

**IN FOCUS****ICMR to test a combination of two AIDS vaccine candidates**

The Tuberculosis Research Centre in Chennai. Inset: Dr. V.D. Ramanathan, Lead Investigator



The National AIDS Research Institute in Pune. Inset: Dr. Sanjay Mehendale, Lead Investigator

The Indian Council of Medical Research (ICMR) has announced plans to initiate a Phase I clinical trial to test a combination of two AIDS vaccine candidates, ADVAX and TBC-M4, in a prime-boost regimen (See Box on Page 2: *The Vaccine Candidates*). The trial will be conducted at two ICMR institutions, the National AIDS Research Institute (NARI) in Pune, Maharashtra, and the Tuberculosis Research Centre (TRC) in Chennai, Tamil Nadu. YRG CARE, Chennai, will collaborate with TRC for advocacy and community mobilisation for the trial. The trial will be conducted under the aegis of a Memorandum of Understanding between the Government of India – through the ICMR and the National AIDS Control Organisation – and IAVI.

'Prime-boost' is a way of combining two different vaccine candidates with the hope of getting a better response from the body's immune system than giving either vaccine candidate alone. ADVAX, a plasmid DNA AIDS vaccine candidate, will be used for priming the immune response. TBC-M4, an AIDS vaccine candidate based on a vector built from recombinant Modified Vaccinia Ankara (MVA), will be used to boost the initial immune response generated by ADVAX.

The decision to conduct the prime boost trial follows promising results of a Phase I trial of TBC-M4 conducted at TRC in collaboration with YRG Care. In that study, the vaccine candidate was found to be safe and well tolerated. It

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generated immune responses – albeit modest – in 100 per cent of volunteers who received the high dose. These results suggested that the candidate merits further evaluation in a regimen designed to enhance the magnitude and breadth of the response it generates.

Dr. V.M. Katoch, Secretary of the Department of Health Research and the Director-General of ICMR, said, "The ICMR is committed to give to the country the best available tools to control HIV/AIDS. This involves their evaluation conforming to the international standard, and adopting the best practices. Our partnership with IAVI is helping us achieve this aim

### **The vaccine candidates**

**TBC-M4** is based on a vector built from recombinant Modified Vaccinia Ankara (MVA). MVA is a weakened form of the vaccine that was used to conquer smallpox. TBC-M4 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 in Kolkata, India. TBC-M4 targets HIV-1 subtype C, the most predominant HIV subtype in India, and contains synthetic copies of 6 HIV genes: env, gag, reverse transcriptase, rev, tat and nef.

**ADVAX** is a DNA vaccine candidate containing synthetic copies of HIV-1 subtype C genes env, gag, pol, nef and tat. The vaccine candidate was designed by the Aaron Diamond Research Centre in New York through a collaboration with Rockefeller University in New York and the International AIDS Vaccine Initiative.

Both vaccine candidates contain only synthetic copies of a part of HIV's genetic material; therefore, they cannot cause HIV infection.

### **The trial**

#### **The Phase I Trial will evaluate the safety and immunogenicity of TBC-M4 and ADVAX**

The trial is a Phase I randomised, double-blind, placebo-controlled trial with 32 volunteers, with approximately 16 at each clinical trial centre at NARI and TRC. The volunteers will be assigned to one of two groups. Group A will receive two doses of ADVAX (or placebo) followed by two doses of TBC-M4 (or placebo) at months 0, 1, 3 and 6, respectively. Volunteers in Group B will receive three doses of TBC-M4 (or placebo) at months 0, 1, and 6, respectively. Neither the study staff nor the volunteer will know who receives the vaccine or placebo. The anticipated total study duration for each volunteer is approximately 18 months.

through not only bringing new vaccines but also in capacity development and infrastructure strengthening. We are delighted to collaborate with the International AIDS Vaccine Initiative in the search for a safe and effective preventive vaccine. We have successfully worked together in the past and, going forward, hope to achieve even greater success through this initiative."

#### **Safe combination**

In previous Phase I studies of different DNA and MVA-based AIDS vaccine candidates in a prime-boost regimen, the combination proved safe and well-tolerated and generated enhanced immune responses when compared with the responses generated by either vaccine candidate alone. In studies of DNA + MVA vaccines in non-human primates using the simian immunodeficiency virus (SIV) model, immunised non-human primates controlled SIV replication, providing an important preclinical test of concept for this vaccine strategy.

