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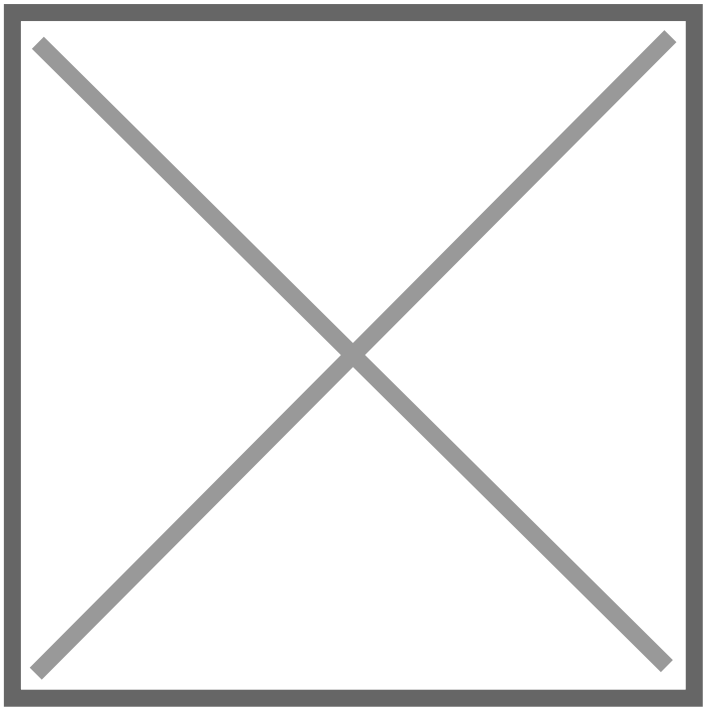

Indigenous AIDS vaccine on the cards

Dr Pradeep Seth, professor and head, department of Microbiology, AIIMS

Today India is home to the world's second largest HIV population after South Africa. From one AIDS case in 1986 to over 5.1 million HIV positive people today, experts claim that the number could quadruple by 2010 in the country. An HIV vaccine is the need of the hour to curb this deadly scourge.

Help will be at hand soon for India's 5.1 million population living with HIV/AIDS. The National HIV Reference Centre at the All India Institute of Medical Sciences (AIIMS) under the leadership of Dr Pradeep Seth, professor and head, department of Microbiology, AIIMS, has not only perfected the technology for an indigenous AIDS vaccine, but has also developed affordable detection kits, PCR tests and even a therapeutic AIDS vaccine.

Indigenous AIDS vaccine

The indigenous rDNA/rMVA vaccine is constructed from select genetic sequences of HIV and is delivered with the help of a plasmid vector in the prime dose and a highly attenuated strain of Vaccinia virus-Modified Vaccinia Ankara (MVA)-as the vector in the boost dose. The vaccine has been tested on mice as well as monkeys with remarkable results suggesting induction of robust immune response. The blood samples from the HIV vaccine immunized animals were found to destroy the cells coated with the HIV virus protein. Special tests were conducted and it was found that the vaccine had induced development of antibodies to the virus, which specifically neutralize HIV virus isolates in vitro. "The vaccine was found to be highly immunogenic and tremendous HIV specific immune response was seen during the animal trials", said Dr Seth. Supported by the Department of Biotechnology (DBT), the HIV vaccine is ready to enter the preclinical toxicology test prior to human clinical trials. The hurdle now facing the scientists is the lack of expertise and infrastructure for producing GMP grade

rDNA vaccine batches for the preclinical toxicity trials. Efforts are presently on, in collaboration with an industry to mass-produce the vaccine for these trials.

An urgent thrust is needed to bring the vaccine to the clinical trial stage, otherwise looking at the alarming AIDS statistics today, it will be a case of too little, too late for the Indian population.

HIV detection kit

Earlier, in 1999, Dr Seth developed an HIV detection kit, which was designed to detect HIV Subtype C, the virus subtype prevalent in the Indian and African continent. The kit, though not commercialized, is highly sensitive and very cost effective at Rs 8-10 per test. For the kit, Dr Seth had used indigenously designed peptides. Having filed a patent for this technology, he is looking at the industry to upscale the technology and make it commercially available throughout the country.

