

SPOTLIGHT

AIDS vaccine research gets more challenging

Experts engaged in AIDS vaccine research are determined not to let recent setbacks deter their quest for a preventive AIDS vaccine

Jyoti Bahri

A vaccine is crucial to end the epidemic over the long term, according to civil society, research and policy experts who spoke at a roundtable session - *AIDS Vaccines – 2010 and Beyond, Charting a course for the future of AIDS vaccine research*. The roundtable was sponsored by IAVI and the Global HIV Vaccine Enterprise at the recent XVII International AIDS conference in Mexico City.

The number of new infections in 2007 outpaced the progress made in providing access to treatment pointed out Dr. David Kihumuro Apuuli, Director General, Uganda AIDS Commission. Quoting UNAIDS estimates, he said that to meet the goal of universal access, it would cost approximately US\$54 billion each year to provide ARVs to those in need in low- and middle-income countries by 2015, which was simply not possible.

"Good research drives good policy and programming," said the Executive Director of the International AIDS Society, Craig McClure. He urged the participants to reflect, to go back to the drawing board, to learn what has been achieved so far and to explore new ideas coming from the scientific field.



Dr Margaret Johnston, Dr Seth Berkley and Mauro Schechter discussing the future of AIDS vaccines at the XVII International AIDS conference

He was, he said, issuing a clarion call for strengthening health systems, laboratory facilities and voluntary counselling and testing services.

The world's ability to control AIDS in the future will depend on research and progress in prevention, including vaccines. There will be no greater tool to end this epidemic than a preventive AIDS vaccine. What **STEP** and Merck trials have revealed is that this marathon is a relay and that the baton may need to pass from generation to generation, McClure said.

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Current challenges for research

AIDS vaccine research is at a turning point, the Director of Vaccine Research and AIDS at the US based National Institutes of Health, Margaret Johnston, told the meeting. She said that the NIH had revised its scientific agenda. A critical link would be the follow up studies on the STEP results, by using data obtained from these trials in collaboration with researchers outside the network and also conducting some additional smaller trials.

Exciting news from the science field had spurred the NIH to plan to develop potentially better **assays** that would predict more accurately the outcomes in a clinical trial than those currently in use, Johnston said. The focus on non-human primate research and the application of genomics research to this area was also discussed. Other areas of planned research included the initiative – Highly Innovative Tactics to Interrupt Transmission (HITIT), to look at novel ways of blocking the interaction of HIV with the host.

The President and CEO of the International AIDS Vaccine Initiative, Seth Berkeley, said the focus in IAVI (as indicated in the Scientific Blueprint released during the conference) was on harnessing innovation throughout the HIV field. He predicted that preclinical studies would need to be designed boldly and strategically. This was the time to engage the pharma industry and seek ideas from other fields, such as biotechnology. There was an urgent need to discover what is required for an effective vaccine and to seek answers from neutralising antibodies, mucosal and cellular immunities and T-cell functional assays.

Working with national research institutions and with local communities must be a long term commitment, a leading Brazilian vaccine researcher told the delegates. The Head of the AIDS Research Laboratory, Universidade Federal do Rio de Janeiro, Brazil, Mauro Schechter, warned that the two vital components of any research – trained researchers and informed, enthusiastic communities – take long to build but are lost very quickly if not kept involved. Therefore, it was important to engage them in some kind of bridging activities until the next clinical trial, he advised. Schechter, who has spent 15 years in AIDS vaccine research in Latin America, said there were interim ways of engaging and maintaining these key partners – conducting trials of potentially-useful treatments, **PrEP studies** and participation in early-phase trials. He cited examples from Latin America where there were attempts to obtain small grants that would allow them to continue to run community based programmes with commercial sex workers.

Maintaining the momentum

Establishing networks and linkages between universities and research institutions in developed countries and research centres in developing countries would be critical to maintaining the momentum for research in prevention, said Dr Suniti Solomon, YRG Care, India. Providing research centres and institutions with small grants and funds, facilitating the development of infrastructure and providing world-class laboratories would help to attract and retain young researchers in developing countries. It is critical that the baton of vaccine research is passed to the new cadre of young researchers to move the AIDS vaccine field forward, she said. ■

Simply put...

Assay – A test used to measure the memory of T-cells to antigens such as HIV, specifically their ability to replicate which happens only if they have ‘seen’ the antigen before.