IAVI, in collaboration with London's Imperial College, has also recently initiated

a Phase I clinical trial in London, UK to test a prime-boost combination of ADVAX and TBC-M4. The UK and India trials are two separate trials and will use different modes of administration of the ADVAX candidate, different dosages, and different vaccination regimens. Collectively, the results of the trials from both countries will help determine whether further development of these AIDS vaccine candidates in a prime-boost combination is warranted.

"AIDS is a global calamity that is not going away," said Dr. Seth Berkley, IAVI President and CEO. "Today, 33 million people worldwide are living with HIV and



*TRC and NARI have world-class lab facilities for the conduct of the trial*

7,500 are newly infected every day. A vaccine offers the best hope of not just reducing the AIDS problem but actually bringing it to an end." ■

**SPOTLIGHT****IAVI on the First AIDS Vaccine Trial in India**

Some articles appearing in the Indian media have raised questions about the country's first AIDS vaccine trial, conducted at the National AIDS Research Institute (NARI) in Pune and supported jointly by the International AIDS Vaccine Initiative (IAVI) and the Government of India through the Indian Council of Medical Research and the National AIDS Control Organisation. IAVI would like to clear up any misperceptions and misunderstandings that may have occurred about the process by which experimental vaccines are tested and the role India plays in the global efforts to develop an AIDS vaccine.

In February 2005, investigators at NARI, Pune began the Indian portion of a trial of an AIDS vaccine candidate called tgAAC09. These tests were part of a Phase I trial of tgAAC09 that was also being conducted in Belgium and Germany.

Like all Phase I trials, this one was designed to test primarily whether the vaccine candidate was safe and well-tolerated in humans. The vaccine candidate did indeed prove to be safe and well-tolerated.

**“The purpose of collecting immunogenicity data in a Phase I trial is to help determine what the proper dose and schedule might be for further testing of the vaccine candidate.”**

Investigators in the Phase I trial of tgAAC09 also collected preliminary immunogenicity data, information about

whether the immune systems of the trial volunteers responded to the vaccine, as indicated by certain markers in their blood. Immunogenicity (inducing an immune response) is an indication that the vaccine candidate might warrant eventual testing to see if it can protect against HIV infection or development of AIDS. The primary purpose of collecting immunogenicity data in a Phase I trial is not to determine whether the immune responses are strong enough; that is tested in a Phase II trial or trials by trying several doses or schedules for immu-

**“When data from all arms of the trial were collected and analysed, researchers were able to confirm that the vaccine candidate was safe and well-tolerated in all populations tested.”**

nisation. Rather, the purpose of collecting immunogenicity data in a Phase I trial is to help determine what the proper dose and schedule might be for further testing of the vaccine candidate.

Because the Belgian and German portions of the Phase I trial of tgAAC09 began first, preliminary immunogenicity data from those arms of the trial became available soon after the start of the Indian portion of the trial. The preliminary data from the subset of volunteers in Europe who received just one dose of the vaccine suggested that the candidate was only modestly immunogenic; three different dosage levels had been administered and even at the highest doses, few of

the volunteers in Europe registered an immune response. After the European data became known, to ensure transparency, all prospective trial volunteers in India were fully informed about the European data as part of the informed consent process. Volunteers who were already enrolled in the trial in India were given the new information and reminded of their option to withdraw from the trial at any time.

***The candidate did not 'fail'***

Some commentators have suggested that the modest size of the immune responses in the preliminary results from Europe was reason to discontinue the Indian arm of the trial. It has even been written that the Indian portion of the trial continued though it was known within weeks of its start that the vaccine candidate had "failed" in tests in Europe.

In fact, the candidate did not fail in tests in Europe. At that time, the candidate was in Phase I testing, for safety and tolerability, and the preliminary data from Europe showed it was performing well on those measures. It's true the preliminary data collected in Europe indicated the candidate was modestly immunogenic, but that information was collected not to determine whether tgAAC09 had 'passed' or 'failed' an immunogenicity test – that's for Phase II – but rather to help investigators determine how much of the candidate to administer in the next phase of testing.

