RESEARCH ADVANCES

Many Challenges to Developing Ebola, Chikungunya Vaccines

Jeffrey L. Fox

The recent outbreak of Ebola virus in West Africa and the expanding footprint of the chikungunya virus in the Americas are driving efforts to develop vaccines against these viruses. In both cases, however, there are striking challenges to overcome before any of several vaccine candidates become public health realities, according to experts who spoke during the 2015 ASM Bio-defense and Emerging Diseases Meeting, held last February in Washington, D.C.

Several versions of Ebola vaccines are being developed, and a few earlier candidates were discarded, according to Nancy Sullivan of the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) in Bethesda, Md. Among the surviving candidate vaccines, several recently began or are soon headed to clinical trials, even as the Ebola outbreak is waning, further complicating efforts to evaluate those candidates.

Among the discarded candidates were a killed-virus vaccine that enhanced disease in guinea pigs infected with Ebola and also a recombinant protein vaccine made in insect cells that partly protected guinea pigs but failed to protect primates, according to Sullivan. Other evidence indicating that filoviruses such as Ebola are adept at evading host antibodies led investigators to realize that an effective vaccine would need to elicit both cellular and humoral immunity, she says.

Thus, NIAID efforts shifted to developing an adenovirus vector-based vaccine to stimulate both T cells and produce antibodies. One prototype incorporated two Ebola genes, one encoding a nuclear protein and the other, one of its glycoproteins, according to Sullivan. Some attention also went into developing a DNA-based vaccine, but it was scrapped because testing led to a “poor antibody response,” she says.

Although one version of the dual-gene vaccine appeared to elicit cytopathic effects, this problem was fixed by introducing a mutation into the Ebola glycoprotein gene. Subsequently, investigators realized that the nuclear gene was not needed, and it was dropped from the adenovirus construct, according to Sullivan. However, some strains of the adenovirus vector being tested failed to generate T cell responses in macaques, leading eventually to choosing a chimpanzee-based adenovirus, which “gave complete protection,” including “good T cells.” Even then, the durability of the response was less than ideal, leading the investigators to follow the adenovirus-based priming step with boosting via a different vector, called modified vaccine Ankara (MVA), but carrying the same Ebola gene.

GlaxoSmithKline continues to evaluate that Ebola candidate vaccine by means of a clinical trial in Liberia. Another vaccine against Ebola, called VSV-ZEBOV and also being evaluated in Liberia, is based on vesicular stomatitis virus, whose gene encoding the VSV outer protein is replaced with a segment of the gene for the outer protein of the Zaire Ebola virus. It was developed by researchers at the Public Health Agency of the National Microbiology Laboratory in Winnipeg, Man.

Countries and territories where chikungunya cases have been reported (as of March 10, 2015). This viral disease, which has recently expanded into the Americas, has been the target of vaccine development efforts, but clinical testing faces difficulties due to the spodic nature of outbreaks and the similarity of its symptoms to that of Dengue virus. (CDC image.)
itoba, Canada, and then licensed to NewLink Genetics Corp through its wholly owned subsidiary BioProtection Systems, both based in Ames, Iowa. Separately, Johnson & Johnson is also developing a dual-component, prime-boost candidate vaccine against the Ebola virus.

Meanwhile, the chikungunya virus is steadfastly making its way into the Americas, initially infiltrating islands in the Caribbean late in 2013, then the South American mainland and Central America a few months later, and into Florida by the middle of 2014, according to Ann Powers of the Centers for Disease Control and Prevention (CDC) in Atlanta, Ga. The Asian rather than the African genotype is the predominant strain of chikungunya virus now circulating in this hemisphere.

Among several approaches to developing vaccines to protect against chikungunya, the apparent front runner is a virus-like particle (VLP) version that entered a phase 1 clinical trial several years ago, according to Julie Ledgerwood of NIAID. Although its principal antigen derives from a West African strain of chikungunya, the antibodies this vaccine elicits are expected to be fully cross-reactive with other strains of the virus, including the Asian genotype now circulating in South and Central America, she says.

The VLP candidate vaccine elicits an “impressive” antibody response, and there is boosting after each injection, according to Ledgerwood. Unlike an older, live-attenuated candidate vaccine for chikungunya, clinical testing of the newer VLP led to virtually no side effects, and it induces neutralizing antibodies at all doses, she says. Although a clinical efficacy trial is a logical next step, officials find themselves stymied because outbreaks tend to be sporadic, making it difficult to plan such a trial. Further, chikungunya and Dengue virus outbreaks intermingle, with both viruses causing nearly identical symptoms—yet another complication for those seeking to plan clinical trials for vaccines targeting either one of these viruses.

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Antibiotics Directly Damage Host Gut Epithelial Cells

David C. Holzman

Antibiotics not only disrupt the host microbiome, they also can induce mitochondrial dysfunctions within host cells along the intestinal epithelia, according to Natalia Shulzhenko and Andrey Morgun of Oregon State University in Corvallis and their collaborators. Details appeared 22 January 2015 in Gut (doi:10.1136/gutjnl-2014-308820).

Separately, tetracycline antibiotics, even at low concentrations, change gene expression and alter mitochondrial functions across a wide range of animal and plant cells types, according to Johan Auwerx of Ecole Polytechnique Federale de Lausanne in Lausanne, Switzerland, and his collaborators there and in the Netherlands. This effect of tetracyclines could confound experimental outcomes, and the data suggest a potential negative impact on the environment and health that should be further explored, they point out.

More generally, antibiotic-induced changes in the gut can be explained by three factors, the researchers note: depletion of the microbiota, direct effects of antibiotics on host tissues, and the effects of remaining antibiotic-resistant microbes, according to Morgun. “Our most surprising finding was that antibiotic-resistant bacteria and the antibiotics themselves caused many of the same toxicities,” he says.

Although antibiotics reduce immune responses in the gut, whether that damage is direct, mediated through the microbiome, or from