The STEP trial – The STEP study was sponsored by Merck and the HIV Vaccine Trials Network (HVTN) and funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. An early analysis of data on half of the 3,000 trial volunteers, released in September 2008, concluded that the vaccine candidate, manufactured by Merck & Co., neither prevented HIV infection nor lessened the amount of virus in those who became infected. According to the trial co-sponsors, the analysis suggested that those who received the vaccine, which cannot cause HIV infection, might have an increased susceptibility to acquiring HIV. Volunteers who had prior natural exposure to the Ad5 vector that was used in the vaccine might be particularly susceptible, the trial sponsors said.

PrEP studies – Pre-exposure prophylaxis (PrEP) refers to an experimental HIV-prevention strategy that would use anti-retrovirals to protect HIV-negative people from HIV infection. PrEP is not proven to work; in the strategy that is currently being tested, studies involve HIV-negative people taking a single drug, or a combination of drugs, daily in hope that this would protect them against HIV infection. Along with AIDS vaccines and microbicides, PrEP is one of the experimental HIV-prevention strategies being tested in clinical trials today.

IN CONVERSATION

"Research is international and knows no boundaries"



Receiving the Padma Bhusan from the President of India

Prof. N K Ganguly, an infectious diseases and biotechnology specialist, is an Advisor to the Union Minister of Health & Family Welfare, Government of India and also Distinguished Biotechnology Fellow & Advisor to the Translational Health Science and Technology Institute. He has spear-headed wide ranging programmes on medical research as Director General, Indian Council of Medical Research from 1998 to 2007. Prof. Ganguly has authored 725 papers and contributed significantly to research on tropical, cardiovascular and diarrhoeal diseases. While he specialises in research on infection, his areas of interest range from immunology, biotechnology to public health. He has won many national and international awards, the latest being the Padma Bhusan awarded by the President of India for 'Medicine' and the Medal of Merit, 2007 awarded by the International Academy of Cardiovascular Sciences, Canada. He spoke to Sankalp about India's role in the quest for a preventive AIDS vaccine.

Partnership between the North and South is imperative to advance the worldwide search for an AIDS vaccine. Under your leadership at ICMR, such a partnership with IAVI was facilitated in India. What benefits do such collaborations offer to Southern countries?

Many benefits have resulted from this partnership. Two state-of-the-art vaccine trial centers have been set up at the National AIDS Research Institute, Pune and the Tuberculosis Research Centre, Chennai. The two Phase I clinical trials conducted at these facilities were conducted according to international standards. Research staff underwent extensive training programmes and there were collaborations among Indian and global scientists to work on the design of the Modified Vaccinia Ankara (MVA) preventive AIDS vaccine candidate. It is a matter of pride for India that a public-private partnership could result in such capacity building. The conduct of trials in the country helped us research local issues of stability of acceptability and conduct specific behavioural studies. We have prepared documents on informed consent and care and treatment of trial volunteers, keeping in mind local conditions and ethical issues for volunteers of trials.

Such collaborations are of tremendous help in raising awareness among politicians and policy makers about HIV, including the highest offices of the President and Prime Minister. A parliamentary committee and the National Council on AIDS have been set up to address better the challenges of the epidemic.

There has been continual engagement of stakeholders from various sectors of the society such as the Scientific Advisory Committee, medical fraternity, social scientists, activists and journalists. This has led to an openness and transparency about the collaborative programme. Queries on a range of topics such as degree of protection by the prospective vaccine and its utility have been raised by these groups and answered by the programme persons.

Does this have a bearing on vaccine availability in developing countries alongside the West?

Vaccines made in the West are unaffordable in developing nations so it is important that we manufacture them in developing countries. A 'consortium approach' in which a clutch of vaccines are tested and moved together in different locations can expedite the development of an effective vaccine. An agreement among Southern countries under which these vaccines could be made in developing countries such as India under open licensing would ensure access. The vaccine manufacturing scenario in India is improving and some of the vaccine companies are working in a collaboration with multinationals. Ultimately it will be possible to make new vaccines in developing countries in parallel to the developed countries and at a cheaper price.