The data gathered in the three-country Phase I trial of tgAAC09 did just that. When data from all arms of the trial were collected and analysed, researchers were

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able to confirm that the vaccine candidate was safe and well-tolerated in all populations tested in the trial. Overall, the vaccine candidate produced an immune response in 16 per cent of trial volunteers. This information served precisely the purpose that immunogenicity data in a Phase I trial is meant to serve: it gave researchers clues about what might be the appropriate dose of the candidate, in this case informing them that they needed to try a higher dose of vaccine in the next round of testing. Researchers had good reason to believe a higher dose would improve immune responses, since they had seen such a result in animal experiments with tgAAC09.

#### **Data suggested a higher dose**

Thus, in the next trial of tgAAC09, conducted in three countries in Africa, a higher dose of the vaccine candidate was tested in some volunteers. The clinical development strategy for tgAAC09 had always been to test the vaccine in Europe, India and Africa, but the preliminary results from the trial in Europe and India, which suggested a higher dose was needed, influenced the design of the Africa trial.

The trial in Africa was called a Phase II trial because of a local practice of using Phase I to refer to the first test of a candidate in humans; because of its small size (91 volunteers), it could otherwise have been called a Phase I trial. One media account questioned why the higher dose of tgAAC09 was tested in a Phase II trial before it was tested in a Phase I trial in the same population. A given dose of a vaccine candidate is always first tested in a small group of volunteers to ensure the safety and tolerability of the dose before it is considered for testing in a

larger group of volunteers. This safety precaution can be achieved in a number of ways. In the trial of tgAAC09 in Africa, it was achieved in this way: the trial involved only 91 volunteers, compared to the 80 volunteers in the Phase I trial in Europe and India, and the observations and laboratory tests to assess safety were equally thorough. Those volunteers were divided into four groups: one received placebo, two received the medium and high doses of the vaccine candidate previously tested in the Phase I trial, and the fourth received a new, higher dose. Thus, only a small group of volunteers received

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the previously untested highest dose, in keeping with the precaution against testing doses for the first time on large groups. This is a common clinical development strategy.

The increased dose of tgAAC09 used in the trial proved safe and well-tolerated. Unfortunately, even at the highest practical dose, the vaccine candidate, in IAVI's view, did not produce sufficiently robust immune responses to justify taking it forward in testing any further as a single agent.

This result was disappointing but not surprising, given the nature of pharmaceutical product development, in which the vast majority of candidates never advance past Phase I and Phase II trials to efficacy testing. Of all the AIDS vaccine candidates that have been developed, only three have advanced to efficacy testing.

It is a disappointment when a candidate does not perform well – to the volunteers who selflessly committed themselves to the trial, to the communities that have supported it, to the researchers and trial sponsors. But such an outcome cannot be known in advance. If it could be, there would be no need for human trials of experimental vaccines and drugs. The only way to develop new vaccines and drugs is by testing in human trials the candidates that appear, from laboratory and animal data, to be the most promising. tgAAC09 was just such a candidate. What's more, from every properly conducted trial, whatever its result, comes new knowledge that helps to illuminate the search for more effective candidates.

#### **The best hope**

IAVI is committed to that search, believing that the best hope for ending the AIDS pandemic resides in a preventive vaccine. We at IAVI believe the effort to develop an AIDS vaccine should be commensurate with the scope of the AIDS pandemic, that the world's best scientists must be engaged in the search, that researchers in the field must move speedily to identify and pursue the most promising approaches, and that they must work flexibly, moving on to different approaches when faced with those that do not merit further advancement. In science, failure is a teacher. It is not a cause for discouragement or disparagement, certainly not when the stakes are as high as they are in the effort to combat the scourge of AIDS. ■

**WATCH GLASS****Indian AIDS vaccine researcher receives G.D. Birla award**

Professor Raghavan Varadraján of the Indian Institute of Science in Bangalore, whose lab is part of IAVI's Neutralising Antibody Consortium (NAC), has been selected for the G.D. Birla Award for Scientific Research for 2008 for his significant contributions in the area of molecular biophysics.

Varadraján's research includes the design of proteins intended for use as compo-

nents of an AIDS vaccine. His lab is among the 20 labs across the world in the NAC that work to create immunogens to provoke the body to produce broadly neutralizing antibodies to HIV so as to prevent infection with the virus.

