SA vaccine trials launched, but future funding not secure

Craig McKune

Following a decade of research, the first two South African-developed HIV vaccines went into clinical trials in July. The two vaccines are both being tested in phase I safety trials in 36 local volunteers at two sites: the Emavundleni Centre in Cape Town and Chris Hani Baragwanath Hospital in Soweto. But the launch of the South African trials has been overshadowed by a funding crisis at the South African Aids Vaccine Initiative (SAAVI), which developed the vaccines but has had its funding from the Department of Science and Technology (DST) terminated.

The new vaccine trials, known as SAAVI 102/HVTN 073, follow on the heels of disappointing 'Step' trials of a candidate vaccine developed in the USA by pharmaceutical company Merck, which were called off in 2007 after it was found the vaccine failed to prevent HIV infection or reduce viral load (see *SAJS* **105**, 168–169; 2009). Testing the same product, the South African Phambili trials were also subsequently dropped. But as the HIV epidemic in southern Africa is dominated by a particular strain of the virus (subtype-C), it was predictable that vaccines developed against other strains would not work optimally here.

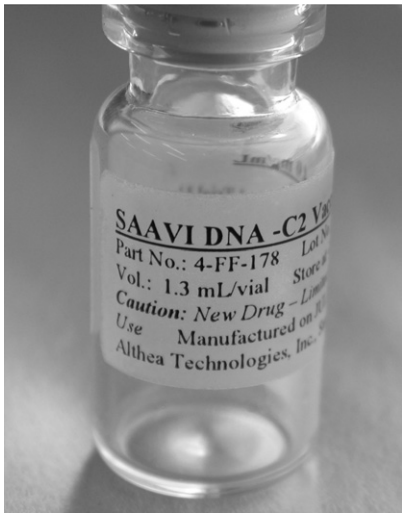
As part of the SAAVI initiative to develop a vaccine specifically for subtype-C, virologist Carolyn Williamson and her team at the Institute of Infectious Diseases and Molecular Medicine at the University of Cape Town (UCT) surveyed HIV from newly infected patients and selected genes that best represented local strains. Building on this, she and Anna-Lise Williamson, from the same institute, refined two vaccines—the two now on trial—by incorporating additional subtype-C genes and modifications to make them more effective.

The new trials are using what is known as a prime-boost response: the synthetic DNA vaccine is given to prime the body's immune response, followed by the MVA vaccine which should boost the immune response. MVA is made from the Modified Vaccinia Ankara virus, similar to the smallpox vaccine—so volunteers must not have received the smallpox vaccine before.

The SAAVI 102/HVTN 073 vaccine trials aim to test if the candidate vaccines are safe for people and how their immune systems respond. Trial participants also have to be HIV-negative and at a low risk of becoming infected. If the results are promising, phase II trials will be conducted also to test vaccine safety and immune response, and phase III trials would test if the study vaccine is effective in preventing HIV infection or slowing its progression to Aids.

The two MVA and DNA study vaccines, however, are all that remain of a pipeline of vaccines that was being developed by SAAVI researchers. As a consequence of the DST withdrawing funding, only seven of SAAVI's former vaccine team of 39 researchers remain employed by the initiative.

Based at the South African Medical Research Council, SAAVI was formed in 1999 with the goal of producing a viable HIV vaccine through coordinated research, development and testing. It was backed by the South African government and local and international donors including Eskom, the US National Institute of Health (NIH) and the HIV Vaccine Trials Network (HVTN).



Anke Binder

SAAVI first ran into trouble when Eskom cut its R15-million grant at the end of 2007, citing its own financial difficulties as the reason. Then in February last year DST announced that it was terminating its contract with the initiative. According to the department (http://www.dst.gov.za/Sharp.pdf), the SA government is 'revisiting' its expectations of HIV vaccine research in favour of 'a strategic combination of interventions', and accordingly has allocated R45 million over the next three years to fund the new South African HIV/AIDS Research (and Innovation) Platform (Sharp), which is to focus more 'holistically' on HIV prevention and treatment research.

The DST website reports that SAAVI has been guilty of under-spending, and 'issues' had been raised in independent audits in 2005 and 2006. Neither SAAVI interim director Elise Levendal nor the DST

Carolyn Williamson: 'SAAVI gave South African researchers incredible leverage'.

would give details of these issues, but Levendal said that only very minor concerns had been reported.

