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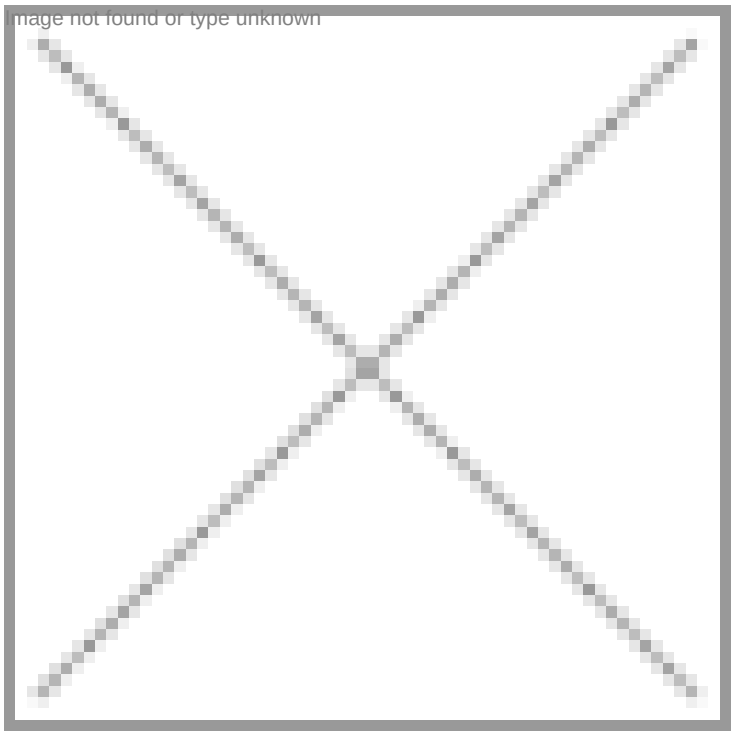

Vaccine development gains momentum

An update on the vaccines being developed in India.

Rotaviral Diarrhoea

Rotaviral diarrhoea vaccine specific to India enters Phase II trials

Rotavirus is the most common cause of severe dehydrating diarrhea in infants and young children.

In India two candidate vaccines 116E and I321 were developed under the Indo-US Vaccine Action Program. 116E was developed by the collaborative efforts of Dr MK Bhan, Dr Pratima Ray of All India Institute of Medical Sciences, New Delhi; Dr Nita Bhandari of Society for Applied Sciences, New Delhi and Dr Roger I Glass, Centre for Disease Control and Prevention, Atlanta, USA, while candidate vaccine I321 was jointly developed by Dr C Durga Rao of the Indian Institute of Science, Bangalore and Dr Harry Greenberg of Stanford Unviersity, USA.

The phase I clinical trials dealing with the safety and immunogenicity studies have been completed in adults, children and infants. The infant trials showed both vaccines to be well tolerated and safe. Vaccine take was reported in 74 percent of recipients of 116E vaccine candidate and 40 percent recipients of I321 vaccine. Further the results revealed that the 116E-based vaccine candidate is more promising and provides up to 70 percent protection with single dose in infants, which may

increase to complete protection with 2-3 doses. Now the vaccine based on 116E has entered phase II trials. Hyderabad-based Bharat Biotech International has produced prototype vaccine 116E under cGMP conditions to ensure its sufficient stock for the phase II and III clinical trials.

Although the commercialization of the Rotavirus vaccine is still a few years away, it provides hope to combat one of the most serious public health problems affecting infants and children.

Cholera

First indigenous r-oral cholera vaccine completes phase I and II clinical trials

Now an indigenous recombinant oral cholera vaccine has been developed in the country, which is based on VA 1.3 strain of V. cholerae. The vaccine has been jointly developed by Dr Amit Ghosh, ex-director, Institute of Microbial Technology, Chandigarh and Dr SK Bhattacharya, National Institute of Cholera and Enteric Diseases, Kolkata. The phase I and II clinical trials have been conducted in adults by Dr D Mahalanobis of Society of Applied Sciences, Kolkata and Dr Rakesh Agarwal of Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow. The results revealed that the vaccine is safe and the vibriocidal antibody response is equal to the best candidate vaccine available in international market. Out of 270 volunteers with 147 vacinees and 123 placebos, 48 percent had a four-fold rise or more and 40 percent had a eight-fold rise or more in Kolkata. The rise as marker of protection is comparable to the level raised with CVD 103 HgR in cholera endemic countries. Currently the preparations for the Phase III clinical trials are on. A field site for Phase III trial is being prepared for which survey and demographic patterns of more than 30,000 slum population has been completed and another 20,000 population is underway. Efforts are being made to transfer the technology and get the clinical grade material prepared for conducting the phase III trials.

