Vaccines revisited

By Tracey Baas, Senior Editor

A team from **Oregon Health & Science University** and **Najit Technologies Inc.** has shown that hydrogen peroxide could be a better way to inactivate viral vaccines than conventional methods such as formaldehyde and β -propiolactone.¹ Najit, which was spun out of the university in 2004, hopes to start a Phase I trial of an inactivated yellow fever virus vaccine in the next 1–2 years.

Noninfectious vaccines are typically produced by chemically inactivating a virus using formaldehyde or β -propiolactone. This approach can damage a virus so that it can no longer replicate, but the approach also can damage the antigenic epitopes required for an efficient immunological response.

Antibodies produced in response to the damaged epitopes may not efficiently interact with a live virus and neutralize it during future infection.

The Oregon team decided to try inactivating virus using a known antimicrobial and antiseptic agent: hydrogen peroxide. Conventional wisdom held that the oxidizing chemical would be too damaging to use for virus inactivation,² but the researchers thought otherwise.

First, the Oregon group showed that hydrogen peroxide inactivated the orthopoxviruses vaccinia virus and monkeypox virus, the flaviviruses West Nile virus (WNV) and yellow fever virus, and the arenavirus lymphocytic choriomeningitis virus (LCMV). In all cases, the result was undetectable levels of replicating virus.

In an ELISA, hydrogen peroxide-inactivated yellow fever virus retained higher levels of antigenicity against serum from yellow fever virus-infected mice than formaldehyde- or β -propiolactone-inactivated virus. This result suggests that hydrogen peroxide inactivation preserves more native antibody-binding sites.

The vaccine platform also provided protective immunity against chronic viral infection and lethal viral challenge.

In mice challenged with LCMV, those previously vaccinated with hydrogen peroxide-inactivated LCMV had a reduction in viral titers of more than 99% or had fully cleared the virus within 7 days, whereas unvaccinated mice remained viremic for at least 35 days.

Finally, mice vaccinated with hydrogen peroxide-inactivated vaccinia virus or WNV survived lethal viral challenge and had higher neutralizing antibody titers than mice vaccinated with formaldehyde- or UV-inactivated viruses.

Data were published in *Nature Medicine*.

“We chose three unrelated virus model systems in order to demonstrate that we have a platform technology that can be used to prevent a wide range of diseases, including both chronic and lethal infection,” said Mark Slifka, professor and senior scientist at the Oregon

National Primate Research Center at OHSU and president and CSO at Najit.

One pathogen at a time

Najit thinks its hydrogen peroxide-inactivated vaccine platform—called HydroVax—will be amenable to producing vaccines against nearly any type of pathogen. The company’s initial focus is on viruses with limited vaccine options.

“We’re going to first focus our attention on a yellow fever virus vaccine,” said Ian Amanna, associate VP of Najit. “Despite the commercial availability of live attenuated yellow fever virus vaccines, they are contraindicated in infants and may place elderly patients at increased risk of severe adverse events.”

Novartis AG markets Arilvax and **Sanofi** markets YF-VAX, both live attenuated virus vaccines against yellow fever. Yellow fever vaccines in the clinic include **Johnson & Johnson’s** Flavimun, a live attenuated virus vaccine in Phase III testing, and **General Electric Co.’s** XR-001, a purified whole-virus, β -propiolactone-inactivated yellow fever vaccine adsorbed to an alum adjuvant. The vaccine is in Phase I trials.

“We are also interested in West Nile virus and dengue virus vaccines because there is currently no licensed vaccine available. However, there are live attenuated vaccines in various stages of clinical development,” said Amanna. “With live attenuated dengue virus vaccines, it has been somewhat challenging to get broad immunity to all four serotypes, but with an inactivated vaccine platform we have preliminary preclinical evidence indicating that this can be accomplished by adjusting the ratio of the different strains in the vaccine formulation.”

Further down the line, Slifka said the company is “interested in showing that our system also works for common viral pathogens such as influenza virus and respiratory syncytial virus.” Respiratory syncytial virus (RSV) vaccines of the past have been tricky. Formaldehyde-inactivated RSV vaccines have been shown to be well tolerated in children, but then exposure to natural RSV resulted in a number of hospitalizations and deaths, which has been attributed to exacerbated disease.

“We will continue to put our main focus on developing vaccines for diseases that already have well-established animal models,” he continued. “It may be awhile before we can test an RSV vaccine to determine if it provides protection or if it might exacerbate disease. It remains an interesting and open question.”

Slifka and Amanna also think the vaccine production technology could be used to inactivate bacteria, parasites and even bacterial spores.

“We have not initiated studies on nonviral targets but hope to begin these studies later this year,” Slifka said. “Who knows—it would be great to develop an effective vaccine for *Mycobacterium tuberculosis*.

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**—Mark Slifka,
Najit Technologies Inc.**

TB is a huge global problem, and current vaccine approaches have had only limited success.”

Ongoing work includes developing improved flavivirus vaccines and cGMP manufacturing of hydrogen peroxide-inactivated vaccines against yellow fever virus, WNV and dengue hemorrhagic fever.

The work is patented by OHSU and is licensed by Najit, which is looking for partners to co-develop or sublicense the technology for vaccine manufacture of specific targets.

Baas, T. *SciBX* 5(24); doi:10.1038/scibx.2012.619
Published online June 14, 2012

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COMPANIES AND INSTITUTIONS MENTIONED

General Electric Co. (NYSE:GE), Fairfield, Conn.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Najit Technologies Inc., Beaverton, Ore.
Novartis AG (NYSE:NVS; SWX:NOVN), Basel, Switzerland
Oregon Health & Science University, Beaverton, Ore.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France