Changes in shark populations can be inferred from fossilized dermal denticles (scales) that have accumulated in coral reef sediments.

connectivity between reefs, which is advantageous to pelagic species. Ultimately, the disparities between shark populations in the Caribbean and Pacific Panama, and their contrasting histories, are caused predominantly by negative human impacts on the Caribbean side and positive environmental factors on the Pacific side.

An important caveat to the study of Dillon *et al*. is the limited resolution of the sedimentary record, which likely obscures changes that have taken place within the past century. Paradoxically, even though global fisheries yield increased by more than 30 million tons in the period 1970–2022 (*7*), a huge portion (35%) of those fish populations are overfished (*8*). Commerical capture increased in many regions across the world's oceans during the first half of the 20th century, but there have also been substantial declines and collapses as stocks have become depleted (*9*, *10*). Despite their minor fraction in global catch weight, sharks are in high demand in some regions, and the slow growth and maturation of many species make them vulnerable to high-intensity harvesting. Whereas the contribution of aquaculture to global fish yield now exceeds that of wild capture (*7*), the geographic distribution of farming is highly heterogeneous and regionally concentrated, and sharks are not farmed. In 2023, out of a total Panamanian fishery yield of 293,040 tons, 99% was wild capture (*7*). The approach of Dillon *et al*. cannot identify changes of species dominance or turnovers of composition because denticles generally lack a sufficient level of taxonomic specificity. The methodology nevertheless demonstrates that history is a powerful and necessary source of information when seeking to explain modern ecological systems.

Humans operate as apex consumers in the oceans through fishing (*11*), but that capability, and the species that people depend on, often have complex and varied cultural and oceanographic contexts. Understanding the current state of natural systems requires an understanding of their histories. That is, the past can be a key to understanding the present, as exemplified by Dillon *et al*. It may also be critical to forecast the future. The seasonal high-productivity upwelling system in the Gulf of Panama—a result of altered patterns of circulation as the ancient seaway closed (*12*)—failed to materialize in 2025 for the first time in 40 years (*13*). Whether this was due to the weak La Niña event (which typically brings cooler ocean temperatures) of 2023–2024, or more broadly to global climate change, remains uncertain, but Dillon *et al*.'s study highlights the risk to the Pacific Panama shark and fishing communities and the ongoing need to synthesize multiple lines of evidence to protect the resilience of natural and human systems. □

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MICROBIOLOGY

A boost for chemical vaccination against malaria

Chemical inhibition of *Plasmodium* plasmepsin proteins offers a new path for drug-based malaria vaccination

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Malaria is one of the world's most devastating infectious diseases, causing an estimated >600,000 deaths yearly, particularly in children up to 5 years old. Two vaccines that became available in the past few years partially protect children against infection with *Plasmodium*, the malaria parasite. However, a need remains to increase vaccine efficacy and expand it to other groups of people at risk (*1*). *Plasmodium* sporozoites infect the mammalian host's liver without causing malaria symptoms, before developing into symptomatic mature merozoites that infect red blood cells. Whole-sporozoite vaccines use sporozoites that have been irradiated or genetically modified before immunization to arrest their liver development or drugs that act on liver- or early-blood-stage parasites to prevent the onset of symptomatic blood-stage infection. On page 683 of this issue, Steel *et al.* (*2*) report using drugs that target the plasmepsin IX and X (PMIX/X) proteins of *Plasmodium* sporozoites to induce protective immunity against malaria in mice.

Clinical trials of irradiated or chemically treated *P. falciparum* vaccines confirmed the long-standing assumption that vaccine efficacy correlates with the extent of development of immunizing parasites in the liver (*3*). Chemical vaccination with chloroquine, a drug that allows complete *Plasmodium* development in the liver and kills blood-stage parasites, or pyrimethamine, which targets liver-stage parasites, provided more protection than vaccination with an irradiated parasite whose development stops soon after it invades liver cells (*4*). Furthermore, the protective efficacy of a late-arresting genetic modification approach was substantially greater than that of early-arresting genetic modification (*5*). PfSPZ-LARC2, a genetically modified parasite that replicates extensively in the liver before its development is arrested (*6*), is presently undergoing clinical evaluation.

