



INFECTIOUS DISEASE

The race for a Zika vaccine is on

Researchers see many approaches—but a vaccine likely will take years

By Jon Cohen

Less than a year ago, Zika seemed too trivial for anyone to bother developing countermeasures. The mosquito-borne virus was racing through the Southern Hemisphere, but, at worst, it appeared to cause a mild fever and rash. No longer: On 1 February the World Health Organization (WHO) declared the “extraordinary” cluster of microcephaly and other neurological complications that have now been linked to Zika a “public health emergency of international concern.” And vaccinemakers, big and small, have begun the race to head it off. They have a good shot at success, several experts say, but they caution that vaccine development requires years of testing.

Isolated in 1947, Zika first caused serious concern in May 2015 after it arrived in South America and suspicions grew that infection during pregnancy might be causing brain-damaging microcephaly in babies. The link, WHO Director-General Margaret Chan in Geneva, Switzerland, stresses, is “strongly suspected though not yet scientifically proven”—as is a potential connection to Guillain-Barré syndrome, which can cause a temporary paralysis in adults. With viral spread increasing, a vaccine is now a top priority.

Vaccine pioneer Stanley Plotkin of the University of Pennsylvania predicts “a straight-

forward developmental pathway” for a vaccine. He notes that Zika belongs to the flavivirus family, and vaccines exist for several of its relatives, including dengue, yellow fever, and Japanese encephalitis. “I don’t see any technical issues such as the ones that obviously exist for vaccines against HIV, tuberculosis, and many other agents,” says Plotkin, who consults with several vaccinemakers.

Still, “there are many puzzles,” says Thomas Monath, a virologist who studied Zika in wild monkeys in Nigeria in the 1970s and is now the chief scientific officer at NewLink Genetics in Devens, Massachusetts, which helped develop a promising Ebola vaccine. For Zika, one unknown is whether infection leads to lifelong protection—a key feature of diseases for which vaccines are most effective, such as yellow fever. Another question is whether natural or vaccine-induced immunity against other related viruses—particularly yellow fever—could offer a measure of “cross protection,” which might confuse efforts to evaluate Zika vaccines. Nor have researchers yet established a much-needed monkey model to enable comparisons of candidate vaccines.

Monath, who has developed vaccines against several flaviviruses, says NewLink will pursue a traditional strategy that inactivates, or kills, the virus with a chemical so it cannot replicate in the body. He thinks an inactivated vaccine has the best chance of

Jorge Kalil (holding box), director of Brazil’s Butantan Institute, says his team hopes to make a Zika vaccine by mimicking a strategy used for the related dengue virus.

winning regulatory approval as a product that pregnant women might use.

At the nonprofit Butantan Institute in São Paulo, Brazil, however, immunologist and director Jorge Kalil is betting that a weakened, live vaccine can be safe and potentially more effective than killed virus. His team plans to exploit a technology that researchers at the U.S. National Institute of Allergy and Infectious Diseases (NIAID) used to make a dengue vaccine, which Butantan licensed and is now testing in an efficacy trial. To weaken that virus, researchers deleted genes so it can copy itself but not cause disease. “Perhaps we can attenuate the Zika virus by using the same deletions of the same sites,” Kalil says, noting that Butantan likely would partner with NIAID to develop its vaccine. The Brazilian institute has a key advantage: Unlike almost every other nonprofit in the world that does vaccine research, it has an industrial-scale manufacturing plant—last year the institute cranked out 40 million doses of influenza vaccine—so it might be able to supply enough product for Brazil without needing help from big pharma.

NIAID Director Anthony Fauci in Bethesda, Maryland, says his institute has a “head start” with a different technology it

used to make an experimental vaccine for West Nile, another flavivirus. The manufacturing process begins with a circular “plasmid” of DNA that holds key viral genes. When it is inserted into bacterial cells, they produce “viruslike particles” that are similar to an inactivated vaccine, because they cannot copy themselves. (The West Nile vaccine worked well in early human studies, but NIAID could not find a commercial partner to take it forward.)

Inovio Pharmaceuticals of Plymouth Meeting, Pennsylvania, boasts it already has an experimental Zika vaccine containing nothing more than a plasmid made of Zika genes. With the help of an electrical zap on the skin, the plasmid goes directly into human cells, which then make Zika proteins that stimulate the immune system. CEO Joseph Kim says his team already has begun tests in mice. But although researchers can quickly make such simple DNA vaccines, they have lost their luster over the past 20 years because they have not triggered strong immune responses. “There are people very knowledgeable in the field who have lost faith in this technology,” Kim concedes. “I want to prove that this technology is viable and perhaps the best option for these types of outbreaks.”

The small Jenner Institute in Oxford, U.K., is putting the Zika surface protein into harmless chimpanzee adenoviruses, which serve as a “vector”—an approach similar to one used in GlaxoSmithKline’s Ebola vaccine, which was tested during the West African epidemic. Vaccinemakers Protein Sciences of Meriden, Connecticut, and Hawaii Biotech of Honolulu—which both specialize in producing viral proteins in insect cell lines—also have projects underway.