In the case of the SAAVI 102/HVTN 073 trials, DST's health innovations director Glaudina Loots says that now that the DNA and MVA vaccines had entered clinical trials, the department's job was done. 'DST's responsibility is up until the phase I clinical trials, and that's it,' she said. Another reason for the cut cited on the DST website was that 'the lion's share' of the funds had gone to Anna-Lise Williamson, but department spokesman Lunga Ngqengelele declined to elaborate on this.

In an effort to keep SAAVI's vaccine effort alive, as the DNA and MVA vaccines were so close to clinical trials, UCT vice-chancellor Max Price met with deputy minister of science and technology Derek Hanekom. 'Hanekom made funds available to continue the project for another year', according to deputy vice-chancellor Danie Visser, and the department has provided an additional R6.6 million since March 2008.

Anna-Lise Williamson argues that it does not make sense for the DST to fund the candidate vaccines only up until the phase I safety trials. 'This is questionable logic. The way a vaccine pipeline works, this vaccine that is going on trial is unlikely to be the last version. We need to see if we are getting a decent immune response, then we must take it back to the labs for more research.' Regular potency assays are still needed to assess the stability of the products.

'[And] we may wish to combine this product with other products to see if we could increase the breadth of responses,' says Carolyn Williamson. 'We could possibly improve the insert to increase immunogenicity. We could use the DNA vaccine as a primer for other vaccines to prime the MVA. All of these things require laboratory investigation to see if they would hold any promise in clinical trials.' But the DST has left the trials—and any future work on the DNA and MVA products—to be funded by international donors and the Department of Health.

'The impact of DST withdrawing its funding has been huge,' said Levendal. 'There are very promising young scientists who have been retrenched, many of whom have still not found new positions.' She said SAAVI has been forced to operate at a more modest level than before. 'We are basically coordinating vaccine research and development now, and we will do that through small grants to basic science, ethical research and community research. It's a major blow, but we're using the limited amount of money we have as well as we can.'—'We had huge capacity that is now gone,' says Anna-Lise Williamson. 'For vaccine research we need to have sustainable money. Vaccine projects take over 15 years to come to fruition, so we have to have buy-in on a different level.'

Anna-Lise Williamson: 'For vaccine research we need to have sustainable money'.

SAAVI is trying to secure alternative funding in a difficult environment: global spending on HIV vaccine research has fallen for the first time since 2000. A report released in July, 'Adapting to Realities: Trends in HIV Prevention Research Funding 2000 to 2008' (http://www.hivresourcetracking.org) by the HIV Vaccine and Microbicide Resource Tracking Working Group, found that HIV vaccine research spending had dropped 10% between 2007 and 2008. The report suggests this relates to shifting scientific priorities, the declining economy and competing health priorities globally.

But Levendal said the Italian national health department had pledged R38 million dedicated to strengthening existing clinical trial sites, and to help build vaccine manufacturing capacity in South Africa. And SAAVI was waiting for the Department of Health to sign an agreement to fund R35 million over the next three years. While Levendal would not elaborate on how this money would be spent, she said part of it would go to the DNA and MVA vaccines, and once it was approved, SAAVI would announce a new call for proposals.

According to Carolyn Williamson, the initiative has provided strong negotiating power with international scientists. 'South Africa is a highly desirable location for HIV vaccine research. The disease has a high impact and rate of spread, it is a unique strain, and the country has good scientific and infrastructural capacity.'—'SAAVI gave South African researchers incredible leverage. Researchers knew that if they wanted to work in South Africa, they also had to contribute to the country,' she said.

Following its first call for proposals in February this year, Sharp now supports nine research projects, which are expected to come up with a new diagnostic test to detect HIV drug resistance; possible new drug targets; potential biomarkers to be used to inform control of HIV infection; and finding molecules or a neutralising antibody which could be used in a vaccine. The intention is to develop an approach to HIV prevention and treatment research that will help to reduce the rate and risk of transmission in the short term 'while awaiting the development of an effective vaccine', reports the department's website.

But Carolyn Williamson said that in terms of producing an actual vaccine product that can be clinically tested, these programmes do not compare to SAAVI's. 'They're funding only basic science in isolation but it is not obvious from the outside what their long term strategy is,' she said.

'If the DST's mission is product development,' she adds, 'I don't think it has a sensible approach. If you develop a product and go all the way to trial and then just dump it, what kind of a science and technology department are you?'

Craig McKune is a science journalist based in Cape Town.