



Health workers carry the body of an Ebola virus victim in Kenema, Sierra Leone, on 25 June 2014.

IN DEPTH

INFECTIOUS DISEASES

Ebola drugs still stuck in lab

Experts discussed—and rejected—bringing experimental vaccines and therapies to West Africa

By Martin Enserink

There's little doubt what Erica Ollmann Saphire would do if she had Ebola or knew she had been exposed. The x-ray crystallographer at the Scripps Research Institute in San Diego, California, is leading an international effort to develop a potent mix of monoclonal antibodies against the virus, some of which have already shown promise in animals. Knowing the staggering case fatality rate of this hemorrhagic fever, Ollmann Saphire says she would take the antibodies—never mind that they haven't been tested for safety. "Believe me, I'd run for the freezer and ask for forgiveness instead of permission," she says.

Many Ebola researchers say they, too, would eagerly try the antibodies—or one of the promising candidate drugs, or an experimental Ebola vaccine. And they would love for people in Sierra Leone, Guinea, and Liberia to have access to experimental therapies as well, as the death toll from the largest Ebola outbreak on record climbs past 600. But it's not going to happen.

As the outbreak in West Africa worsened, debates intensified among scientists, government officials, and company executives about

bringing some of these unapproved products to Africa on a so-called compassionate use basis—after all, "something is better than nothing," Ollmann Saphire says. "I have been on at least half a dozen conference calls about this," says Lisa Hensley, an expert in hemorrhagic fever viruses at the National Institute of Allergy and Infectious Diseases (NIAID) in Frederick, Maryland.

But the organizations fighting Ebola on the ground say they simply can't bring an untested, unlicensed drug to a population that's already distrustful of the teams try-

ing to stamp out the outbreak. "Some people are throwing stones at us," says Armand Sprecher, a public health specialist at the Brussels office of Doctors Without Borders. "There are rumors that we are spreading disease, harvesting organs, and other horrible things. Bringing in unlicensed things to experiment on people could be very counterproductive." A representative for the World Health Organization (WHO) adds that using vaccines now "would not be ethical, feasible, or wise."

Longtime Ebola researchers say they accept that decision, but they're frustrated. "It's very, very disappointing," says Heinz Feldmann of NIAID's Rocky Mountain Laboratories in Hamilton, Montana, who has helped develop a promising vaccine candidate. But Feldmann hopes the tragedy will at least help unclog the product pipeline.

With 1048 reported cases and 632 deaths since March—a 60% fatality rate—the West African outbreak shows no signs of tapering off. People in the affected countries are more mobile than in the central African regions struck by Ebola in the past, Sprecher says, giving the virus more options to spread. What's familiar are the cultural problems in battling Ebola. The measures that will contain the virus—strictly isolating patients, tracing and monitoring their contacts, and burying the dead quickly and safely—are often difficult for the local population to accept.

Despite the media's fascination with Ebola, the disease is exceedingly rare, which has slowed the development of countermeasures. Before the current one, all known outbreaks had caused fewer than 2400 cases, across a dozen African countries over 3 decades. Add the poverty of those countries, and the market for drugs and vaccines looks unpromising. (Complicating matters, Ebola-Zaire, now raging in West Africa, is just the most common of five Ebola species; each needs its own countermeasures.) Most research has been funded by the U.S. government in response to worries about biowarfare and bioterrorism.

But that support hasn't been enough to bring a single product to the market. Feldmann's vaccine, for instance, consists of a livestock pathogen called vesicular stomatitis virus (VSV) in which one gene has been replaced with that for Ebola's surface glycoprotein. It gives rhesus macaques full protection against Ebola-Zaire and saved four out of eight animals when

Too little, too late

A selection of Ebola vaccines and drugs in development. Only TKM-Ebola has entered a phase I trial, which was halted by FDA.

VACCINES	DRUGS	DEVELOPERS
● VSV-based vaccines		Profectus BioSciences; Public Health Agency of Canada
● Adenovirus-based vaccines		At least three different labs/companies
● TKM-Ebola (RNAi-based)		Tekmira Pharmaceuticals Corp.
● Nucleoside analog		U.S. Army Medical Research Institute of Infectious Diseases
● Monoclonal antibodies		Many labs/companies
● AVI-7537 (antisense-based)		Sarepta Therapeutics

given 30 minutes after an otherwise lethal dose of the virus. But the Public Health Agency of Canada (PHAC) in Winnipeg, Feldmann's previous employer, has yet to take it to phase I safety trials in human volunteers. Profectus BioSciences in Tarrytown, New York, which is developing a similar vaccine, needs some \$2 million to produce it under good manufacturing practice standards, a prerequisite for any human study.

A leading drug candidate has more funding and is further advanced, but it also faces obstacles. The compound, identified by U.S. Army researchers and based on RNA interference, is in development at Tekmira Pharmaceuticals Corp., a Burnaby, Canada-based company that has a Pentagon contract worth up to \$140 million to produce it. But on 3 July, the company announced that the Food and Drug Administration had put a phase I trial on hold because it wants more data and a change in the protocol to protect participants' safety. Tekmira says it expects to resolve the issue by the end of the year.