Acquired Immuno Deficiency Syndrome (AIDS) is caused by the Human Immunodeficiency Virus, which infects CD4+ cells, also known as T-helper cells or helper T lymphocytes, a vital part of the body's immune system. There are mainly two types of HIV virus, HIV-1 and HIV-2. HIV-1 causes most of the infection all over the world and AIDS is diagnosed when an infected person has a CD4+ cell count below 200 cells per micro liter of blood or/and shows specific opportunistic infections and/or cancers.

The HIV infection is normally associated with a "window period"- the length of time after infection that it takes for a person to develop enough specific antibodies to be detected. This period generally ranges form eight to twelve weeks and is a potentially dangerous period. As the presently approved HIV antibody detection tests used for the detection of HIV infection are not able detect it during the window period, hence it may unknowingly get transferred to many unsuspecting individuals. Dr Seth's lab has developed a "Matrix Real Time PCR" test, which can detect the presence of the virus during the window period also. The test is very sensitive and has the ability to detect a small number of about 100 copies of the virus in the body. And it can analyze 1000 samples at a time, making it an ideal tool for the diagnostic labs and also blood banks.

In addition, Dr Seth has developed a "RT PCR" test by which the exact viral load in the body can also be detected. He has filed a patent for both these technologies. Once upscaled at a commercial level, these tests would be available at a very affordable cost for the Indian masses. The Matrix RT PCR test would cost about Rs 40-50 per test where as RT PCR test would cost Rs 700-800 as against to Rs 3000-4000 per test presently available in the market.

Therapeutic AIDS vaccine

In a quest to further conquer this rapidly spreading disease, Dr Seth has recently developed a therapeutic AIDS vaccine by adding adjuvant to his existing HIV vaccine candidate. This aims to control the virus replication in AIDS patient, thus considerably enhancing the health and life span of the patient while simultaneously reducing his dependence on antiretroviral drugs. Significantly, once developed, this would be the first of its kind of therapeutic HIV vaccine in the world. Today, about 60 percent of HIV-positive adults who do not receive treatment develop AIDS after 12 or 13 years. Many with positive HIV develop opportunistic infections early and succumb to such infections. Presently only antiretroviral drugs offer some hope to AIDS patients, but they can have serious side effects. In such a scenario, a therapeutic AIDS vaccine is the need of the hour.

Based on his extensive studies of immunodeficiency virus, Dr Seth has also designed PCR based genotypic and phenotypic tests to identify/screen the quasi mutant or resistant HIV strains in patients to avoid unnecessary retroviral medication to them, as studies have indicated that nearly 5-15 percent of infected individuals have primary resistant strains.

What makes Dr Seth's research work on the AIDS virus all the more impactful is the fact that all of it is based on HIV-1 Subtype C, the most prevalent virus subtype in India. It causes infection in more than 80 percent of the cases in India. Overall, there are ten genetic variants of HIV known as subtypes - from A to K, which are in circulation in different geographical areas. In India HIV-1 Subtype C is prevalent, while in Europe and America, subtype A and B are common.

AIDS vaccine clinical trials

Worldwide over 30 AIDS vaccine candidates are in human clinical trials in 19 countries, according to the International AIDS Vaccine Initiative (IAVI), which is supporting research in India among other countries. Since 2001, IAVI has been partnering the National AIDS Control Organization (NACO) and Indian Council for Medical Research (ICMR) for developing a vaccine to counter HIV subtype C prevalent in India. Human trials of vaccines against different strains of the virus are already being conducted in the US, Europe, Africa and South America.

Human trials of a US-made HIV vaccine are due to start in Pune early this year. The National AIDS Research Institute (NARI) based in Pune will be conducting the research. The first phase of testing of the vaccine, named Adeno Associated Virus based HIV sub-type C, will be conducted on about 30 adult volunteers. The central ethics committee of the Indian Council of Medical Research and the Drugs Controller General of India has approved the trial. The NARI scientists will monitor the volunteers over a period of one year to test for side effects and the immune system's response to the vaccine. These trials are

a part of the multi-national multi-centric study involving two sites each in Germany and Belgium in addition to the Pune site.