How do you see research endeavours from across the world working together to develop new AIDS vaccine candidates? What is

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WATCH GLASS

India continues to progress in AIDS vaccine development efforts

Phase I clinical trial of a preventive vaccine shows encouraging outcome

A second Phase I AIDS vaccine clinical trial in India was successfully completed by the Indian Council of Medical Research, the National AIDS Control Organization and the International AIDS Vaccine Initiative. The results of the trial of an MVA-based AIDS vaccine candidate (TBC-M4), which was conducted in Chennai, indicated that the vaccine candidate had acceptable levels of safety and was well tolerated.

The proportion of volunteers whose immune systems responded to the vaccine candidate suggests the candidate holds promise. The trial was done using two doses of the candidate vaccine. After three injections, 82 per cent of the volunteers who received a low dose and 100 per cent of those who received a high dose registered immune responses to the vaccine. The 100 per cent response rate is greater than that seen with the majority of AIDS vaccine candidates tested in humans to date. However the strength and diversity of

these immune responses were modest. It may be possible to boost the immune response, if this vaccine is used in combination with other candidate AIDS vaccines.

"We are pleased to see that the MVA-based candidate tested in Chennai was safe and showed promising initial immune responses. We do not know whether these observed responses will ultimately translate into an effective vaccine that will help protect individuals from HIV infection, but hope to learn more through further testing," said Dr S K Bhattacharya, Additional Director General of the Indian Council of Medical Research. "India is playing a significant role in global AIDS vaccine discovery efforts given our strong medical and scientific capabilities. There is a need for continued efforts for the creation of novel, reliable mechanisms for long-term research on AIDS vaccines and other new prevention technologies," he said.

The Phase I clinical trial was initiated in January 2006 at the Tuberculosis Re-

Fact Sheet
Phase I clinical trial : TBC-M4

- Was initiated in January 2006 and completed in February 2008.
- The vaccine candidate, TBC-M4, is based on a vector built from recombinant Modified Vaccinia Ankara (MVA). It was designed by a biotech firm in the U.S. in collaboration with Dr Sekhar Chakrabarty from the National Institute of Cholera and Enteric Diseases (NICED). It targets HIV-1 subtype C, the most predominant HIV subtype in India.
- A Phase I trial is the first human test of a candidate vaccine for evaluation of safety, and to a lesser extent, analysis of the immune responses evoked by the vaccine, different vaccine doses and immunisation schedules.
- The trial was conducted under the aegis of a MoU between the Government of India-through ICMR, NACO and IAVI.

search Center (TRC), an Indian Council of Medical Research (ICMR) institute in Chennai, and was completed in February 2008. This trial was conducted under the aegis of a Memorandum of Understanding between the Government of India-through the Indian Council of Medical Research (ICMR) and the National AIDS Control Organization (NACO)-and the not-for-profit International AIDS Vaccine Initiative (IAVI). YRG CARE, based in Chennai, collaborated with TRC to mobilise the community around the Phase I trial.

Dr. Narayanan, former-Director of the Tuberculosis Research Centre added, "Consistent innovation in science despite setbacks has ensured development



Standing side row from left to right: Dr M Jayashri, Mrs K Subapriya, Mr S Manohar Nesa Kumar, Mrs C A Lekshmi **Standing back row from left to right:** Mrs P V Lakshmi, Mr T Sekar, Mr C Manogaran, Mr D Rajasekaran **Standing front row from left to right:** Mrs M Revathy, Ms B Anandhi, Dr P R Narayanan, Mr S K Noorllah, Mr P Sathyamurthi, Mr N Baskaran, **Sitting from left to right:** Ms S Angelene Nelcy Hannah, Mrs P Devi Bagavathy, Dr V D Ramanathan, Dr M Makeesh Kumar and Mr G Charles

of many effective prevention technologies. The successful conduct of the trial in Chennai reaffirms the need for continued vaccine development initiatives, where learnings from every effort will contribute to global advancement of the AIDS vaccine field."

Phase I MVA-based (TBC-M4) AIDS vaccine trial

The trial was a double blind, dose-escalation, randomised, placebo-controlled trial, which was initiated after receiving all necessary regulatory and ethical clearances. The objectives of such a Phase I trial are to evaluate the safety of the vaccine candidate and to gather preliminary results of immune responses induced by the candidate. The total duration of the trial was approximately 24 months. The volunteers recruited for this trial were 32 healthy, HIV-uninfected men and women be-

tween 18 and 50 years of age, from all socio-economic strata. Three intra-muscular injections of TBC-M4 or placebo were administered to the volunteers.