Rabies

Animal vaccine slated for launch during 2006 after regulatory clearances

The first combined DNA-based rabies vaccine for the control of rabies in dogs has been jointly developed by Prof. G Padmanaban, Emeritus
Professor and distinguished biotechnologist and Prof PN Rangarajan of the Indian Institute of Science (IISc),
Bangalore in collaboration with Dr VA Srinivasan of Indian Immunologicals, Hyderabad. Last year, studies were conducted at the IISc to analyze the residual DNA present in the germline doses of the vaccine. The PCR results indicated that that plasmid DNA was not detectable in the germline tissue of any inoculated animals. These results were submitted to the RCGM and GEAC, which gave the clearance for animal trials.

The industrial partner, Indian Immunologicals, has prepared a batch of the combination rabies vaccine which has passed all the mandatory tests and conforms to the standards laid down by the Indian Veterinary Pharmacopoeia. The formulated vaccine is currently undergoing trials in Kerala. In future, clinical trials are also planned in Chennai, Mumbai, Bhubaneshwar and Delhi. The results of the trials will be submitted to the regulatory authorities. The study so far conducted clearly indicates that the combined DNA rabies vaccine provides tremendous boost to the inoculated animals. The animal vaccine is slated for launch this year after the necessary regulatory clearances. Subsequently the human trials will be undertaken in 2007.

Typhoid

New Vi-conjugate developed and technology transferred to industry

Dr Ramesh Kumar and Dr BL Jailkhani of AIIMS, New Delhi developed Vi polysaccharide conjugate typhoid vaccine using Salmonella typhi outer membrane protein from conjugation. This Vi conjugate has been shown to be immunogenic in mice. The Typhoid Vi Vaccine is presently undergoing trials in Kolkata.

Recently the Biotech Consortium India Limited (BCIL) entered into a License Agreement with USV Limited, a Mumbai-based biopharmaceutical company, to upscale, manufacture and market the novel conjugate typhoid vaccine

Japanese Encephalitis

Tissue culture based, inactivated Japanese Encephalitis vaccine developed at NII

A tissue culture based and inactivated Japanese Encephalitis vaccine was developed by the team of Dr Sudhanshu Vrati at the National Institute of Immunology, New Delhi. The scientists had grown an Indian strain of Japanese Encephalitis Virus (JEV) in Vero cells to high titers and formalin inactivated it. Inactivated virus produced high titers of JEV neutralizing

antibodies and challenge experiments in mice indicated that the preparation provided 100 percent protection to the immunized mice against lethal dose of JEV given intra-cerebrally.

Further the technologies for high density culture of Vero cells using micro carriers in a spinner flask; high titer culture of an Indian strain of JEV in Vero cells and its formalin inactivation were standardized and transferred to New Delhi-based Panacea Biotec. Meanwhile, Panacea has also obtained Vero cells from the WHO and standardized JEV cultures. Now the company will soon initiate the preclinical toxicity trials and is planning to start the Phase I clinical trials subsequently.

In another approach to evaluate the immunogenicity of the DNA JEV vaccines, Dr Vrati has developed a candidate DNA-based JEV vaccine (replication-defective recombinant adenoviruses). Rhesus monkeys have been immunized with the JEV DNA vaccine candidates and immune response of these plasmids is being studied.

Leprosy

A leprosy vaccine called "Immuvac" was developed at the National Institute of Immunology, New Delhi and the technology transferred to Cadila Pharmaceuticals, Ahmedabad. The product is also recognized as an orphan drug, which is available in the market.

In a notable development, Mycobacterium W has shown its potential as therapeutic agents by reducing the chemotherapy duration in leprosy patients. Based on the results, a multi-centric project is being supported using a uniform clinical protocol involving several centres to study the safety and efficacy of Mw immunomodulator as adjunct to ATT therapy in all categories of pulmonary tuberculosis patients. The centres involved are: AIIMS, New Delhi; LRS Institute of TB and respiratory diseases, New Delhi; Central JALNA Institute for Leprosy, Agra; SMS Medical College, Jaipur; NHL Municipal Medical College, Ahmedabad; RNT Medical college, Udaipur; National Tuberculosis Centre, Bangalore and Tuberculosis Research Centre, Chennai. The trials are currently in progress.

Malaria

The International Centre for Genetic Engineering and Biotechnology (ICGEB) has been working on understanding the biology of the malaria parasite and developing novel therapeutic strategies against it. Recently, Dr VS Chauhan and Dr Chetan Chitnis at ICGEB, New Delhi were able to produce the recombinant candidate antigens of P. falciparum and P vivax under GLP conditions. Now the method of producing the recombinant antigen has been scaled up in collaboration with industrial partner, Hyderabad-based Bharat Biotech International Ltd (BBIL). The company has successfully produced three consistent batches of clinical grade material at 10L scale for preclinical toxicology studies under cGMP conditions. Currently the safety and phase I clinical trial studies are being planned, while the toxicity trials have started.

