Chikungunya is moving fast, but so are researchers in the field

In early 2005, public health authorities on Réunion Island, a French territory in the Indian Ocean, noticed several cases of chikungunya virus, a mosquito-borne pathogen that can cause rashes, chronic joint pain and, occasionally, death. It was the first time that this disease had been seen outside continental Africa and southern Asia. Within a year, more than one-third of the island's 770,000 inhabitants had been infected (*Emerg. Infect. Dis.* **12**,1994–1995, 2006). The virus has since reached Europe, Latin America and the US.

A decade into this pandemic, researchers have revealed substantive insights into the complex ecology and pathogenesis of the virus, and they have developed several promising vaccine candidates. However, the limitations of current animal models, as well as nagging questions about the virus's ability to establish chronic infections, are still hindering progress toward effective prevention strategies and treatments.

Chikungunya is also proving difficult to tackle because of its adaptability to different mosquito vectors. Unlike most vector-borne viruses, chikungunya can acquire mutations that enable it to replicate in different vectors yet do not affect its fitness once it transfers to a mammalian host.

Scott Weaver, scientific director of the Galveston National Laboratory in Texas, and his colleagues have found that one lineage of the virus can switch from using *Aedes aegypti* mosquitoes as vectors to using *Aedes albopictus* by acquiring a single amino acid change in one of its proteins (*Antiviral. Res.* **120**, 32–39, 2015). "It's a very interesting virus, and one of the very few examples where there's been a clear switch in host range" for which scientists have identified the relevant mutations, he says.

The findings have daunting implications for the spread of chikungunya to cooler parts of the US and Europe, as well as to more areas of the tropics. *A. aegypti* occurs mostly in urban areas in the tropics, whereas *A. albopictus* prefers suburban and rural environments and ranges into more temperate zones. In theory, such an adaptable virus could travel worldwide. It nearly has.

Revisiting vaccines

Researchers now hope to fight back with vaccines—for the second time. The discovery of chikungunya virus in Tanganyika, Africa, in 1952 stimulated a flurry of research, culminating in the US Army's development of a promising vaccine in 1971 (*J. Immunol.* **107**, 643–647, 1971). But interest and funding faded along with the initial outbreaks, and that vaccine was shelved before receiving final regulatory approval.

The Army vaccine was an inactivated virus, a well-tested approach used for many other vaccines. In principle, vaccinologists could simply repeat the old procedures and produce an effective immunization, and there is some suggestion that non-governmental organizations might pursue this. "There's no reason that it couldn't be done fairly easily; it's a proven technology." Weaver says. "But I think there's an emphasis now on newer technologies." Also, a protocol published decades ago can probably no longer be patented, rendering commercial backing unlikely.

Instead, Weaver's team is working on a live, attenuated vaccine against chikungunya virus with support from the Japanese drug giant Takeda Pharmaceuticals. Another group, backed by Themis Bioscience, is developing a vaccine using an attenuated measles virus that expresses proteins from the chikungunya virus. "The measles virus is sort of a carrier," explains Bernd Jilma, a professor of clinical pharmacology at the Medical University of Vienna in Austria. The engineered virus does not contain enough of either the chikungunya or measles genomes to cause human disease , but it stimulates a robust immune response against chikungunya virus antigens. In May, Jilma and his colleagues published the results of a phase 1 clinical trial of their vaccine, showing a good safety profile and the production of neutralizing antibodies in all 42 participants. The scientists hope to enter phase 2 trials soon (*Lancet Infect. Dis.* **15**, 519–527, 2015).

Weaver's vaccine is still in preclinical testing. One major hurdle has been developing a good assay to show that the attenuated chikungunya virus can't revert to a pathogenic form, even in people whose immune systems are compromised by HIV infection or other conditions. In a step toward developing a better assay, Weaver's team recently demonstrated that wild-type chikungunya virus could persistently infect an immunosuppressed mouse model that they developed, but that their attenuated vaccine strain cannot (*PLoS Negl. Trop. Dis.* **9**, e0003800, 2015).

Model mysteries

Researchers have developed other mouse models of chikungunya virus infection, each with its own strengths and limitations. "There are multiple models that can be used, and it kind of depends on exactly what your question is," says Thomas Morrison, an associate professor of immunology at the University of Colorado School of Medicine in Aurora. For example, researchers who want to study the joint inflammation associated with chikungunya can inoculate an adult mouse's foot pad with a clinical isolate of the virus, leading to localized infection and inflammation in the joint closest to the site of inoculation. That model doesn't, however, produce the systemic viremia typical of a human chikungunya virus infection. Young mice or those that lack specific immune regulators, in contrast, develop systemic viral infections but do not provide good models of joint inflammation.

Another challenge is faithfully modeling chronic chikungunya virus infection. Morrison's group has been able to detect chikungunya virus RNA with a long-term presence in the joint tissues of wild-type mice. "That means the virus had to get there, establish an infection and is now remaining there," Morrison says, explaining that it is a sign of viral persistence. But not everyone agrees with that interpretation. "People keep pulling out viral nucleic acids, viral proteins, [but] whether there's actually live, replicating virus that can transmit, I'm unconvinced," says Matthew Albert, head of the dendritic cell immunobiology unit at the Institut Pasteur in Paris, France.

Albert's group has developed its own mouse models for chikungunya virus infection, using animals with defective type 1 interferon signaling. Albert says that the virus becomes undetectable in his mouse experiments within a couple of weeks after infection. "It's a self-limiting disease in my mind," he says. Instead, he argues that patients' chronic arthritis-like joint pain and other lingering symptoms could be due to autoimmune reactions.

Morrison concedes that the issue is still open: "I think this is one of the big questions in the field, what explains the chronic disease symptoms, and I don't think we have the answer to that." Obtaining deep-tissue samples from people who are in the throes of a painful joint disease hasn't been practical, so the virus's long-term pathology is hazy.

Meanwhile, both the tendency of chikungunya virus infection to mimic arthritis and the virus's expanding range complicate diagnosis and control efforts. In the Caribbean and Latin America, chikungunya virus now co-circulates with the closely related Mayaro virus, as well as dengue fever virus. All three cause similar symptoms and share the same vectors. "It's very unfortunate for the afflicted people that [chikungunya virus] has been introduced into the Western Hemisphere," says Helen Lazear, an assistant professor of microbiology and immunology at the University of North Carolina in Chapel Hill. She adds, however, that "it does present an interesting opportunity to observe an introduction of a new virus and its interaction with a pre-existing ecology."

Alan Dove