cooler, at about 18–22 °C, than the 26 °C or so at which other malaria parasite species were routinely transmitted to mosquitoes in the laboratory. One year later, in 1966, came the successful transmission of two other rodent parasites to mosquitoes; *P. berghei yoelii* (now known as *P. yoelii*), and *P. chabaudi*, in Garnham's own laboratory in London. These parasites had just been discovered and isolated in the Central African Republic by Irène Landau of the Museum National d'Histore Naturelle in Paris [4,5]. They transmitted at the more usual tropical temperature of 26 °C[1].

Now that a malaria parasite system with which the whole life cycle could be completed, and in which there was likely to be extensive genetic diversity was available, Beale and Garnham could begin to do something useful with protozoan genetics. Garnham sent David Walliker, who had recently completed his PhD on the protozoans

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[1] Following the advice of Laurent Renia (A-STAR Singapore), greater success has been achieved with the transmission of *Plasmodium yoelii* to *Anopheles stephensi* in our laboratory when the temperature of the insectary is maintained at temperatures at or slightly below 24 °C.

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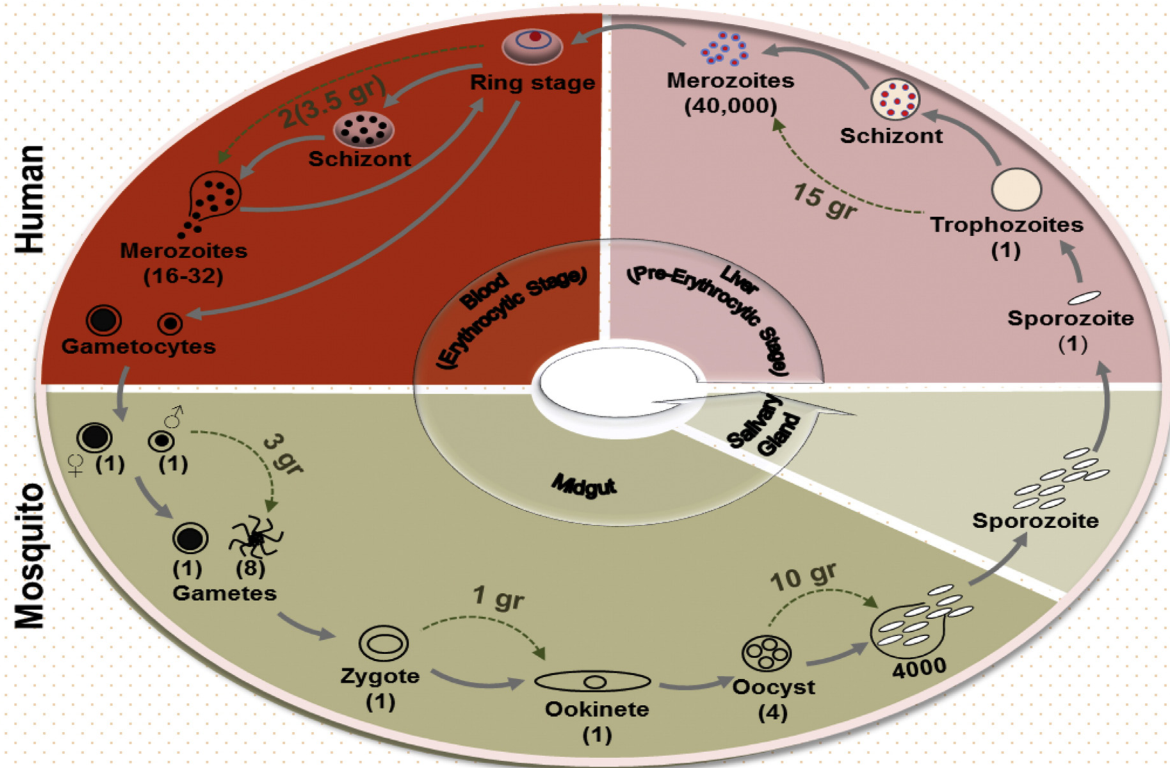

