In search of an AIDS vaccine

BY DANIEL SARAGA PHOTOS THIERRY PAREL

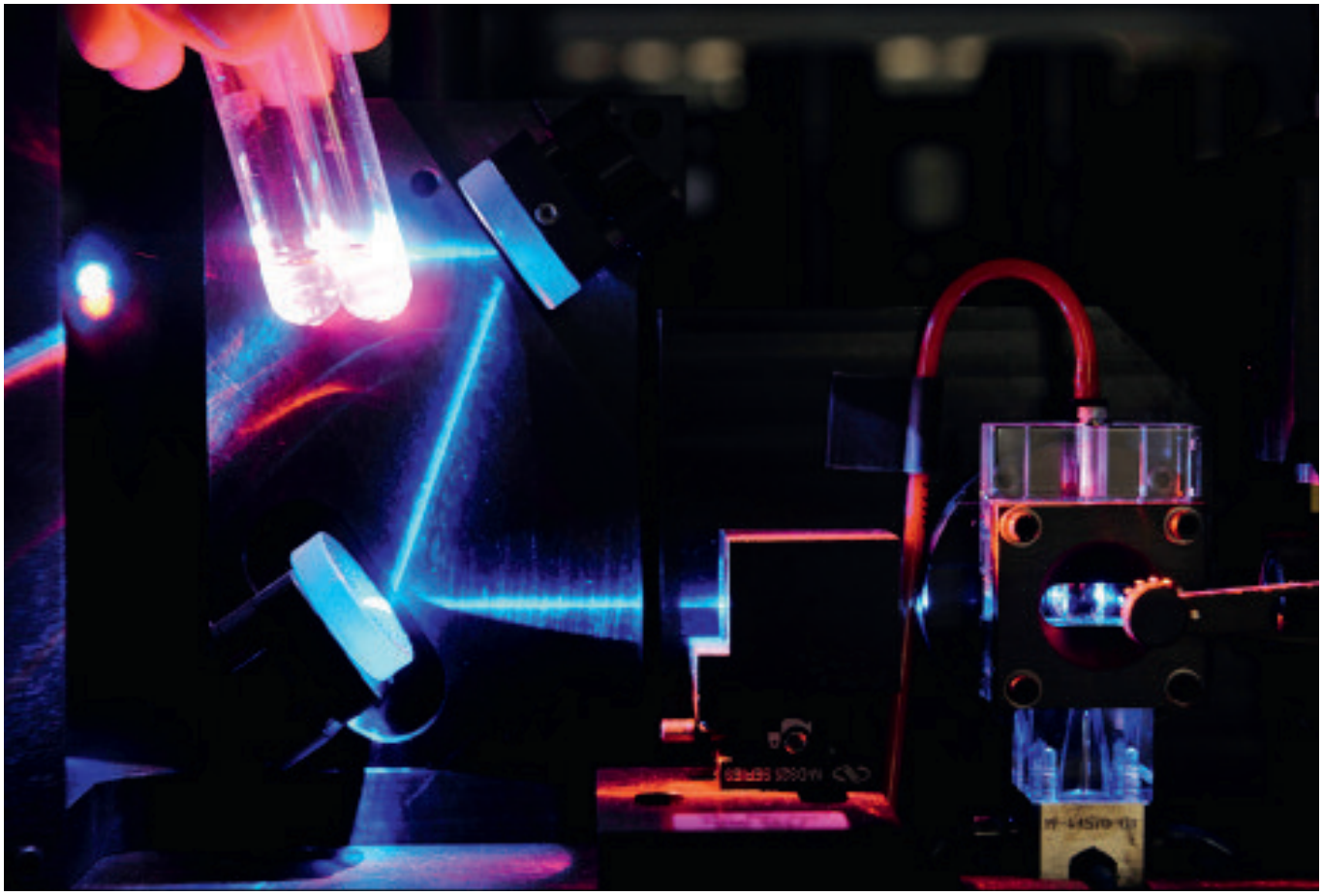
World-renowned AIDS expert Giuseppe Pantaleo and his Lausanne team have been funded by the Gates Foundation. They are now conducting trials with dozens of volunteers.

In late 2007 the scientific community received a rude shock: STEP, the most promising AIDS vaccine trial to date, had been abandoned because Merck's V520 vaccine was ineffective. Even worse, it appeared that those receiving the vaccine were more susceptible to infection and, once infected, might experience an increased viral load. After more than 25 years of fruitless work, many researchers became pessimistic.

Some, however, are continuing the fight. A Lausanne-based team led by professor Giuseppe Pantaleo forms the core of EuroVacc, a large European HIV/AIDS vaccine research network. The Division of Immunology and Allergy (IAL) at Lausanne's University Hospital (CHUV) has developed a reputation as an international center of expertise in this area.