Predicting when a vaccine will come to market is a mug’s game, but NIAID’s Fauci thinks animal studies could be completed in a few months and small human studies to evaluate safety and immune responses could begin by the end of 2016. Even if a promising candidate surfaces, large-scale efficacy trials are probably years away, he says. Getting a vaccine approved and supplying millions of doses could take the resources of a major manufacturer. Of the four big pharma companies that make vaccines, only Sanofi Pasteur of Lyon, France—which produces all three existing flavivirus vaccines—has launched a Zika program, though the others say they are watching the field closely.

As a stopgap measure for pregnant women, Kalil says Butantan hopes to produce a protective serum, which the institute already makes for several diseases, by injecting Zika virus into horses and harvesting the antibodies the animals make. “This would take a little over a year,” Kalil says. “That’s the best timeline—if you’re very, very optimistic.” ■

NUCLEAR NONPROLIFERATION

Risky reactor fuel to linger

Getting highly enriched uranium out of research reactors will stretch to at least 2035, U.S. study concludes

By Adrian Cho

Since 1978, the United States and other nations have been pushing to eliminate the use of highly enriched uranium (HEU)—which a terrorist or rogue nation could use to make a bomb—as fuel in dozens of civilian research reactors around the world. But achieving that goal will take far longer than previously hoped, according to a study from the National Academies of Sciences, Engineering, and Medicine. Experts had once hoped to eliminate HEU fuel by 2018, but 2035 is more realistic, the 28 January report concludes.

“Clearly there have been unexpected challenges, both technical and nontechnical,” says Julia Phillips, a former vice president of Sandia National Laboratories in Albuquerque, New Mexico, and chairperson of the panel that wrote the report, which Congress requested in 2012.

Research reactors are relatively small facilities that focus on materials science, reactor design, and the production of medical isotopes. That work generally requires fluxes of neutrons higher than those produced in commercial power reactors. Whereas power reactors make do with uranium enriched to about 4% of the fissile isotope U-235, research reactors run on uranium that is more highly enriched, in some cases to about 90%—the level of weapons-grade uranium.

Globally, the civilian research stock of HEU—uranium enriched to at least 20%—totals 60 tons, enough to make roughly 1000 bombs, and nonproliferation experts worry that it may be less secure than far bigger military supplies. Since the 1970s, dozens of civilian research reactors have either closed or converted to safer low enriched uranium (LEU), including 28 since 2009. That leaves 74 similar reactors that are still using, or

plan to use, HEU. “The long and short of it is that the easy conversions have been made,” Phillips says.

On the technical side, nuclear scientists and engineers have struggled to develop adequate replacement fuels based on LEU. To maintain the needed neutron fluxes, the fuels need a high density of uranium. Researchers in Europe and Asia are developing a so-called dispersion fuel, in which granules of a uranium molybdenum alloy are embedded within an aluminum matrix. In con-

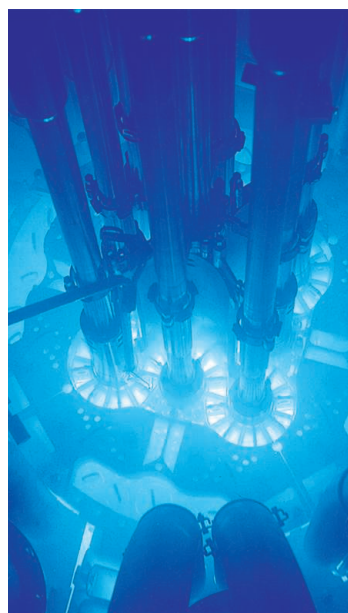
trast, the United States is developing a “monolithic” fuel that consists of a single ribbon of uranium-molybdenum alloy clad in aluminum. Development of both fuels will likely take another 12 to 17 years, the report estimates.

On the nontechnical side, Russia has expressed little interest in converting its 32 research reactors. “This is not a priority with the Russian government,” says William Tobey, a panel member and nonproliferation expert at Harvard University.

The report makes seven recommendations, including engaging Russia in greater collaboration and planning for facilities to replace the

eight aging U.S. civilian research reactors. Most controversially, as an interim step it calls for converting those reactors to a somewhat less enriched form of HEU. The United States has designated 20 tons of 93% enriched weapons-grade uranium for civilian research. The report recommends diluting that supply to 45% enrichment and using it until LEU fuel is available.

That’s a bad idea, says Alan Kuperman, a political scientist at the University of Texas, Austin. Using 45% enriched HEU would perpetuate commerce in HEU and undermine efforts to develop LEU fuel, he says. Simply put, Kuperman says, “it’s incredibly stupid from a policy perspective.” ■



The core of the Advanced Test Reactor at the Idaho National Laboratory holds 43 kilograms of highly enriched uranium.

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Science, 351 (6273), • DOI: 10.1126/science.351.6273.543

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