Varadraján's major work is on understanding the relationship between protein sequence, shape and stability. He has developed diverse experimental

and computational tools to probe these shapes and measure the strengths of various molecular interactions that help maintain the shape.

The award, instituted by the K.K. Birla Foundation in 1991, carries a cash prize of Rs 1.5 lakh. It is given to Indian scientists who live and work in India. A board, headed by the president of the Indian National Science Academy, selects the awardees. (*Hindustan Times and IAVI*)

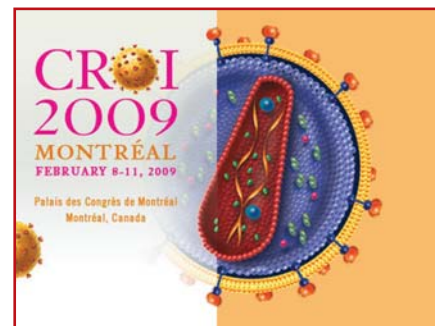
**Encouraging results from a microbicide candidate**

A new study released at the 16<sup>th</sup> Conference on Retroviruses and Opportunistic Infections in Montreal, Canada, in February shows that a microbicide candidate or vaginal gel known as PRO2000, designed to lower the risk of HIV infection when applied before intercourse, appears to have a 30 per cent level of effectiveness in preventing HIV infection. The finding is promising, although not statistically significant, and additional evidence is needed to conclusively determine whether PRO2000 is an effective microbicide.

Data from the multi-site clinical trial, known as HPTN 035 and conducted by the Micro-

bicide Trials Network, showed that women who received the PRO2000 candidate plus condoms had 30 percent fewer HIV infections than those who received condoms or condoms plus a placebo gel.

According to Dr. Salim Abdool Karim of the Centre for the AIDS Programme of Research in South Africa, "It's very exciting that PRO 2000 might have a positive effect. Now we need a trial that's big enough to show whether this is a statistically significant effect." Researchers conducting a separate efficacy trial of PRO2000 in South Africa, Tanzania,



Uganda and Zambia, which is in its final stages, will soon obtain more definitive data regarding the candidate's effectiveness.

IAVI strongly supports the continued research and development of microbicides.

**In search of success stories in global health**

Millions of lives can be improved – or saved – by sharing the knowledge, resources and technology of the developed world with those who need it most. For myriad reasons, advances in health care and prevention often fail to find their way to the developing world.

The Bill & Melinda Gates Foundation, the World Health Organisation's Special Programme for Research and Training in

Tropical Diseases, Global Health Progress, the International AIDS Vaccine Initiative (IAVI) and the Association of University Technology Managers have joined together to form the Global Health Case Study Initiative. This groundbreaking project seeks to create efficiencies by collecting case studies that would provide others with information on current practices and insight on 'lessons learned' (both positive and negative) in the course

of conducting activities relating to global health matters.

The case studies will highlight collaborations that are built and/or transactions that are entered into that address a global health concern. "Global health concern" refers to those diseases that have a disproportionate impact on developing countries but need not be the sole focus of the collaboration or transaction.

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**UPDATE****More on the upcoming prime-boost trial in India*****Why are NACO, ICMR and IAVI doing this trial in India?***

Both the National AIDS Research Institute (NARI) in Pune and the Tuberculosis Research Centre (TRC) in Chennai have a wealth of experience in conducting clinical trials. Both have previously conducted Phase I AIDS vaccine clinical trials. Both clinical trial centres house state-of-the-art laboratory facilities. AIDS vaccine candidates in development need to be tested in a variety of settings, which is why IAVI and others test vaccine candidates in multiple regions across the world, including those regions where an AIDS vaccine is most needed. TBC-M4 and ADVAX are also being tested in a prime-boost regimen in a separate Phase I trial in the UK.

***Could this vaccine eventually be used in India?***

It is not yet known if the ADVAX plus TBC-M4 combination will protect against HIV infection or slow progression of dis-



*An Immunogenicity Laboratory*

ease, and this trial is not designed to test efficacy. This is a Phase I trial designed to test the safety and preliminary immune responses of the prime-boost vaccine regimen. The results will be evaluated at the conclusion of the trials to determine whether the candidate merits further testing. Ultimately, the

goal is to find a vaccine that would work anywhere in the world.