Fig. 1. ***Plasmodium falciparum* lifecycle**: During a blood meal, the female *Anopheles* mosquito ingests male and female gametocytes; the microgametocyte undergoes 3 rounds of genome replication producing 8 gametes which fuse with female gametes to generate a diploid zygote. The zygote undergoes meiosis, becomes an ookinete which traverses the midgut epithelium on which it encysts as an oocyst containing up to 4 distinct haploid nuclei. Each of these nuclei undergoes 10 rounds of DNA synthesis (10 genome replications) yielding about 4000 sporozoites which then migrate to the salivary glands where they lie dormant until the mosquito bites another host. This developmental process takes approximately 10 days. Sporozoites travel to the liver, invade hepatocytes, and undergo exo-erythrocytic schizogony producing about 40,000 merozoites (15 genome replications in 5 days). The liver schizonts burst releasing these merozoites into the bloodstream where they invade red blood cells, and develop into trophozoites. These undergo schizogony (3–4 genome replications) in 2 days and mature into schizonts which rupture releasing about 16–32 merozoites. As gametocytes are not thought to be produced during the first round of blood stage schizogony, there must follow at least one more round of intra-erythrocytic shizogony (3.5 gr in 2 days) before the first gametocytes are produced. This time, a proportion of the invading merozoites become gametocytes upon invasion, and mature for 12 days (0 gr) before becoming infectious to mosquitoes again. Therefore, in high transmission setting where there are lots of mosquitoes, a typical *P. falciparum* malaria parasite line would undergo approximately 423 genome replications in one year.

infecting fresh water fish in London's ponds, to Beale's newly formed malaria genetics laboratory with a remit to produce a genetic cross between rodent malaria parasites.

This required a number of essential preliminary steps (including the construction and maintenance of a mosquito insectary, the ability to transmit the parasites through mosquitoes, and development of a blood-stage parasite cryopreservation technology), and most crucially it required the existence of genetically diverse parasite strains of a particular species that could be crossed. Until this point, nothing was known of the natural genetic diversity of malaria parasites.

Performing and characterizing a cross necessitates the ability to type parasites at polymorphic loci–genetic markers. Beale realized that one such genetic marker might be generated if one of the strains could be made resistant to an anti-malarial drug. Then, these parasites could be phenotyped, and differentiated from sensitive lines by exposing them to the drug, and observing their response.

Indeed, resistance to the antimalarial drug pyrimethamine in the avian malaria parasite *P. gallinaceum* had formed the basis for the very first laboratory cross between malaria parasite strains. In 1954, Greenberg and Trembley had reported the simultaneous passage through mosquitoes of two strains of *P. gallinaceum*, one of which was resistant to pyrimethamine and virulent, the other drug sensitive and avirulent. The resulting sporozoites were found to proceed to blood-stage parasite infections in chicks which were drug-resistant and avirulent; demonstrating genetic exchange between the parental strains [6]. This work was, however, never followed up, and the lack of variant strains of *P. gallinaceum* rendered this system unsuitable for extensive genetic investigations [7].

At least two markers are required in order to assess whether recombination has occurred, and, for the second marker, Beale turned to Richard Carter, who joined his laboratory as a PhD student in 1967. He was tasked with identifying enzyme variations between rodent malaria parasite strains that could be characterized through protein electrophoresis. Carter's work showed that while *P. berghei berghei* and *P. berghei yoelii* (today's *P. berghei* and *P. yoelii yoelii*) could be distinguished at each of four enzyme markers, there were no variation between strains within *P. b. berghei*, and variation in only one enzyme between strains of *P. b. yoelii*. Nevertheless, this variation in glucose phosphate isomerase (GPI) between *P. b. yoelii* strains was enough to allow validation of a proposed genetic cross between two of the strains, 17X (clone A) and 33X (clone C), provided one of them could be persuaded to develop resistance to an anti-malaria drug. This was duly achieved in Beale's laboratory by Sonia Morgan, working towards her Ph.D., who successfully selected a line of *P. yoelii* 17X (clone A) for resistance to pyrimethamine [8].

The stage was now set for the first laboratory rodent malaria parasite cross. Passing gametocytes of two strains through mosquitoes and showing that the resulting progeny population contained parasites carrying genetic markers from both parents would be proof that recombination had occurred; it would not be proof, however, that this recombination had occurred through fertilization of a macrogamete (female) by a microgamete (male) in the mosquito.

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