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Fresh hopes emerge in AIDS vaccine research

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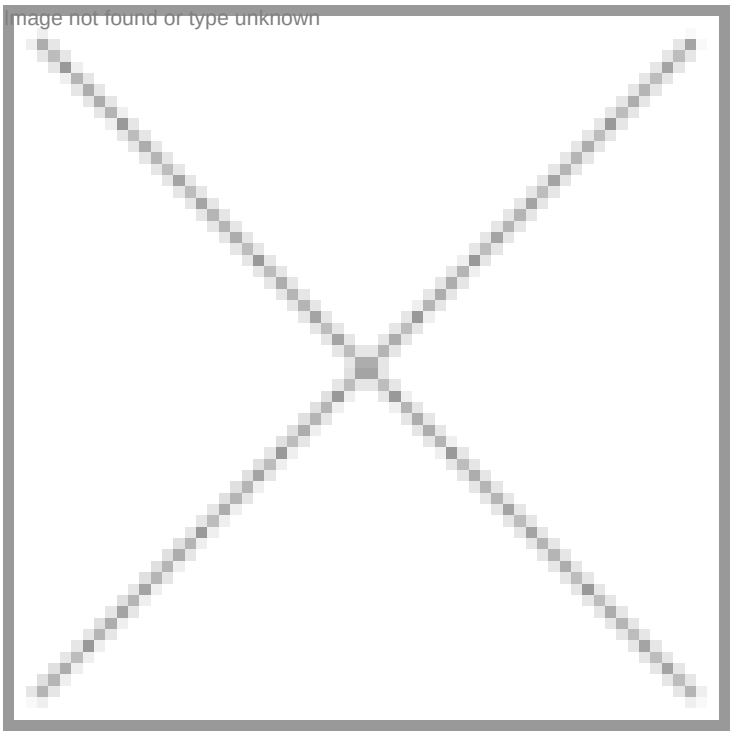

The structural characterization of a number of broadly neutralizing antibodies has boosted the efforts to tame the highly mutable HIV virus, thus raising hopes for an AIDS vaccine after years of trial and error in the field

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Hivpic Is there a magic protein out there that will neutralize the HIV virus? That is the question plaguing scientists like Dr Wayne Koff. He is the chief scientific officer at the International AIDS Vaccine Initiative (IAVI) and has worked on the HIV virus since the time be began his career, almost 25 years ago.

Recently, in India, at the invitation of the Department of Biotechnology to participate in the symposium titled â€œvaccines-from discovery to translationâ€? Dr Koff was involved in deliberations with 100 other experts from the field of vaccinology.

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Broadly neutralizing antibodies have the ability to neutralize varied forms of the HIV virus and thus exhibit cross reactivity between diverse genetic subtypes."

Dr Wayne C Koff
CSO and senior vice president, IAVI

Given the variability of the HIV virus, developing a vaccine for HIV is a tough challenge. The virus integrates and hijacks the host genome and induces latency. Also, immune responses in case of HIV infection are inadequate and ineffective and are not fully known. The development is based on the HIV envelope proteins, which are exposed to the immune system, that mainly comprise one large protein called gp120. Initially, vaccines were targeted against gp120 and intended to generate antibodies against HIV-1 envelope to neutralize the virus.

According to experts, till October 2011, 168 clinical trials have been completed using about 42 vaccine candidates. These include peptide immunogens, VLPs, purified HIV-1 envelope proteins (gp120), HIV-1 plasmid DNA encoding viral proteins, HIV-1 proteins (gag/pol/env) and viral vectors. The highly mutable virus has so far eluded all efforts to tame it. The big question is on the mutability part of HIV and the length of dendrograms also adds to the variability factor. The HIV virus,

through a number of conformational changes, denies a neutralizing antibody response.

RV 144 boosts hope

Hope came in the form of RV 144 vaccine trial that involved 16,000 volunteers in Thailand. The RV144 vaccine is also a viral vector prime and recombinant gp120 protein boost that has shown an efficacy of 31 percent. Result of the immune correlate study, recently declared at the AIDS 2011 conference, indicate a possible protective role of antibodies against the V1/V2 loop of gp120 in uninfected participants. While the results generated only 30 percent protection and is considered not satisfactory, it has demonstrated for the first time that a vaccine can indeed protect humans from HIV infection.

"I think a first generation vaccine would be available by 2020, and the second-generation vaccine by 2025."

Dr David N Cook
executive vice president & COO, IAVI

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Besides, the structural characterization of a number of broadly neutralizing antibodies has boosted the vaccine development efforts. â€œIt was reported that certain individuals infected with HIV did not show any symptoms of AIDS. These elite protectors who had been living with the virus for almost 20 years without the disease were found to contain broadly neutralizing antibodies (bNAbs) that were isolated and their structures were determined by X-ray crystallography,â€? informs Dr Koff of IAVI. â€œbNAbs have the ability to neutralize varied forms of the HIV virus and thus exhibit cross reactivity between diverse genetic subtypes.â€?

Dr Koff elaborates, â€œThe antigen bound structures of the bNAbs provided precise information as to how the bNAbs recognized and interacted with their antigens. Based on this structure information, scientists across the world, including India, are attempting to design immunogens that can elicit bNAbs.â€?

The antibody neutralizing trials project involves Africa, India and Australia in a major way. Currently, there are 10,031 GCP trained employees, 350 sites and 18 clinical accredited labs working under the IAVI consortium. Also, around 200,000 people have received training and consultation in HIV/AIDS by the organization.