***Are the vaccine candidates safe?***

For both vaccine candidates, extensive safety data has been collected in animal studies. The vaccine candidates have also been tested individually in Phase I

human studies and were found to be safe and well tolerated. Previous Phase I studies with different DNA-MVA AIDS vaccine combinations demonstrated that these prime-boost regimens were safe and well tolerated.

***Can the vaccine candidates protect against HIV infection?***

It is not known if this prime-boost combination can protect against HIV infection. The purpose of this Phase I trial, an initial human test conducted with a small group of people, is to gather safety data and preliminary results on the immune responses induced by the vaccine candidate. A Phase I trial does not test the efficacy of a vaccine. If initial results warrant (meaning the candidates produce different or better responses than candidate vaccines that have failed in efficacy tests), further safety and efficacy tests are conducted at a later stage in the product development process with a large group of volunteers to determine whether the vaccine candidate prevents HIV infection and/or disease.

***Is this prime-boost combination the most promising approach currently***

*Jean-Marc Giboux/Getty Images*

*A medical evaluation in progress at the Chennai Vaccine Trial Centre*

***available? How does it relate to other vaccines in development?***

Just as it is not yet known if this prime-boost combination will be able to help protect against HIV infection or slow progression of disease, the same is true for other AIDS vaccine candidates currently in clinical trials. The different DNA and MVA-based AIDS vaccine candidates differ in their design and manufacturing and quality control process. Studies of effects of vaccine candidates on disease have to use an animal model, the simian immunodeficiency virus (SIV), and SIV vaccines rather than HIV vaccines; these studies may not precisely predict the potential of vaccine candidates to provide benefits in humans. It is therefore difficult to say precisely how ADVAX and TBC-M4 compare to other DNA and MVA-based AIDS vaccine candidates and to alternative approaches. However, despite these limitations, the results obtained in the previous TBC-M4 Phase I trial are promising, and the prime-boost trial aims to gather additional understanding of the promise of this vaccine candidate alone and in combination with



Jean-Marc Giboux/Getty Images

A research assistant at work in the safety lab at the Tuberculosis Research Centre

ADVAX. No DNA vaccine candidate has been tested in large-scale trials. There is an efficacy trial ongoing in Thailand to evaluate a prime-boost combination of two AIDS vaccine candidates called AIDSVAX and ALVAC. The Thai trial is proceeding well, no harm has been detected by the independent monitoring committee. It will end next year. Nothing is known yet about the efficacy of the candidates tested.

**What is the value of testing the combination of ADVAX and TBC-M4 in a prime-boost regimen?**

Prime-boost vaccination involves giving one vaccine (prime), followed by or together with a second type of vaccine (boost). A prime-boost combination may induce different types of immune responses and/or enhance overall responses induced by either type of vaccine alone. In the proposed prime-boost trial, it is expected that this strategy would increase the magnitude (a little bit like the height of a protecting wall) of the response and its breadth (the thickness of the wall).

**Why was this combination selected?**

Previous Phase I studies, testing different vaccine candidates, indicate that a DNA vaccine in a prime-boost combination generates enhanced immune responses

compared to a single vaccine regimen without the DNA vaccine. Previous Phase I studies with a prime-boost regimen of different DNA-MVA combinations showed that it was well tolerated, and generated favourable immune responses.

The TBC-M4 vaccine

was tested recently in a Phase I trial and found to be well-tolerated and able to generate immune responses in most volunteers, in the case of the low-dose vaccine, or all volunteers, in the case of the high-dose vaccine. These results warranted further investigation. In studies of DNA + MVA vaccines in non-human primates using the SIV model, immunized non-human primates controlled SIV replication, providing an important preclinical test of concept for this vaccine strategy.

**How many and what kind of volunteers are being recruited?**

The trial is designed to recruit 32 healthy HIV-negative male or female volunteers 18 to 50 years of age, who report that they are at low risk for HIV infection.