In July 2007 a different, European vaccine passed into phase II trials. "We had already demonstrated the safety of the vaccine, as well as its capacity to generate an immune response," explains Pantaleo. "With the new EuroVacc 3 trial, we want to consolidate these results using a larger number of volunteers." The trial will also test a new vaccination strategy that changes the number of injections given. "The optimization of the vaccination regime is very important for the success of a vaccine," he emphasizes. "Especially in developing countries, where it's difficult to give regular injections. Ideally, a single dose of the vaccine would be effective."

In 2006, Pantaleo received more than $15 million from the Bill and Melinda Gates Foundation to pursue vaccine research. That funding permitted the creation of



Researchers determine the effectiveness of vaccines using a flow cytometer. By stimulating fluorescent molecules with laser beams, this technological marvel can automatically analyze millions of white blood cells.

the Swiss Vaccine Research Institute in Lausanne, which brings together Swiss expertise in infectious diseases (see box). The IAL has also become the first European site in the U.S.-based HIV Vaccine Trials Network (HVTN), the largest AIDS vaccine development network in the world.

The Lausanne researchers have been working on a new form of the vaccine since 2005. “First, we want to create a targeted response to other parts of the HIV genome,” explains Pantaleo. “Then we want to get the vaccine vector to replicate. That should increase the immune response.” For now, the replication of the vaccine is restricted for security reasons. The scientists are also working on clinical treatment, with a program exploring therapeutic uses of the vaccine. In individuals who are already HIV-positive, the vaccine could stimulate an immune response, giving them the opportunity for a break in their heavy “triple cocktail” treatment regimen.

CHOOSE YOUR TROJAN HORSE

The human immunodeficiency virus (HIV) that causes AIDS is one of the world’s most rapidly mutating pathogens; it can even mutate within a single person. As a precaution, the scientific community has forbidden its use in a vaccine – even when dead or rendered inactive. “That would be far too dangerous,” emphasizes Pantaleo; “we’d be running the risk of infecting the entire planet! Because even if we remove vital bits of DNA, there is risk of recombination – incomplete DNA can find its missing pieces.” Imagine creating a mutant virus even more virulent that the original.

The researchers must therefore settle for a “synthetic” vaccine, and insert tiny bits of the HIV genome into another virus, a vector that plays the role of a Trojan horse. If possible, these pieces of DNA should be common to all known strains of HIV. “This approach is difficult. The most effective vaccines are those that closely resemble the pathogen. There are 30 vaccines in the world, and only two are synthetic; those against hepatitis B and papillomavirus. All the others are derived from the targeted virus.”

“We recently published a hypothesis to explain what happened in the STEP trial,” continues Pantaleo. “The V520 vaccine used an adenovirus as a vector, a virus that causes the common cold. People who were already

EPFL joins the Swiss Vaccine Research Institute

Launched in December 2007, the Swiss Vaccine Research Institute is tackling three infectious diseases that ravage developing countries: AIDS, tuberculosis and malaria. The institute brings together the CHUV, the University of Lausanne, EPFL, the Ludwig Institute of Cancer Research in Epalinges and the Institute for Biomedical Research in Bellinzona. "We can use the same strategy to fight different diseases," explains director Giuseppe Pantaleo. "We don't use the pathogen itself, but another virus as a vector."

At EPFL, research in the Global Health Institute and the Institute of Bioengineering concentrates on molecular processes involved in the onset of these diseases. "We are developing innovative approaches, such as the use of nanoparticle vaccines," says Didier Trono, dean of the School of Life Sciences. EPFL has one of the largest biosafety (level 3) laboratories in Switzerland, which allows researchers to study extremely virulent pathogens. Fifteen more scientists will be hired to make up three additional research groups.

immune to this virus had a bad reaction to the vaccine. When it was injected, the vaccine formed a complex with adenoviral antibodies and stimulated the production of white blood cells, T CD4 lymphocytes. Unfortunately, these are HIV's favorite targets, which would have then helped accelerate its multiplication."

In contrast to the Merck vaccine, the European approach uses an attenuated form of the smallpox virus as a vector. It's a judicious choice; smallpox has been eradicated for more than 30 years, and very few sexually active adults have been immunized against the disease. The unpleasant surprise encountered in the STEP trial,

Tracking down HIV

For more than 20 years, the Swiss HIV Cohort has been following more than half of Switzerland's seropositive population. The group collects anonymous statistical data from more than 15,000 people. Chaired by Patrick Francioli, dean of the Faculty of Biology and Medicine at the University of Lausanne, this database is one of the most complete in the world, and has been used in more than 400 publications. Using this data, improvements have been made in the treatment of patients through studies of the efficacy of various medications and their side effects and studies exploring the possibility of individually-adapted therapies. The analysis of genetic aspects of AIDS development and the study of the emergence of resistance has also contributed to fundamental research.

most likely created by a reaction with vector-specific antibodies, should not repeat itself in EuroVacc.