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Drrajatgoyal

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***Dr Rajat Goyal**, country director India, IAVI*

The International AIDS Vaccine Initiative (IAVI) is playing an important role globally to bring together various organizations to partner on vaccine research. The organization has major presence in countries like the US, Africa, India and Australia. At the IAVI India, Dr Rajat Goyal provides strategic direction to the country program. The India program has garnered strong national and state support and has an extensive program of information dissemination, community involvement and AIDS vaccine trial site preparedness activities. In an informal chat with BioSpectrum, Dr Goyal elaborates on the Translational Health Science & (THSTI) project.

Can you elaborate on the THSTI project?

Launched in early 2011, the HIV Vaccine Design Program in India, is jointly established, operated and funded by the Gurgaon-based Translational Health Sciences and Technology Institute (THSTI) and the International AIDS Vaccine Initiative (IAVI). The program will capitalize on recent research advances that have sparked a renaissance in AIDS vaccine R&D. The focus of the program will be on one of the greatest scientific challenges of AIDS vaccine design and development: the elicitation of antibodies capable of neutralizing a broad spectrum of circulating HIV variants, a problem that stems in large part from the almost unparalleled mutability of HIV.

The IAVI-THSTI collaborative program will participate in a coordinated, global effort to create replicas of bNAb targets in the laboratory for use as immunogens, which are the active ingredients of vaccines. This program will be charged with the complex task of developing, testing and then implementing strategies to rapidly screen large numbers of bNAb-based immunogens against HIV-1 and to prioritize them for further evaluation in preclinical studies. It is expected that the program using high throughput (HT) screening will ultimately lead to strategies for next generation immunogen design and expand the number of AIDS vaccine candidates available for assessment in human trial.

At what stage is this project currently?

The Translational Health Science & Technology Institute (THSTI) project has already started and we are in the process of hiring. It has 43 manpower positions, including administration staff. The appointments will be of a lab director, three principal investigator and 35 scientists.

There is a lot on agenda. We will roll out the scientific plans in 2012. There has been a significant amount of funding from the government. Initially, the project is operating out of interim labs in Gurgaon, and will move to the Faridabad

biocluster, once that is ready in 2015. The current focus is on creating infrastructure, lab and hiring.

â€œCurrently, the screening under Protocol G, which is a large, multicenter effort to find new, naturally occurring antibodies capable of neutralizing a wide variety of HIV strains, is underway in African countries, US and Australia. The criteria for choosing individuals for trials include the condition that the persons must have remained healthy for at least three years after becoming infected and they should not be on anti-retroviral drugs,â€? says Dr Koff. â€œThe important finding is that the exact shape of the four binding sites is now known. The researchers are also exploring the possibilities of having more sites.â€?

Dr David N Cook, executive vice president & chief operating officer, IAVI, says, â€œWith this development we have moved closer to the vaccine. I think first generation vaccine would be available by 2020, and the second-generation vaccine by 2025. The next milestone would be to test the vaccine candidate neutralizing antibodies in the animal model and the target for that is end of 2013 or early 2014. To get there, we need to screen hundreds of candidates each year. The problem is that in science the results cannot be predicted.â€?

Talking about the efficacy of the vaccine, Dr Cook says, â€œThe 20-to-40 percent efficacy against the viruses is considered to be weak and between 60 and 80 percent can be considered to be effective. But in this case if efficacy is at 50 percent, then it may later rise to even 80 percent and then 90 percent with time. However, the vaccine having 50 percent efficacy will only work in some specific populations. The targeting of specific populations helps in terms of risk group identification and, therefore, is cost effective.â€?

India rises to the challenge In India, efforts are on to bring industry and academia together in the field of vaccine R&D, and provide a scientific basis for vaccine design and development. The IAVI and the Department of Biotechnology (DBT), Ministry of Science & Technology, Government of India, have joined hands with the Vaccine Grand Challenge Program, Vaccine and Infectious Diseases Research Centre, Translational Health and Technology Institute and Clinical Development Services. This symposium was a part of that effort.

The initiatives for structure-based immunogen design of HIV vaccine is globally supported by a neutralizing antibody consortium of the IAVI. Two Indian institutions, International Center for Genetic Engineering and Biotechnology (ICGEB), New Delhi, and the Indian Institute of Science (IISc), Bangalore, are active members of this consortium.

The isolation of a large number of nABs from different HIV-infected donors provides proof-of-concept that such antibodies could be elicited in humans. Since classical approaches to produce protective antibodies have not been successful, the rational structure-based immunogen design seems to hold the key. The affected people have lesser copies of T cells. Lead Control is less than three percent of the affected population.

Talking about the steps used to put all the discoveries together, Dr Cook says, â€œThe first is identification of antibody, the second one is elucidation of structure that it binds to and finally, the idea about how the immune response develops.â€?

â€œThe deep sequencing technique has helped in finding how T cells and immune responses develop with time. It put us on the edge of developing the new vaccine,â€?

Dr Cook adds, while appreciating the role played by technology. Due to the unavailability of a proper drug to treat AIDS, an HIV vaccine that can elicit enough immune responses to protect the host against the disease will certainly be of great benefit to mankind, as Antiretroviral Therapy (ART) can take us only so far.

Rahul Koul & Nandita Singh in New Delhi