Moving forward

The results of the Phase I vaccine trial of TBC-M4 suggest that further research is warranted. Currently two additional Phase I trials testing the MVA-based candidate in a prime-boost regime are planned and under review by the relevant authorities in India and approved in the UK. The trials are designed to use different modes of administration of the priming vaccine, different dosages and different vaccine regimens. It is hoped that the prime-boost regimen will help to strengthen the modest immune responses observed in the Phase I trial of the MVA-based candidate alone. Collectively the results will help

determine whether and how to move forward with additional testing of this MVA-based AIDS vaccine candidate.

Simultaneously, IAVI has undertaken work to modify the MVA-based vaccine candidate so that it is ready for large-scale manufacturing should the trial results suggest further testing is warranted.

AIDS Vaccine Blueprint launched at AIDS Conference 2008

The *AIDS Vaccine Blueprint 2008*, IAVI's biennial report on the state of AIDS vaccine research and development and a roadmap for the field, was released at the XVII International AIDS Conference in Mexico City in August. It issues several challenges to AIDS vaccine researchers and outlines interim goals toward overcoming many of the obstacles impeding vaccine development, and list the milestones by which the field can measure its progress. To view the *Blueprint*, visit www.iavi.org

In Conversation

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the contribution of the Indian Medicinal Chemistry programme being carried out in collaboration by the Department of Biotechnology and IAVI?

Research is international and knows no boundaries. Collaborations can lead to a large pool of knowledge and information on multiple subtypes of HIV found in different countries. Globally many projects are on to develop strategies for broadly reacting neutralising antibodies. Some of these have been funded by IAVI.

The Indian Medicinal Chemistry programme is a collaborative effort by scientists from India and the US. The principal investigators of the IMC programme are a part of the global Neutralising Antibody Consortium.

At the moment, the research is in a preliminary stage. There are many immunogens that could potentially elicit broadly neutralising antibodies and lead to the development of AIDS vaccines candidates that elicit neutralising antibodies. Continuous funding and multi-disciplinary participation are key to the success of such collaborations. This will make it possible for India to contribute to the AIDS vaccine discovery and keep pace with developments around the world.

The scientific community worldwide has been advocating prime boost trials where two vaccines are administered - one to prime the immune system and the second to boost the immune response to determine whether the breadth, magnitude and duration of the immune

response could be improved, compared to giving one vaccine alone. What are your views on this approach?

This is one strategy which the world is taking and if the science behind the combinations is good, it will lead to something better. In the initial stages the DNA vaccines did not work very well when used alone, hence some antigens were added or these vaccines were used in conjunction with other vaccines. It soon became evident that different vaccines used in combination may induce different types of immune responses and/or enhance overall responses induced by either type of vaccine alone. So it all depends on what kind of combination one chooses. There is a lot of science behind it. ■

IN FOCUS

A bigger role for NGOs

The AIDS epidemic in India is changing. How are NGOs planning to change with it? As new research and lessons from the field come in, it is time to reassess strategies. Sankalp spoke to representatives of three prominent NGOs from different parts of the country on what they see as their role in the coming years.

Shree Venkatram

For over two decades, Indian NGOs have been playing a key role in battling HIV. They have risen to various challenges, doing commendable work – be it spreading awareness, launching prevention initiatives and making treatment and care more accessible. When IAVI came to India, they helped in taking the vaccine research programme to the people.

"India has had a very strong civil society response to most issues. But the way civil society organisations have worked for HIV prevention and care is unparalleled. There is a lesson to be learnt the way



Anjali Gopalan

HIV was tackled," says Anjali Gopalan of the Delhi-based Naz India Foundation, which works with men who have sex with men (MSM) and children affected by AIDS. "Positive people are being made part of the discourse. We have worked with MSM and sex workers, for example. But a lot more needs to be done for the problem is large," she adds.

She advocates a better understanding and a working relationship between the government and the NGOs. "We need to build trust and work together. Along

with the trust, there has to be transparency and accountability on both sides. For example, when funds are not released on time, NGOs' work is greatly hampered. She recommends that there should be some flexibility in programme implementation to keep with the changing needs of the community. Giving an example she says, "We may be working on HIV prevention, but find that we need to provide for those already affected."