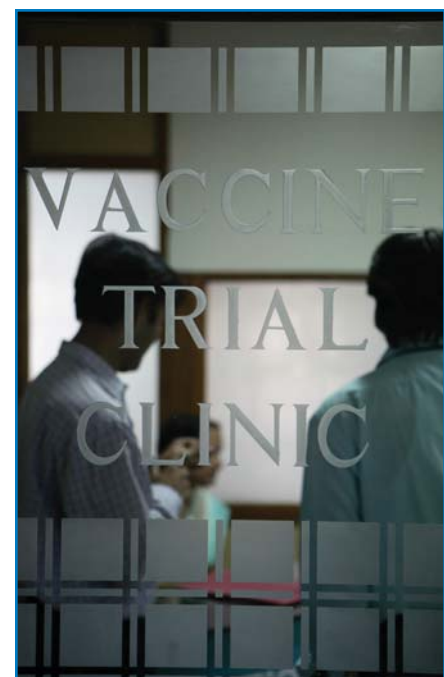
**How are the rights of volunteers guaranteed?**

The trial is conducted according to established international guidelines for ethical treatment of all volunteers in pharmaceutical and vaccine trials. All potential volunteers will be counseled on informed consent – a written agreement to participate in a trial based on the volunteer's complete understanding of all relevant information. Throughout the trial, volunteers will receive extensive counseling on how to reduce their risk

of exposure to HIV, as well as access to prevention methods such as condoms. A volunteer can decide to leave the study at any time without explanation. All the necessary clearances for the trial have been received from the NARI and TRC Ethics Committees, NARI and TRC Scientific Committees, Genetic Engineering Approval Committee, Drug Controller General of India (DCGI) and Health Ministry's Screening Committee. The trial will also be monitored by an independent Safety Review Board.

**Is there an expectation that this trial could be a breakthrough?**

The trial is not designed to test the ability of the vaccine candidates to protect against HIV infection or to slow progression of disease. A Phase I trial is the first stage of human testing. In this case, the



Jean-Marc Giboux/Getty Images

The AIDS Vaccine Trial Clinic at the National AIDS Research Institute in Pune

trial will assess the safety and tolerability and immune responses elicited by the ADVAX and TBC-M4 vaccine candidates in a prime-boost regimen. If the results are promising, further testing will be considered. ■

**NEW APPOINTMENTS**

**Dr. Rajat Goyal to lead IAVI India**

**D**r. Rajat Goyal has joined IAVI as the Country Director for India. He comes to IAVI with a wide array of experience. He was, until recently, Vice President at ICON Clinical Research where he was responsible for managing ICON's clinical operations in the Asia-Pacific Region. He has held the post of the Global Project Director for the Advancing Rotavirus Vaccine Development

Project at PATH. He was also in charge of product development for a wide range of new vaccines and other health technologies. He developed and managed viable public-private sector partnerships for sustainable, culturally ethical and adaptive health interventions.

Dr. Goyal also served as Vice President of Reliance Life Sciences heading the Reliance Clinical Research Services in

Mumbai, India. Before that, he was Medical Advisor with Dabur India Ltd.

Dr. Goyal received his medical degree from King Edwards Memorial Hospital in Mumbai. He specialised as a hemato oncologist. In addition, he was a research fellow at Rush Cancer Institute in Chicago and a visiting fellow at Beth Israel Hospital in Boston and Royal Marsden Hospital in the UK.

**Neeta Vinay joins as Director of Programme Operations**

**A**s the new Director of Programme Operations for IAVI India, Neeta Vinay will provide financial, administrative, human resources and operational management support to the regional office.

Neeta has 25 years of work experience in private, public and non-profit sectors. Before joining IAVI, she worked as the national programme officer at the National AIDS Control Organisation

(NACO). She was the Asian Regional Operations head for IntraHealth International Inc. She administered programmes in Yemen, Oman, Bangladesh, Indonesia and India. Neeta established systems for PATH's exponential growth.

Neeta has consulted on strategy development, performance planning, human resources, financial management and proposal development with a wide range

of international organisations, among them Save the Children, Population Services International, Packard Foundation, PA Consulting Group, Mott MacDonald, the Bill & Melinda Gates Foundation and Institute of One World Health.

She studied business management at the India Institute of Management and graduated from Lady Irwin College in New Delhi. ■

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The intended audience for this initiative includes organisations and individuals currently involved or interested in helping to fulfill global health objectives.

Stakeholders are encouraged to submit an idea for a case study at <http://www.casestudiesforglobalhealth.org/>. Stakeholders include private funders, international and multilateral organisations, universities and non-profit research centers, pharmaceutical and biotech companies, public private partnerships, non-governmental organizations, and governments.■

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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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