Williamson's Vaccines a First for Africa

Renowned UCT scientist Professor Anna-Lise Williamson and researchers from UCT's Institute of Infectious Disease and Molecular Medicine (IIDMM) reached a research and innovation milestone last year with the announcement that two of their new preventative HIV vaccines were set for the first stage of human clinical trials.

A first for Africa, the trials represent almost a decade of exhaustive research and is a major accomplishment for Williamson and her colleagues. It also makes South Africa one of the few developing nations to have successfully created an HIV vaccine that has gone forward to human clinical trials.

The initial human trial is being conducted jointly with the HIV Vaccine Trials Network and the NIAID, part of the US National Institutes of Health. The Desmond Tutu HIV Centre, based at the IIDMM, is one of three international sites that will conduct the trials, with the others located in Johannesburg and Boston in the United States.

Williamson reports that the first Phase 1 trial HVTN 073 / SAAVI 102 has been completed and that the initial immunogenicity results look promising.

"The lab work still needs to be completed in Johannesburg and the USA. Participants in this trial will be invited to participate in a modified protocol where they are immunised with a protein vaccine made by Novartis. A second trial is also planned to look at different combinations of the SAAVI DNA-C2, SAAVI MVA-C and the Novartis protein vaccine. We are looking for financial support to fund the manufacturing of our vaccines for a Phase 2B efficacy trial," she says.

These vaccines are the culmination of eight years of research by scientists at the IIDMM, UCT, and collaborators from the US National Institutes of Health and the Vaccine Research Centre. Their development and testing has been underpinned by funding from the South African AIDS Vaccine Initiative (SAAVI) and the US National Institute of Allergy and Infectious Diseases (NIAID).

Williamson is dedicated to her research work because of vaccines potential to greatly reduce global health burdens. "Vaccines are designed to be given a limited number of times and are the best way of preventing diseases. Millions of lives are saved because of the immunisation of children throughout the world. For example, smallpox was eradicated by vaccination."

She attributes her success in vaccine development to her early initial research she conducted into veterinary vaccines. "It was because I had so much vaccine expertise, it enabled me to achieve in the HIV field," she explains.

The UCT group is investigating a number of different strategies to make HIV-1 vaccines, based on HIV-1 subtype C virus, which is the dominant strain circulating in southern Africa. The mission of this group is to develop HIV-1C vaccines which are both effective and affordable, and through a comparative strategy, to advance the most promising vaccines or combination of vaccines to clinical trials.

Among Williamson's multidisciplinary research team are Principal Investigators Professor Carolyn Williamson, Associate Professor Enid Shephard and Professor Ed Rybicki. Together they have notched up significant progress on a number of candidate HIV vaccines. Ed Rybicki and Anna-Lise Williamson have also made progress on the development of novel Human Papillomavirus (HPV) vaccines.

"Our most successful project is our HIV vaccine project because we went from the basic concept all the way to clinical trials. And that's a major achievement in South Africa to be able to get a vaccine to human trials," says Williamson.

The first vaccines selected to move forward to clinical trials are DNA vaccines (SAAVI DNA-C2) and a modified vaccinia virus Ankara vaccine (SAAVI MVA-C). This DNA prime – MVA boost combination is regarded as one of the most promising vaccine strategies. The bacterial vaccine group is developing vaccines based on live recombinant Bacillus Calmette-Guérin (BCG) and previously also worked on Salmonella bacteria, while the subunit vaccine group was making candidate vaccines using baculovirus and tobacco expression systems prior to SAAVI funding being stopped.

Therion Biologics (USA) and Althea Technologies (USA) have produced the vaccine doses that are being used in the clinical trial. The UCT SAAVI development team included both the Williamsons and Shephard, as well as Dr Katrina Downing, Dr Joanne van Harmelen, Dr Gerald Chege and Dr Wendy Burgers. They are working in partnership with NIAID (NIH, USA); the HIV Vaccine Trials Network (HVTN) of the National Institutes of Health (NIH, USA), Professor Clive Gray of the NICD in Johannesburg and Professor Glenda Gray of Chris Hani-Baragwanath Hospital.

The next most promising vaccine, developed by Rybicki and Dr Ann Jaffray, is the virus-like particle (VLP) vaccine based on an HIV-1 subtype C Pr55 Gag protein, which is produced in insect cells via recombinant baculovirus. This vaccine induces an excellent immune response in mice as well as non-human primates. If successful, this will be a cheap and effective production system for the subunit vaccines. (see article on Ed Rybicki on page 17)

In another project, Williamson's group, together with Dr Ros Chapman, are optimising bacterial vectors as vaccine delivery vehicles. Williamson explains that BCG – which is better known as the TB vaccine - has many advantages as a vaccine vector. Production costs are also very low in comparison to other vaccine production strategies. Although rBCG expressing our HIV-1 proteins induces an immune response in mice and in baboons, it is not yet optimal for use as a vaccine. Several different approaches are being taken to improve this response." Williamson elaborates.

Willamson's group has also been at the forefront of research on human papillomavirus (HPV) – the virus responsible for cervical cancer and a number of other cancers. "Our group has been active in HPV research for almost two decades. We have an on-going interest in studying HPV types associated with cervical and oral disease throughout the region," she says.

"The papillomavirus projects are just a totally different type of project," she says. "We've done a lot of work to show what different HPV types are prevalent in the country, so that if vaccine were introduced into South Africa we would know the impact on circulating HPV types."