Anjali advocates that 'care' be looked at holistically. "It must be seen in the context of poverty with the individual at the centre. The individual needs nutrition, drugs, resources to come to a centre to avail of treatment, and support in finding and retaining a job. The government cannot get into all these areas. It needs to work with NGOs," she says.

Addressing stigma a priority

Sri Krishnan, research manager of YRG Care, an organisation actively engaged in HIV research in Tamil Nadu, lists addressing stigma and discrimination as a priority area for work.

"There is need for an HIV workplace policy to be put in place. NGOs can provide support by ensuring that the policy is implemented. In Tamil Nadu, YRG is collaborating with over 30 NGOs and PLWA networks to provide various facilities. For example, CD4 testing has been made available at more than 20 centres. We counsel the persons and with their informed consent conduct the

testing. We also tell them on the need for regular CD4 testing," he says.



Sri Krishnan

He points out that in many districts, NGOs are helping people access ART. They provide the linkages, put them in touch with CBOs, who in turn, do outstanding work in providing support for orphans and women with HIV. Tackling stigma and discrimination has become very important for we are moving away from HIV being a pandemic to a lifetime disorder, he states.

Promoting ART adherence

Dr S I Ahmed's AIDS Prevention Society has been working in Assam among injecting drug users, truckers, sex workers and migrant populations. "NGOs have access to the community, especially marginalised populations who

“Tackling stigma and discrimination has become very important for we are moving away from HIV being a pandemic to a lifetime disorder”

need to be informed about the risks of HIV because of their lifestyle," he says. It is only when they are informed that they can safeguard themselves. NGOs



Dr S I Ahmed

can promote health-seeking behaviour among those who need HIV treatment and promote its adherence.

He sees NGOs playing an equally important role in nutrition education, monitoring access to treatment and delivery of services – checking for viral loads, Hepatitis, kidney profile and CD counts. It is well known that ART reduces infectiousness of HIV positive individuals. Therefore the role of NGOs is even more critical in ensuring proper adherence to ART, consequently reducing transmission of the virus. In this context, NGOs have a challenge ahead of them to operationalise this strategy into effective programmes at the community level.

NGOs can also fight stigma and ensure that the rights of HIV positive persons are not violated, Dr Ahmed says. For example, many of them are thrown out of jobs and have great difficulty in finding accommodation. NGOs could help with advocacy at the workplace and the neighbourhood. Illustrating the powerful role they can play, he recounts the case of a leading

AIDS activist from his state who was unable to get accommodation as she was HIV positive. Finally, the government had to accommodate her in a flat that it owned. An NGO decided to educate the community and began its campaign by addressing students in the city. At one educational institute, soon after the activist's address, a young girl approached her crying. She informed her that she and her family were among those who had been instrumental in her ouster at an earlier place she occupied. But she was very repentant about her behaviour now.

“The extended search for an AIDS vaccine means that NGOs may need to play an even bigger role in that effort”

The extended search for an AIDS vaccine means that NGOs may need to play an even bigger role in that effort, according to Anjali Gopalan. "We agree we need a vaccine and must continue to work on it. But as it is a long drawn out process, NGOs

would have to deal with many issues like controlling the expectations of the people, while at the same time keeping their interest alive and sustained by giving regular updates," she says.

IAVI had brought together NGOs from different parts of the country in an effort to reach out to the community with knowledge about the development of an AIDS vaccine. As they met for discussions, they felt the need to debate on a variety of issues pertaining to the health needs in the country. Some key NGOs formed a group called the National Coalition on Health Initiatives (NCHI), which is especially concerned that the marginalised communities and the disadvantaged get a fair deal.

NGOs know the epidemic will never be defeated without effective prevention. And as experts point out, no single prevention strategy will suffice. A portfolio of biomedical, behavioural and structural interventions is needed. More importantly, NGOs need to play a bigger role in overcoming the socio-cultural and logistic barriers to reach out to populations most in need. ■

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IAVI is a scientific organisation founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive AIDS vaccines for use throughout the world. IAVI focuses on four key areas: accelerating scientific progress; education and advocacy; ensuring vaccine access and creating a more supportive environment for industrial involvement in AIDS vaccine development.

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