Monoclonal antibodies are similarly stymied. In the \$28 million NIAID-funded project that Ollmann Saphire is leading, 25 labs from seven countries are pooling their antibodies to see which cocktail best blocks the virus. But again, none of these has entered a phase I trial. The same is true for a powerful nucleoside analog—a small molecule that's cheap to make—developed by the U.S. Army Medical Research Institute of Infectious Diseases. A promising antisense-based compound by Sarepta Therapeutics in Cambridge, Massachusetts, was put on ice after the Pentagon ended its funding in 2012.

Still, an exception was once made for compassionate use of an Ebola therapy. In 2009, when a German researcher pricked her finger with a syringe containing Ebola, the VSV vaccine was rushed from Winnipeg to Hamburg, where she received it 48 hours after the accident and remained healthy. Whether the vaccine helped can't be determined.

But that was a single case in an intensive care unit in a Western hospital where the patient could be monitored closely for side effects and treated if needed, says PHAC virologist Gary Kobinger. Doing the same for hundreds of people in Africa is virtually impossible, he says. Getting informed consent would be a huge challenge. And no drug or vaccine is going to work once patients are very ill, says Ebola researcher Thomas Geisbert of the University of Texas Medical Branch in Galveston; if patients seek care too late, that could create the mistaken impression that the interventions are useless. "If something goes wrong this could be a disaster," Feldmann says. "So we have to work hard and come up with a really good plan for the next outbreak." ■

PLANETARY SCIENCE

Road hazards threaten rover

To limit wheel damage from sharp rocks, the Curiosity Mars rover detours into sandy valleys

By Eric Hand

John Grotzinger, the project scientist for NASA's Curiosity rover, is eager to study the rocks on Mars. But right now he fears them. "Today the rover planners were so tense that they only agreed to drive 10 meters," he says. "It's killing us."

The problem: Daggerlike rocks are tearing into Curiosity's featherweight aluminum wheels. The rover has been returning increasingly alarming pictures of punctures in the metal, which is just 0.75 millimeters thick,



Holes in one of Curiosity's 0.75-mm-thick wheels.

and scientists and engineers both on and off the team are concerned. Even Alcoa, one of the world's largest aluminum producers, has offered suggestions for minimizing the damage, says Grotzinger, a planetary scientist at the California Institute of Technology in Pasadena. "I've got a nation of back-seat drivers," he says.

Soon after landing 2 years ago, on 5 August 2012, the rover struck pay dirt, drilling into an ancient lakebed that revealed a formerly habitable environment (*Science*, 24 January, p. 386). And a few months ago, the mission scientists announced that they had found signs of organic molecules called chlorobenzenes, although they don't know whether the compounds derived from meteoritic debris or could be a byproduct of ancient life (*Science*, 28 March, p. 1419). Those findings and others have made them itchy to get to the main event: a mountain, ringed by water-altered sediments, that rises 5.5 kilometers from the middle of Gale crater. For the past

year, the rover has been on a fast-track route across swaths of sharp-rocked terrain.

But its latest troubles have forced operators to back off the throttle. By January, mission engineers saw that damage to the wheels was accumulating at an alarming rate. Geologists on the team worked to map the terrain, using instruments on the Mars Reconnaissance Orbiter, and quickly picked out the offending rock formation. It was tightly cemented, retained a history of more craters than surrounding formations, and formed a cap rock, jutting above the landscape. Fractures in the cratered rock have allowed the wind to whittle the rock into sharp pyramidlike pieces.

The mappers charted a new route that took the rover off the cap rock and into narrow, sand-filled valleys. The detour risked trading one hazard for another: ripples of sand piled up 30 to 40 centimeters high in the center of the valleys. Although the miniature sand dunes shouldn't pose much of a problem for the 2-meter-high rover, the team has played it safe by sticking to valley edges, where the ripples taper, says Raymond Arvidson, a planetary scientist at Washington University in St. Louis who

has led some of the rerouting efforts. "You don't want to get all six wheels on sand going uphill," he says. The new route paid immediate dividends: Damage rates plummeted, and the odometer ticked along faster. Last month, in one of the valleys, Curiosity drove 143 meters in 1 day—the second longest drive of the entire mission.

Recently the rover climbed back onto cap rock. But engineers at the Jet Propulsion Laboratory (JPL) in Pasadena are working on other ways to ease the wear and tear on the wheels. One is driving backward; Project Manager Jim Erickson likens the benefit to that of dragging a roller bag over a curb rather than pushing it. He says the team is also working on software changes that could cut the torque applied to an individual wheel when it senses a hazardous object.

Others are trying to understand how the wheels could ultimately break. In the Mars Yard at JPL, engineers have created a sandy racetrack so that three wheels—half of

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