Newsfronts

'Stalled' Malaria Parasite Becomes Vaccine Fodder

A genetically engineered parasite could offer new hope to researchers and patients desperate for a safe and effective malaria vaccine.

The mosquito-borne malaria parasite *Plasmodium falciparum* poses a major health threat in many parts of the world, with studies indicating that it kills more children under 5 years of age than any other infectious agent. Sadly, no proven and reliable vaccine is currently available.

There are a number of obstacles to the development of 'subunit-specific' vaccines for malaria and other parasites. First, parasites typically have larger genomes than bacteria or viruses; *P. falciparum* has more than 5,300 genes, many of which exhibit considerable variability. In addition, parasites typically undergo multiple life stages, each with unique gene expression patterns and tropisms. Finally, genomic data for these organisms are generally limited, slowing the identification of target proteins.

As such, many investigators have focused their attention on whole-organism vaccines for malaria, such as the use of irradiated *P. falciparum*. Now, a new article from *Nature* (online 5 December 2004, doi: 10.1038/nature03188) presents a promising new approach, using the first genetically modified attenuated malarial parasite. This work, a collaborative effort between investigators at the Heidelburg University School of Medicine (Heidelburg, Germany) and the Seattle Biomedical Research Institute (Seattle, WA), benefited from the recent assembly of complete genomic sequences for several *Plasmodium* species. Working with these data, the researchers selected a gene, *UIS3*, expressed in the late stages of liver infection that precede blood cell infection; by targeting this stage, the researchers hoped to attenuate the liver-stage parasite without affecting the stage at which the parasite is mosquito-transmissible.

The group worked with *P. berghei*, the rodent malaria parasite, to engineer a *UIS3*-deficient strain. These modified parasites showed partial ability to progress through their life cycle, including the mosquito-borne stage, but were incapable of full maturation, suggesting that pathology should be blocked. Indeed, mice showed no ill effects after immunization and a pair of boost injections—they did, however, exhibit full protection against wild-type parasites introduced either intravenously or by mosquito. These mice remained fully protected against large doses of parasite (50,000 sporozoites—roughly 500 times the number in a mosquito bite) even two months after immunization.

Data obtained since publication have continued to support their strategy. "We have just challenged another set of immunized animals after 3 months," says author Stefan Kappe, "and we still get complete protection [against] mosquito bite and i.v. inoculation with sporozoites. The bite experiments are important, because that's really the natural mode of transmission." Buoyed by this success, Kappe and his colleagues are awaiting approval to begin human clinical trials. "We are collaborating with the Walter Reed Army Institute of Research to do those trials," he tells *Lab Animal*, "[and] I would say if everything works and funding comes in, we hope [to] conduct some trials by the end of next year."

—Michael Eisenstein

Mice Benefit from Viral Sun Screen

A viral-based gene therapy strategy could one day lead to better protection for patients suffering from the skin cancer–predisposing genetic disorder xeroderma pigmentosum (XP).

Xeroderma pigmentosum is a skin disorder resulting from defects in one of seven different genes involved in DNA damage repair, designated *XPA*–*XPG*. Patients suffering from XP face a 1,000-fold increased risk of skin cancer, primarily because of an increased sensitivity to ultraviolet (UV)-induced DNA damage, and, although skin cancer can be relatively straightforward to treat surgically, the severity of the malignancies that can occur as a result of XP result in a typical lifespan of 30–40 years.

Xeroderma pigmentosum is a promising candidate for gene therapy–based treatment strategies, however, because the genes involved in this disease have been fairly well characterized, and the skin offers an easy target for vector delivery. In a new study, a team of investigators led by Carlos Menck of the Universidade de São Paulo (São Paulo, Brazil) describes their pilot effort to develop such a therapeutic agent (*Proc. Natl. Acad. Sci. USA*, online 14 December 2004, doi:10.1073/pnas.0406304101). Menck's team worked with a mouse strain containing an inactivated *Xpa* gene, mirroring the genetic defect seen in the largest percentage of human XP patients. This strain similarly exhibits a highly elevated risk of developing tumors in response to UV exposure. To counter the mutation, the researchers generated an adenoviral construct containing the cDNA for human *XPA* and then introduced the virus subcutaneously.

Strong *XPA* expression was detected in the skin surrounding the injection site, with particularly high expression in the area posterior to the injection. To test for protection against tumor formation, infected and mock-infected mice were subjected to a 4-day course of UV exposure. The mock-infected mice showed early abnormalities in response to irradiation; within 3 weeks of treatment, lesions were clearly visible on the skin surface, and by 2 months, the vast majority of the irradiated mice developed squamous cell carcinomas. By contrast, the infected mice closely resembled wild-type animals in their response to this treatment. A few weeks after the treatments ended, some mild lesions had appeared, but these soon disappeared, and none of the mice went on to manifest carcinomas, even after 5 months.

Menck and his colleagues indicate that this study should provide a strong incentive to develop such strategies further for the treatment of XP, and that pending resolution of some of the inherent hurdles involved in working with adenoviral vectors, this approach could offer a viable therapeutic solution for XP patients.

—M.E.