COLLABORATION BETWEEN ITALIAN AND SOUTH AFRICAN SCIENTISTS ON A TAT-BASED HIV VACCINE

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The urgent need to find an effective HIV vaccine, and the challenges this presents, have forced scientists to investigate various innovative approaches. Most of the attempts made in the last 15 years have focused on the structural proteins of HIV aiming at inducing immunity by blocking virus entry. However, the failure of this approach so far has led some scientists to investigate strategies aimed at controlling viral replication and blocking disease onset. Recent approaches aimed at eliciting immunity against the HIV regulatory gene products tat, rev and nef have shown good results. Tat vaccination appears capable of controlling primary infection with highly pathogenic SHIV (simian HIV) viruses providing evidence of cross-protection in non-human primates. The tat gene is relatively well conserved in its immunogenic regions among most subtypes of HIV-1 and therefore may lead to the development of a vaccine that could be used globally.

THERAPEUTIC VACCINES

HIV vaccines can be preventive (preventing infection in the first place) or therapeutic (slowing down disease progression in infected individuals by keeping viral load low and CD4 counts high) or both. Most research so far has been aimed at developing a safe, effective, preventive vaccine for use in HIV-negative individuals to prevent infection. However, there is also a focus on developing a safe, cross-subtype reactive, therapeutic HIV vaccine that can be used in people who are already infected.

Therapeutic vaccines are particularly important for South Africa because there are already large numbers of people living with HIV (the latest antenatal survey results estimate that 4.7 million, or one in nine, South Africans are already infected), who are unable to access expensive antiretroviral treatments.

COLLABORATION

Bilateral South African-Italian collaborative projects were established last year to accumulate baseline data on the possible use of a tat-based preventive *and* therapeutic HIV vaccine in South Africa. These projects were funded by the South African AIDS Vaccine Initiative (SAAVI).

Currently in development is a new collaborative application to be submitted to UNAIDS by the Insituto Superiore di Sanita (ISS), the HIV/AIDS Vaccine Division at the Perinatal HIV Research Unit (PHRU) in Soweto and the Medical Research Council in Durban to expand the existing collaboration and begin preparing South African sites for phase II clinical testing of a tat-based vaccine. The overall principal investigator is Dr Barbara Ensoli from the ISS, and the principal investigators from the two South African sites are Dr Eftyhia Vardas, Director of the HIV/AIDS Vaccine Division at the PHRU, and Dr Mark Colvin of the MRC.

'It was decided to have two independent South African sites because of the potential biological diversity of the Soweto and Durban populations and probable virological diversity,' says Dr Vardas.

It is hoped that phase I trials will be done first in Rome at the ISS towards the end of 2001. If the vaccine is found to be safe, phase II trials could begin soon after in South Africa and Italy.

The South African sites will do both preventive and therapeutic phase II trials, while the ISS will probably only do the preventive phase II trial.

'Separate trial enrolment requirements are required to be able to measure the preventative and therapeutic outcomes of the vaccine, i.e. negative and positive

individuals,' says Dr Vardas. 'Each phase I trial will also have various trial arms to assess important safety and immunogenicity aspects of the vaccine (including adjuvants and antigen dosage).'

DEVELOPING RURAL AND URBAN-BASED TRIAL SITES – THE HIV/AIDS VACCINE DIVISION OF THE PERINATAL HEALTH RESEARCH UNIT

The HIV/AIDS Vaccine Division of the Perinatal Health Research Unit (PHRU) is developing both urban and rural South African trial sites for phase I, II and III HIV vaccine trials. The PHRU of the University of the Witwatersrand is a unique research institution within the African region, recognised internationally as a centre of excellence. The unit is headed by Professor James McIntyre and Dr Glenda Gray, while Dr Eftyhia Vardas heads the vaccine division. Funding for the development of vaccine trial sites is from both the South African AIDS Vaccine Initiative and the International AIDS Vaccine Initiative. The unit is in the process of expanding, which involves the recruitment of a laboratory manager, researcher and community workers.

The unit provides access to a number of potential cohorts for expansion of urban-based phase III vaccine trials. Current large-scale projects include four large sexually transmitted disease (STD) projects and a study of contraception and HIV risk in Orange Farm, Soweto. The experience of cohort development and community involvement in these sites makes them possible vaccine trial sites.

Rural phase III site and cohorts are also being developed at the Agincourt Health Centre and demographic site in collaboration with Professor Steve Tollman and Dr Kathy Kahn from the Department of Community Health at the University of the Witwatersrand. This demographic site was established in 1991 by the Health Systems Development Unit (HSDU) of the Department of Community Health, University of the Witwatersrand, and Tintswalo Health Service, and sited in a rural subdistrict of Bushbuckridge in the Northern Province of South Africa. The Bushbuckridge area lies approximately 500 km north-east of Johannesburg in the central lowveld of the Northern Province. The Drakensburg escarpment and commercial forestry plantations bound the area to the west, the Kruger National Park to the east, Hazyview to the south and the Hoedspruit farming area to the north. The Agincourt site is one of a series of international field demographic surveillance system field sites with continuous demographic evaluation of populations and their health in developing countries.

Since 1992, the programme has maintained a demographic and health surveillance site encompassing a subdistrict of approximately 63 000 people living in 20 villages. Research has included projects on the impact of labour migration on men's contraceptive use and sexual risk behaviour; circulatory disease and interpersonal violence among adults; kwashiorkor and respiratory syncytial virus in children under 5; the links between refugee health and legal/employment status; and evaluation of service and social interventions that address mental health, adolescent health, STD/HIV transmission and TB. The subdistrict is also a national pilot site for the strengthening of HIV/TB district services.

The site is ideally situated to be part of a phase II and III HIV vaccine-testing site because of the well-described demographic profile of these communities and the well-mapped geography of the region. Initially studies will be done to determine the incidence and prevalence of HIV infection, the willingness of the community to participate in HIV vaccine trials and the development of community education on vaccines. Systems for HIV rapid testing will be set up at the rural site to strengthen disease surveillance and diagnostic services in the area.

WOULD SOWETO RESIDENTS PARTICIPATE IN AN HIV VACCINE TRIAL?

A preliminary study to assess the attitudes towards HIV vaccine research in Soweto residents has also been done by the PHRU and the University of Chicago. Volunteers from clinic waiting areas and shopping centres in Soweto were recruited.

Of the 57 Soweto residents interviewed, 68% indicated that they would 'definitely consider volunteering' for an HIV vaccine trial, 16% were undecided and 16% said they would not consider ever being in an HIV vaccine trial. Overall, the majority of respondents admitted that they would prefer to participate in a trial that offered them access to free HIV tests (67%), care for STDs (75%), and access to risk-reduction counselling (79%) and condoms (67%).

Seventy per cent of respondents thought that researcher sponsors should be responsible for providing general medical care to vaccine trial participants, 39% thought that research sponsors were responsible for providing antiretroviral therapy, 46% thought this was not an obligation, and 14% answered 'Don't know'.

A new project will expand this pilot study. The aim is to accumulate relevant baseline community demographic data, community attitudes to vaccines and HIV vaccine research, as well as establishing HIV prevalence and incidence figures in both the urban (Soweto) and rural (Agincourt) HIV vaccine test sites. This comprehensive large-scale study will start towards the end of June.