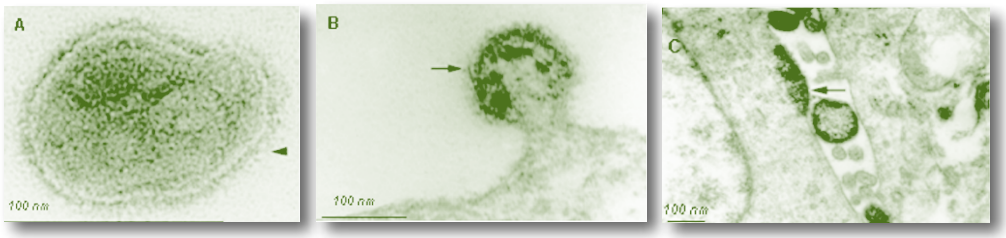
# A Lassa Fever Vaccine is Safe Even in Immunocompromised Animals

Lassa fever may not be as well-known as Ebola or Marburg, but it causes more deaths every year than either of those hemorrhagic fever viruses. This is mainly because so many people are infected with Lassa virus--about 300,000 people each year in endemic regions of West Africa. Lassa can be treated using Ribavirin, an antiviral drug. Unfortunately, Ribavirin is not only fairly toxic, but it is only effective if given a few days after exposure to the virus. The high prevalence of this deadly disease and the less-than-ideal treatment options led researchers to search for a Lassa fever vaccine.

Dr. Igor Lukashevich and Dr. Maria Salvato at the Institute of Human Virology (IHV) successfully developed a Lassa vaccine candidate that was safe and effective in animal models. But they were still concerned that this vaccine might cause an adverse reaction in immuno-compromised people, such as AIDS patients. This was an important concern: areas endemic for Lassa fever virus also have a very high incidence of AIDS, says Dr. Salvato. Critics continued to question the wisdom of conducting an immunization program in West Africa where many people are already immunocompromised.

To address this question, Salvato decided to test the safety of the vaccine in an animal model for AIDS. In a study funded by the National Institutes of Health, the researchers looked for high levels of the vaccine virus and signs of Lassa disease in immunocompromised animals injected with the vaccine. The animals showed no viremia (the presence of the virus in the bloodstream) or disease, indicating that the vaccine was safe. The vaccine also produced a specific immune response against Lassa virus. These results showed that this Lassa vaccine could be useful even in areas where AIDS was widespread.

The vaccine strain that Lukashevich and Salvato developed, called ML29, is a "live-attenuated" vaccine. This means that it can replicate and create an immune response, without causing disease. As a live-attenuated vaccine candidate for Lassa fever, ML29 produced a stronger immune response than other Lassa vaccine candidates, and was the only one that protected against a broad range of Lassa strains.




*A, LASV purified from isopycnic sucrose gradient, negative staining (x200,000). Panels B and C depict ultrathin sections of LASV-infected cells. B, a particle which appears to be budding from plasma membrane (x170,000); C, the arrow indicates the discrete area of membrane thickening associated with viral buds. Arrows on panel A and B show glycoprotein projections on viral surface.*

But it was the live-attenuated nature of the vaccine that caused the researchers to take extra steps to ensure that it was safe in immunocompromised individuals. "This is a very important question, because there is a notion that you can reactivate a live-attenuated vaccine in immunocompromised individuals," says Lukashevich. Because of this fear that the live-attenuated vaccine could cause disease, ML29 is classified as a bio-safety level 3 virus strain, the same level as the pathogens causing anthrax and SARS. This entails extra safety measures that make its commercial production prohibitively expensive. "What's frustrating is that in Europe and Africa it's considered level 2, which means it can be produced more cheaply," says Salvato. She hopes to collaborate with drug companies in Europe or Africa to produce the vaccine. But even though ML29 has a number of advantages over other Lassa fever vaccine candidates, it isn't currently the most likely to be commercially produced, says Salvato. According to her, a yellow fever-vectored vaccine is much more popular in third world countries because it can be inexpensively produced in existing facilities.

*Drs. Maria Salvato and Igor Lukashevich in an IHV lab*

Salvato and Lukashevich hope to interest the government of Nigeria, where Lassa is endemic, in their vaccine. "Our goal is to find good partners in Nigeria," because the IHV has a well-established infrastructure there, says Lukashevich. But the Nigerian government "has many other problems and they're not sure that this is a priority," says Salvato.

But Salvato has hope for another approach--vaccinating the rats that are the carriers for the disease. The vaccine could be delivered in rodent bait, from where it could spread easily among the rats. The vaccine could not only prevent the rats from carrying Lassa virus, but as an added benefit, would probably also decrease litter size, says Salvato.

The researchers would like to overcome the various obstacles to ML29's commercial production, and hope that showing that the vaccine is safe in immunocompromised patients will help. In the meanwhile, ML29 will still be extremely useful for laboratory studies; "it's a way to produce something that looks to cells like Lassa fever virus, and yet its replication is attenuated," says Salvato. "It's what we're using in regular daily research in our lab." Among other things, researchers can infect the same cell with Lassa virus and HIV, and study the interactions between the two viruses. Interestingly, the researchers noticed that "when we applied this vaccine immediately after infection with Lassa virus, it was also protective against Lassa disease," says Lukashevich and this is also something they plan to look at. Who knows--with more research, ML29 may be useful not just as a vaccine and as a laboratory strain, but even as a form of treatment.