Treatment with PMIX/X inhibitors enables the development of chemo-attenuated liver merozoites (CALM) of *P. berghei*, which are mature merozoites that are noninfectious to red blood cells (*7*). After infecting mice with *P. berghei* parasites, Steel *et al.* treated them with one of two PMIX/X inhibitors, WM382 or MK-7602, to promote the development of CALM. This subsequently elicited the production of antibodies and $CD8^+$ T cell responses that conferred long-term (up to 21 months) protection against subsequent infection with fully infectious *P. berghei* parasites. Parasite attenuation occurred before they exited the liver and entered the bloodstream and at a later stage than previously achieved with late-arresting genetic modification or chemi-

Alternative malaria vaccination strategies are urgently needed, particularly for children.

cal treatment with pyrimethamine. Moreover, CALM did not cause the transient infection of red blood cells that characterizes chemical vaccination with chloroquine. CALM-mediated antimalarial protection was achieved through a single injection of a low dose of sporozoites or two sessions of bites from 10 to 15 parasite-infected mosquitoes. Notably, a study in humans showed that a single immunization with bites from 50 mosquitos delivering late-arresting genetically modified *P. falciparum* can be highly protective (*8*).

The applicability of CALM for malaria prevention in humans remains to be demonstrated. Steel *et al.* observed that WM382 treatment of mice engrafted with human liver cells and infected with *P. falciparum* prevented the development of the parasites into merozoites capable of infecting human red blood cells. However, no PMIX/X inhibitors have yet been approved for human use, although WM382 has been tested in preclinical studies and MK-7602 has been assessed in a phase 1 clinical trial (*9*). Moreover, as the authors acknowledge, a drug of this type should be available in a long-acting injectable formulation to reduce the safety concerns associated with oral intake (such as patients not following the therapy schedule), which could fail to attenuate the parasites and cause disease (*10*). Nevertheless, the durability of protection achieved with a single dose, the low number of immunizing parasites that are needed to elicit a response, and the resulting low cost of this approach justify clinical evaluation of CALM-based strategies.

Such studies should bear in mind several challenges presently associated with whole-sporozoite vaccination. The protection afforded by these approaches in malaria-endemic regions is consistently lower than that achieved in volunteers who were never previously exposed to malaria. It is also consistently lower when immunized volunteers are exposed to *P. falciparum* strains that are different from that used for vaccination (*3*). Furthermore, chemically treated *P. falciparum* vaccination in malaria-endemic regions is much more effective when the individuals receiving the vaccine are previously treated with antimalarial drugs to eliminate parasites that they may carry even if they do not have symptoms (*11*). Notably, vaccination with irradiated *P. falciparum* did not prevent infection in children aged 1 to 12 years, which suggests that more potent vaccines may be needed for this age group (*12*). Other challenges to the deployment of whole-sporozoite vaccination in malaria-endemic regions include difficulties in optimizing immunization schedules, the diversity of *P. falciparum* antigens, the requirement for direct venous inoculation with the vaccine, and manufacture and distribution obstacles (*10*).

Existing whole-sporozoite vaccination strategies exclusively target *P. falciparum* stages before the parasite infects red blood cells. However, *Plasmodium* sporozoites could be genetically modified to elicit protection against different life-cycle stages of the malaria parasite. For example, a mouse-infecting *P. berghei* parasite engineered to express the *P. falciparum* circumsporozoite protein, a surface protein that elicits the production of host antibodies, has been validated in phase 1/2a clinical trials (*13*). Genetically modified chimeric *P. berghei* (*14*) or *P. falciparum* (*15*) parasites expressing the *P. vivax* circumsporozoite protein can also induce antibodies against this often-neglected human malaria parasite. Genetic engineering could even be used to simultaneously target multiple liver pathogens, including viruses, or, potentially, noninfectious diseases such as liver cancer. For example, additional genetic modifications could be introduced into PfSPZ-LARC2, although this would involve multiple steps of genetic engineering that could hamper regulatory approval of a future vaccine. By contrast, generating CALM-based vaccines against multiple targets would only require one step of genetic modification to introduce the antigens of interest into the parasite, which could facilitate their approval for human use. Regardless of regulatory considerations, the pursuit of diverse whole-sporozoite strategies should be encouraged to address the pressing need for improved vaccination against malaria. □

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