HELPING RESEARCH

Lausanne's CHUV plays a key role in the European collaboration. This is where immunogenicity analyses are done and the largest contingent of volunteers is found. For the new trial, 30 of the 140 volunteers are from Lausanne. Despite the apprehension that AIDS provokes, the IAL team has had no problem meeting its quotas. "We recruit primarily at the CHUV, at the University of Lausanne and at EPFL," explains Séverine Burnet, clinical trial coordinator. "Our participants must have a low risk profile, because right now we are only analyzing the immune response in healthy volunteers." It's still too soon to say if the vaccine is effective against a real HIV infection.

"This kind of trial is very heavily regulated," adds Burnet, "and must be authorized by an ethics commission that verifies several details. For example, we respect complete anonymity with our volunteers, to avoid any chance of discrimination." Even for seemingly harmless tests, the word AIDS can scare people. Questionnaires filled out by participants verify that they have understood the information they've been given – in particular, the fact that they are not protected by the vaccine.

"I saw the ad in the locker room," recalls Juliette (not her real name), a nurse at the CHUV who decided to participate in the trial. "I was initially attracted by the payment, about 2,000 Swiss francs for 13 one-hour sessions. I also appreciated the medical check-ups I got throughout the trial. But it's also very satisfying to be able to help with research." Juliette, who is separated from her husband, told her son and a close friend about her participation. "We were well informed, it was all very transparent. Basically, I trust them. I'm convinced that the trial won't put my health in danger." A medical or scientific background surely helps someone understand the subtleties of a vaccine made up of bits of DNA inserted in another virus.

Blood samples are regularly drawn and sent to the lab. To analyze and observe the immune response, researchers use an impressive machine: a flow cytometer, a rare technological marvel. "Measuring the lymphocyte level in the blood is not enough to test a vaccine," explains Alexandre Harari, a project leader at IAL. "We also have to determine their functional profile." It turns out that some lymphocytes (a type of white blood cell) mobilized during an immune reaction are powerless against an HIV infection, and that several responses

Can HIV resistance be transplanted?

A bone marrow transplant has made it possible to transfer the natural resistance of an "elite controller" to an HIV-positive person. In November, more than 24 months after the transplant operation, Gero Hutter, a doctor in Berlin's Charity Hospital, announced that there was no trace of HIV in his patient. Thirty similar operations had already been done between 1982 and 1996, but HIV disappeared completely in only two of those cases. Because one-third of bone marrow transplants are fatal, they cannot be done for a majority of HIV patients. The Berlin patient was also suffering from leukemia, which justified the transplant.

are possible. Different kinds of lymphocytes must be identified and measured along with cytokines, substances they produce while fighting an infection. "Certain cytokines launch the recognition of an infection or activate the proliferation of white blood cells," explains the researcher. "Others directly attack the virus, or cells that are already infected. The important thing for a good defense is multifunctionality – a varied response."

To conduct the analysis, researchers attach fluorescent molecules to antibodies. These react with the cytokines or with markers found on the lymphocytes. In the machine, four lasers stimulate the fluorescent molecules; the light they re-emit is measured by sensors, thus quantifying the levels of cytokine and white blood cells in the sample. Drop after drop, millions of lymphocytes are counted and analyzed. These techniques have made the Lausanne laboratory a European center of excellence whose services are available to biotech companies for testing new vaccines against a variety of diseases.

THE HOPE OF "ELITE CONTROLLERS"

Currently, only three phase III trials have been launched to test the capacity of a vaccine to protect against a real HIV infection. These campaigns must involve at-risk populations, such as prostitutes or intravenous drug users. Researchers always take advantage of information sessions to encourage prevention (use of condoms, etc.) – even though they are resigned to the fact that a certain number of participants won't follow their advice and will become infected. "The failure of STEP will make these trials even more difficult," says Séverine Burnet. "Some representatives of the gay community in the U.S. have been very critical of new trial projects based on the same strategy as STEP."

In 2004, a trial was launched involving 16,000 people in Thailand, despite serious reservations expressed by researchers who thought that preliminary results were not encouraging enough. Events seem to be proving them right: initial results indicate that the efficacy of the vaccine will be modest at best. The results of the trial, which cost nearly $100 million, will be announced this summer.

World-renowned AIDS expert Giuseppe Pantaleo and his team are developing new HIV vaccines in Lausanne, analyzing their effectiveness and coordinating Europe's largest clinical study.

Even though an AIDS vaccine has eluded researchers for 25 years, patience is the order of the day. Vaccines against any number of diseases (polio, typhoid, measles) took between 40 and 100 years to develop, and about 20 vaccines have been advanced, albeit unsuccessfully, against malaria. The hope for conquering AIDS is maintained by the existence of "elite controllers," people in whom the disease does not progress, even without any treatment at all. Although it represents less than 1% of the HIV-infected population, this group still proves that a solution exists. Now we need to understand how to reproduce it. ■