Rolly Dureha

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Bacterium uses sonar-like strategy to "see" enemies

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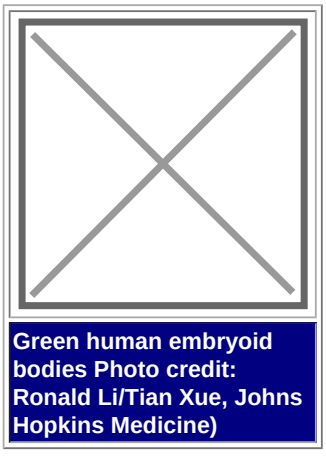
For the first time, scientists have found that bacteria can use a sonar-like system to spot other cells (either normal body cells or other bacteria) and target them for destruction. Reported in the December issue of Science, this finding explains how some bacteria know when to produce a toxin that makes infection more severe. It may lead to the design of new toxin inhibitors. "Blocking or interfering with a bacterium's "detection" mechanism, should prevent toxin production and limit the severity of infection," said Michael Gilmore, lead author of the study, and currently director of research at the Schepens Eye Research Institute and professor of ophthalmology at Harvard Medical School.

Gilmore and his team have spent years studying the bacterium Enterococcus faecalis, one of the leading causes of hospital-acquired infections, to find new ways to treat them. These infections are frequently resistant to many, and sometimes all, antibiotics. Scientist have known since 1934 that especially harmful strains of Enterococcus produce a toxin that destroys other cells, including human cells and even other types of bacteria. They also knew that this toxin was made only under some conditions. Until this study, scientists were unable to explain how the bacterium knew when to make it.

In the Science study, Gilmore and his team found that this toxin is made whenever there is another cell type in the environment near the bacterium, such as a human blood cell. They discovered how these bacteria know when other cells are present, and respond accordingly. In the laboratory, the team found that Enterococcus releases two substances into the environment. One substance sticks to foreign cells. The second substance reports back and tells the bacterium to make the toxin. If no cells are in the area, the first substance sticks to the second, preventing it from reporting back, and as a result, no toxin is made.

Stem cells might make biological pacemaker

Researchers from Johns Hopkins have found the first evidence that genetically engineered heart cells derived from human embryonic stem (ES) cells might one day be a promising biological alternative to the electronic pacemakers used by hundreds of thousands of people worldwide. Electronic pacemakers are used in people with certain heart conditions that interfere with a normal heartbeat. However, these life-saving devices cannot react the way the heart's own pacemaker normally does.



Green human embryoid bodies Photo credit: Ronald Li/Tian Xue, Johns Hopkins Medicine)

In the researchers' experiments, described in the online edition of Circulation, human ES cells were genetically engineered to make a green protein, grown in the lab and then encouraged to become heart cells. The researchers then selected clusters of the cells that beat on their own accord, indicating the presence of pacemaking cells. These clusters triggered the unified beating of heart muscle cells taken from rats, and when implanted into the hearts of guinea pigs, triggered regular beating of the heart itself.

"These implanted cells also responded appropriately to drugs used to slow or speed the heart rate, which electronic pacemakers cannot do," said study leader Ronald Li, assistant professor of medicine. "But many challenges remain before

this technique could be used for patients. We want to bring this to the clinic as fast as possible, but we need to be extremely careful. If this process isn't done properly, it could jeopardize a very promising field."

The genetic engineering of the ES cells, accomplished by Tian Xue, a postdoctoral fellow at the School of Medicine, inserted a gene (for green fluorescence protein) so that the human cells would be easily distinguished from animal cells in the experiments. "To our knowledge, these are the first genetically engineered heart cells derived from human ES cells," said Xue. "We're now using genetic engineering to customize the pacing rate of these cells, for example. For any future clinical applications, you want to make sure that the beating rate is what you want it to be."

The stem cell approach isn't the first Johns Hopkins research to create a biological pacemaker, but it is likely to be a better choice if the heart is very damaged. In 2002, Hopkins scientists reported that inserting a particular gene into existing heart muscle cells in a guinea pig allowed the cells to create a pacemaking signal. "If heart damage is extensive, however, it might be preferable to introduce new pacemaking cells, rather than to convert existing cells into pacemakers", noted Li.