The development of HPV vaccines and exploring different immunisation strategies are a core focus and Williamson's laboratory has established various working models to evaluate papillomavirus vaccine production strategies, taking into account the need to develop inexpensive vaccines, appropriate for the continent.

For Williamson the milestones in this domain have included the extensive collaborations on HPV projects which have provided information on the immune response to HPV and the molecular epidemiology of HPV types in cervical cancers, pre-cancers, women with normal cytology, as well as the impact

of HIV. "A particular highlight was the demonstration by my post-doctoral fellow, Dr Vandana Govan, that BCG expressing papillomavirus genes could successfully protect against infection with cotton tail rabbit papillomavirus" she says.

Her group is no longer working on HPV vaccines and this work has been taken up by Ribicki's research group. "My group is now concentrating on projects investigating the impact of HIV co-infection on HPV. HPV causes cervical cancer and women with HIV are at much higher risk of getting cervical cancer because they have more persistent HPV infections. We are also interested in oral HPVs."

In relation to her HIV vaccine work, Williamson believes that several important factors aligned to ensure this research was successful. Firstly, she credits the international partnership with the NIH in the US which resulted in access to both funding and expertise, and secondly acknowledges the initial funding made available by the South African government.

"We couldn't have done it without that NIH partnership, it was absolutely essential. They committed an enormous amount for our infrastructure. They also provided the expertise to manage the projects in the instances where we didn't have the expertise."

Williamson clarifies that an academic group can only manage so much along the innovation chain. "There comes a point where you need to hand over to someone to run with things that we can't do. We got a lot of training in the process, and we are a lot better than when we started, but it's still a very big problem embarking upon these kinds of projects in South Africa."

"One reason why the HIV vaccines initiative was so successful was not only did we have good international partners but there was initially a lot of funding from government – R10-million a year which enabled us to set up a very sophisticated group with enough depth and flexibility to deliver. Those resources gave us huge capacity and the ability to respond rapidly. Government's cut in funding has, however, had a negative impact on this ability."

"Long-term, secure funding has to be obtained for vaccine research as the time frames needed to test vaccines tends to be longer. This is because in order to test a vaccine in an efficacy trial, there is the need to recruit people at risk of the disease. Enough people have to be recruited to get a statistically valid result to show that the vaccinated arm of the trial differs in protection from disease from the placebo arm of the trial."

Williamson explains that in a drug trial "sick" people are recruited and then treated, so the time to show efficacy is reduced. However, it can take just as long to develop effective drugs compared to effective vaccines depending on the disease targeted. Both vaccine and drugs have to go through stringent phase one and phase two trials – to show safety and determine dosage – before doing efficacy trials.

Williamson is justifiably proud of the progress made thus far. "We have learnt to function within the global HIV milieu and our collaboration with people within South Africa as well as NIH and HVTN has helped us bring two products to clinical trial which is a huge achievement for our research group. Ed and I are inventors on a number of patents and so novel IP has been generated. Lastly, but not least, we have trained many students."

She believes the future of her group lies in continuing with BCG based and poxvirus vaccine vector development. Aside from the continuing exploration of local poxviruses as vaccine vectors, Williamson maintains an abiding interest in veterinary vaccine development using poxviruses as vectors and is determined to continue to work on HPV and the impact of HIV co-infection.

"Vaccine research is appropriate research for Africa and, if successful, could have a massive impact on people's lives. It has been very rewarding to be involved in these projects and to be surrounded by such a dedicated team of people as well as wonderful collaborators. However, the funding environment has been challenging and so at times we have found it extremely stressful!"

On a personal level Williamson notes that she has been fortunate to have worked on these projects with close family, her sister Carolyn and her husband Ed Rybicki. "It has been wonderful to work with them over the years. I work much more closely with Ed and we have shared supervision of a number of students and collaborated on projects since I came to Cape Town in 1987. We both really enjoy our research but try and limit "work" conversation around our children because they feel excluded!"

Inventors and Title	Granted Regions	Pending Regions
Halsey, R.J., Rybicki, E.P., Tanzer, F.L., Williamson, A-L. Chimaeric HIV-1 Subtype C GAG-Virus-Like Particles.	ZA	IN
Heath, L., Rybicki, E.P., Williamson, A-L. Beak and Feather Disease Virus Sequences, Compositions and Vaccines and the Use Thereof in Therapy, Diagnosis and Assays.	ZA, EP	AU
Meyers, A.E, Rybicki, E.P., Williamson, A-L. A Method for the Production of HIV-1 Gag Virus-Like Particles.	ZA, NA	
Rose, R.C., Rybicki, E.P., Williamson, A-L. Oral Immunization with Papillomavirus Virus-Like Particles.	US	JP, EP, CA
Rybicki, E.P., Varsani, A.D., Williamson, A-L. Pharmaceutical Compositions and a Method of Preparing and Isolating Said Pharmaceutical Compositions, and Use of Said Compositions for Prophylactic Treatment of Lesions and Carcinomas.	IN, CN, ZA	_
Rybicki, E.P., Varsani, A.D., Williamson, A-L. Vectors, Constructs, and Transgenic Plants for HPV-11 and HPV-16 L1 Capsid Protein.	ZA, CN	ARIPO
Hitzeroth, I.I., Maclean, J.M., Rybicki, E.P., Williamson, A-L. Expression of Proteins in Plants.	_	CN, ZA, EP, IN, US
Williamson, A-L., Shen, Y-J., Douglas, N. Recombinant Lumpy Skin Disease Virus for Preventing Aids.	_	ZA