The malaria vaccine trial site has been developed at Sundergarh district of Orissa to evaluate the malaria candidate vaccinogens through collection of clinical, entomological and molecular epidemiological/immunological indicators from the study.

Tuberculosis

Efforts have been made to develop novel recombinant DNA-based candidate vaccine and recombinant BCG containing relevant antigens of Mycobacterium tuberculosis by Dr Anil K Tyagi of Delhi University (South Campus), New Delhi. For developing novel candidate vaccines, his group has expressed six antigens of M. tuberculosis using different vectors in E. coli expression system. All the DNA candidate antigen were found to elicit specific immune responses in experimental animals. Testing in aerosol challenge models is in progress to select the best candidate for human studies. The group has also initiated work on the DNA vaccine approach for the development of candidate TB vaccine by using three M. tuberculosis antigens. These proteins have been cloned and expressed in E. coli. Simultaneously efforts are being made to express these in eukaryotic system. Antibodies have been raised against these three recombinant proteins in rabbits and their immunoreactivity is being studied.

Dengue

The existence of multiple but distinct dengue virus serotypes is a major factor that has hindered dengue vaccine development efforts. Available evidence indicates that immunity against an infecting serotype is life-long, whereas cross-protection against other serotypes is transient. Protection against only one or two dengue viruses could actually increase the risk of potentially fatal dengue haemorrhagic fever and dengue shock syndrome. Therefore, a safe and effective dengue vaccine should ideally be "tetravalent" or capable of providing solid and long-lasting immunity to all four serotypes. Taking this approach further, Dr Navin Khanna and his group at ICGEB are developing a tetravalent dengue vaccine candidate. The strategy is to make non-

replicating sub-unit vaccine based on a critical domain of the major dengue structural envelope protein that is involved in the host receptor reception and in the induction of robust protective immunity. Each subunit is being expressed using Pichia pastoris as the expression host.

HIV/AIDS

HIV/AIDS continues to ravage many parts of the world. A DNA/MVA based vaccine has been developed by Dr Pradeep Seth, ex-professor and head, Department of Microbiology, AIIMS, New Delhi for HIV-1, subtype 'C' prevalent in India. The indigenous recombinant DNA/MVA 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 is currently poised for GMP production and preclinical toxicology studies. After successful completion for the preclinical studies, the clinical trials in human volunteers will be initiated after mandatory approval by the regulatory agencies.

Anthrax

Anthrax is a zoonotic disease caused by gram-positive sporulating bacteria bacillus anthracis. The recombinant protective antigen (rPA) against anthrax was developed by Dr Rakesh Bhatnagar of Jawaharlal Nehru University (JNU), New Delhi and the technology was transferred to New Delhi-based Panacea Biotec. The efficacy and immunogenicity of recombinant vaccine was tested in New Zealand white rabbits and Rhesus monkey by pre exposure and post exposure prophylactic studies. The phase I and phase II A trials have been completed, while the company is geared up for the Phase II B and Phase III trials. In addition, a protocol for experimental trials of recombinant anthrax vaccine in animals has also been developed.

Human Papiloma Virus

The Department of Biotechnology (DBT) has generated an end-to-end mission project on the development of vaccine candidates for Human Papilloma Virus. The efforts include: identifying oncogenic strains prevalent in different geographical regions of India, validating self-collection methods using cervical swabs, assessing molecular variations if any and development of indigenous test systems. The groups are also expressing L1/L2 proteins of HPV 16/18 as Virus Like Particles (VLPs) and Capsomere Like Particles (CLPs) as possible prophylactic vaccine candidates. It is also envisaged making chimaeric proteins using various combinations of L1/L2 and E6/E67 proteins in order to make therapeutic candidates. The target population in Indian social conditions would be HPV infected women. Hence it is relevant to make efforts in the direction of therapeutic vaccine candidates.

FMD Vaccine

The FMD is a highly contagious viral disease of cloven-hoofed animals and causes serious production losses. Recently Panacea Biotec collaborated with the National Research Development Corporation (NRDC) for in-licensing of technology to produce and market the Foot and Mouth Disease (FMD) vaccine developed by the Indian Veterinary Research Institute (IVRI).

The NRDC will facilitate the transfer of know-how for the
process of FMD vaccine manufacturing incorporating a new adjuvant developed by the IVRI, while Panacea will manufacture and market it in the country. The latest technology of the vaccine can replace the Ultra Filtration Method of virus concentration with an alternate technology. It can also replace the imported oil adjuvant with the indigenously developed oil adjuvant. The vaccine has been tested for toxicity (standard tests) and found to be safe. The vaccine is expected to be rolled in the market in the coming 18-24 months.

Others

R&D efforts are being initiated for several other vaccines such as recombinant DNA based vaccines for filarial, pneumococcal, bovine tuberculosis, brucellosis and duck plague.

Rolly Dureha